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Coagulation assessment with the new generation of oral anticoagulants

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ABSTRACT

Long-term oral anticoagulant (OAC) therapy is used for the treatment and prevention of thrombosis and thromboembolism. As OAC use is so widespread, emergency physicians are likely to encounter patients on anticoagulant therapy in the emergency department (ED) on a regular basis, either for the same reasons as the population in general or as a result of the increased bleeding risk that OAC use entails.

The vitamin K antagonist warfarin has been the standard OAC for several decades, but recently, the newer agents dabigatran etexilate, rivaroxaban and apixaban (collectively, novel OACs, non-vitamin K OACs, or simply 'NOACs') have become available for long-term use. Protocols for assessing and managing warfarin-treated patients in the ED are well established and include international normalised ratio (INR) testing, which helps guide patient management. However, the INR does not give an accurate evaluation of coagulation status with NOACs, and alternative tests are therefore needed for use in emergency settings. This paper discusses what information the INR provides for a patient taking warfarin and which coagulation tests can guide the physician when treating patients on one of the NOACs, as well as other differences in emergency anticoagulation management.

INTRODUCTION

Oral anticoagulants (OACs) are indicated for the treatment of thrombosis and in the prevention of thromboembolism.¹ This includes the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), prevention of thrombosis in medically ill and postsurgical patients, and the prevention of thromboembolic stroke in atrial fibrillation. Patients using OACs are likely to be seen in the emergency department (ED) for the same reasons as other individuals of similar age and health, but also because all anticoagulant therapies carry a risk of treatment-related bleeding that, if it occurs, may require emergent evaluation and treatment.¹⁻⁴

The vitamin K antagonist (VKA) warfarin (eg, Coumadin, Bristol-Myers Squibb, New York, New York, USA) has been the standard OAC for >50 years, with >30 million prescriptions written annually in the USA alone.⁵ As well as the increased bleeding risk common to anticoagulants, the complex and variable pharmacokinetics and pharmacodynamics of warfarin create the further challenge of avoiding unpredictable subtherapeutic or suprathreshold anticoagulation.^{1 2 4} Bleeding resulting from suprathreshold activity ranges in severity from clinically manageable epistaxis to life-threatening intracranial haemorrhage.^{1 2 6-9} In a prospective observational study in the UK, warfarin

was implicated in 10.5% of adult hospital admissions for adverse drug reactions over a 6-month period ending in April 2002.¹⁰ Following a survey (2004–2005) of nationally representative public health surveillance data in the USA, which disclosed that warfarin was implicated in 17.3% of ED visits for adverse drug events in older adults, Budnitz *et al*¹¹ observed that despite frequent emergency visits for warfarin-related adverse drug events, as one of a small group of 'often critical' medications, warfarin should not be labelled as inappropriate for use in older adults, according to Beers criteria. Many patients on warfarin who are seen in the ED for anticoagulation-related or other issues have either a subtherapeutic or a suprathreshold international normalised ratio (INR).^{12 13} More than 90% of warfarin-related emergency hospitalisations in older patients are attributed to unintentional overdose.¹¹

Non-warfarin oral anticoagulants (NOACs, formerly 'novel' oral anticoagulants and now sometimes referred to as non-vitamin K OACs, target-specific OACs or direct OACs) are now appearing in clinical practice. For example, most patients with non-valvular atrial fibrillation requiring a long-term OAC are still prescribed warfarin, but increasing numbers, currently approximately 17%,¹⁴ are prescribed the direct thrombin inhibitor dabigatran etexilate (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut, USA).^{15 16} Dabigatran has been approved for the reduction of risk of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days and for the reduction of the risk of recurrence of DVT and PE in previously treated patients.¹⁷

The factor Xa (FXa) inhibitor rivaroxaban (Xarelto, Janssen Pharmaceuticals, Titusville, New Jersey, USA) has been approved for stroke prevention in non-valvular atrial fibrillation, treatment of venous thromboembolism (VTE) and VTE prophylaxis after elective major joint replacement surgery.¹⁸ The FXa inhibitor apixaban (Eliquis, Bristol-Myers Squibb and Pfizer, New York, New York, USA) also has been approved by the US Food and Drug Administration (FDA) for stroke prevention in non-valvular atrial fibrillation and for treatment of VTE.¹⁹ Another agent in this class, edoxaban (Daiichi Sankyo Co, Tokyo, Japan), has recently completed pivotal clinical trials²⁰ and received FDA approval for the reduction of risk of stroke and SE in patients with non-valvular atrial fibrillation, and for the treatment of DVT and PE subsequent to initial therapy with a parenteral anticoagulant for 5–10 days.²¹ Therefore, while most



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Table 1 Approved US indications and dosing for NOACs

Indication	Dabigatran ¹⁷	Rivaroxaban ¹⁸	Apixaban ¹⁹	Edoxaban ²¹
To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation	For patients with CrCl >30 mL/min: 150 mg orally, twice daily For patients with CrCl 15–30 mL/min: 75 mg orally, twice daily	For patients with CrCl >50 mL/min: 20 mg orally, once daily with the evening meal For patients with CrCl 15–50 mL/min: 15 mg orally, once daily with evening meal	5 mg orally twice daily In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily	CrCl needs to be measured before initiating therapy. 60 mg once daily in patients with CrCl >50 to ≤95 mL/min For patients with CrCl from 15 to 50 mL/min: 30 mg once daily Edoxaban should not be used in patients with creatinine clearance (CrCl) > 95 mL/min because of increased risk of ischaemic stroke compared with warfarin at the highest dose studied (60 mg)
For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)	For patients with CrCl >30 mL/min: 150 mg twice daily after 5–10 days of parenteral anticoagulation	For patients with CrCl >30 mL/min: 15 mg orally twice daily with food for the first 21 days for initial treatment 20 mg orally once daily with food for long-term treatment	NA	After 5–10 days of initial therapy with a parenteral anticoagulant For patients with CrCl >50–≤95 mL/min: 60 mg once daily 30 mg once daily for patients with CrCl 15–50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors
To reduce the risk of recurrence of DVT and PE in patients who have been previously treated	For patients with CrCl >30 mL/min: 150 mg orally, twice daily	For patients with CrCl >30 mL/min: 15 mg orally twice daily with food for the first 21 days for initial treatment 20 mg orally once daily with food for remaining treatment, and the long-term reduction in risk of recurrent DVT or PE	NA	NA
Prophylaxis of DVT following hip or knee replacement	NA	For patients with CrCl >30 mL/min: 10 mg orally, once daily with or without food	2.5 mg orally twice daily	NA

CrCl, creatinine clearance; NA, not approved; NOACs, non-warfarin oral anticoagulants.

patients presenting to the ED who are taking an OAC are likely to be taking warfarin, it is important for all emergency care providers to gain familiarity with the NOACs. The currently approved indications for use and recommended dosing for the approved NOACs can be found in [table 1](#).

Familiarity with warfarin may influence ED staff practices, with the result that many patients receiving NOACs who are treated in the ED may be subjected to standard coagulation testing. However, the results of standard prothrombin time (PT)/INR assays used to assess coagulation during warfarin therapy may not provide clinically meaningful results with the NOACs, unless, as with rivaroxaban, a specific reagent, neoplastin, is incorporated and the test calibrated accordingly.^{22–31} The results could lead to confusion over coagulation activity in patients who are taking one of the newer agents.

The evidence cited in this narrative review was assembled on the basis of the author's clinical expertise, extensive reading of the relevant literature and broad experience teaching emergency medicine. The reality is that at the present time there is no definitive guidance on the management of medical emergencies due to NOAC-associated bleeding events. Therefore, in the absence of solid data from randomised clinical trials, the objective for this review was to develop a practical guide for clinicians in the field.

This article discusses the rationale for testing anticoagulant activity, examines why the INR is not appropriate for quantifying the extent of anticoagulation in patients on the NOACs, reviews the assay options that are or will soon be available for these agents and discusses current options for treatment of bleeding emergencies.

WHY ASSESS ANTICOAGULANT ACTIVITY?

When a patient presents in the ED, and is known or suspected to be on OAC therapy, it is often helpful to be able to measure the level of anticoagulation.

1. The patient has unintentionally or intentionally overdosed on the OAC, but there are no related symptoms; for example, in the case of warfarin, the patient's routine monitoring could have given an overly elevated INR value, which might be owing to an overdose or a pharmacological interaction.
2. The patient is experiencing a spontaneous episode of external or internal bleeding, or the latter may be suspected.
3. The patient has suffered an injury causing external or internal bleeding.
4. An urgent surgical or other invasive procedure is deemed necessary because of trauma or acute illness, and it is essential for the surgical team to know the level of anticoagulation in the patient.

THE RELEVANCE OF THE INR FOR VKA-TREATED PATIENTS

The INR is a standardised method for reporting results of the PT assay, which is sensitive to the coagulation factors prothrombin, tissue factor and factors V, VII and X.^{4 32–34} As these coagulation factors depend on vitamin K for synthesis, the INR reflects anticoagulation owing to warfarin.^{4 33 34} For a warfarin-anticoagulated patient, the INR can aid decision-making around the measures that may be needed to normalise coagulation activity and stop or stabilise bleeding.

Elevated INRs can arise from direct overdosing, as well as interactions between warfarin and numerous other drugs or herbal remedies, as the result of fluctuations in dietary vitamin K owing to dietary changes or intake of nutritional supplements, or as a consequence of alcohol abuse.^{35–38} Concurrent conditions, such as hepatic or biliary disease, gastrointestinal illness or sepsis also can increase the INR.^{37–39} In such situations, the cause of the elevation needs to be identified so that repeated incidents and the resultant increased bleeding risk can be avoided. In the event of a self-reported and/or unexplained elevation in INR, retesting in the ED can confirm the elevation and exclude erroneous

Table 2 Coagulation assays responsive to dabigatran, rivaroxaban, apixaban and edoxaban

Assay	Responsive within therapeutic range?	Included in US drug prescribing information?*
Dabigatran ^{22–24 26 28 45–47}		
aPTT	Provides estimate of effect	Yes
ECT	Quantifiable dose–response	Yes
TT	Too sensitive to give quantifiable results	No
Diluted TT	Quantifiable dose–response	Not in the USA
Rivaroxaban ^{29–31 48–52}		
PT (rivaroxaban-calibrated)	Quantifiable dose–response if PT performed with neoplastin	Yes
aPTT	Dose-dependent, but variable and less sensitive than PT	No
FXa (clot-based, eg, HepTest)	Quantifiable dose–response	No
FXa (chromogenic)	Quantifiable dose–response	No
Apixaban ^{42 43 53 54}		
PT/INR	Small and variable response	No
aPTT	Small and variable response	No
FXa (chromogenic)	Quantifiable dose–response	No
Edoxaban ⁸⁰		
PT	Large variability between reagents	No
aPTT	Less variability between reagents	No
Thrombin generation	Three times more sensitive to edoxaban	No

Assays that can give quantifiable responses will typically require drug-specific and laboratory-specific calibration.

*Routine use of coagulation assays is not required with the novel oral anticoagulants.

aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; FXa, factor Xa; INR, international normalised ratio; PT, prothrombin time; TT, thrombin time.

results. However, in the ED itself, testing artefacts such as under filling tubes when drawing blood for INR testing can yield falsely elevated INR results owing to excess levels of citrate in the test sample.⁴⁰ Errors can be avoided by use of the correct sample tubes and ensuring that they are adequately filled.

Finally, patients are treated with warfarin to manage thrombosis or reduce the risk of stroke or other thromboembolic events. Therefore, when a VKA-treated patient presents at the ED, the INR should be confirmed to be in the therapeutic range, and intervention may be required when it is not. If necessary, the patient should be referred for appropriate warfarin management on discharge.¹³

INR TESTS GIVE MISLEADING RESULTS WITH NOACS

Dabigatran inhibits coagulation by directly and specifically binding thrombin (factor IIa); rivaroxaban and apixaban directly and specifically bind FXa.^{22 31 41} These modes of action differ from that of warfarin and make the results of PT/INR tests unreliable in patients treated with the newer agents. The INR is relatively insensitive to dabigatran-induced anticoagulation, yielding normal or near-normal results at therapeutic dabigatran plasma concentrations and only slight increases at higher drug levels.^{22 24 26} INR testing with point-of-care devices in dabigatran-treated patients is similarly unreliable.^{25 27} The FXa inhibitors rivaroxaban and apixaban have been reported to give variable results with PT tests, which are relatively insensitive to FXa inhibitor-induced changes in coagulation.^{28 30 31 42–44} Therefore, for a patient treated with dabigatran, the PT will not give valid information and could give the erroneous impression that the patient's coagulation status is normal or near-normal.

DETERMINING ANTICOAGULATION LEVELS WITH THE NOACS

Assays that respond to the NOACs are summarised in table 2.^{45–54} The thrombin time test is too sensitive to give interpretable information with dabigatran.^{22 24} This has led to development of a diluted thrombin time test (dTT) calibrated for dabigatran.^{45–48} The dTT, which has been approved for clinical use in several

countries (although not yet in the USA), and the ecarin clotting time (ECT), are two commercially available assays that are responsive to dabigatran within its therapeutic range (table 2).^{22 24 26 45} Either of these assays, but not the INR, may be used to evaluate coagulation activity in patients on dabigatran.¹⁷ At peak therapeutic plasma concentrations of dabigatran, the activated partial thromboplastin time (aPTT) is increased to two to three times control values, and at trough concentrations (eg, 12 h after the last dose) it falls to approximately 1.3 times control values. However, the aPTT prolongation response plateaus at therapeutic dabigatran concentrations;^{22 24 26 55–57} therefore, the aPTT only gives an approximate assessment of the effect of dabigatran on coagulation. The ECT and the dTT assays have a linear response to plasma dabigatran across its therapeutic range^{25 27 48 58} and is no doubt a more useful test.^{22 24 45 48} The ECT is in clinical use under an FDA Humanitarian Exemption for monitoring anticoagulation with the parenteral direct thrombin inhibitor hirudin for patients undergoing cardiopulmonary bypass who have heparin-induced thrombocytopenia,^{3 59} but is not yet available in a form calibrated for dabigatran.

Some coagulation tests, including the aPTT, PT and clot-based FXa assays (eg, HepTest, Sekisui Diagnostics, Framingham, Massachusetts, USA), are affected by the oral FXa inhibitors (table 2). Chromogenic FXa assays (eg, Rotachrom Heparin anti-Xa assay, Diagnostica Stago, Parsippany, New Jersey, USA) appear to show the most promise for quantifying the anticoagulant effects of the direct FXa inhibitors.^{28 30 52} Such FXa inhibitor assays are likely to be available in the near future for clinical use with rivaroxaban and apixaban.^{44 48–50 53} The use of a specifically calibrated PT assay for determining rivaroxaban-induced anticoagulation also has been reported.^{50 51} However, as yet, there are no specific recommendations on anticoagulant assays for use with the oral FXa inhibitors in the clinical setting.^{29 42 48}

Reversal of OACs

The effects of warfarin on coagulation extend over the drug's half-life of several days; hence, simply stopping warfarin will

Table 3 Overview from published guidelines of interventions for patients anticoagulated with warfarin according to INR status, need for invasive procedures and bleeding risk or severity

Presentation	Intervention
INR in therapeutic range, but non-urgent invasive procedure required ^{4 32}	▶ Interrupt warfarin for ≥ 1 doses until INR falls to required value*
INR in therapeutic range, minor bleeding ³²	▶ Interrupt warfarin*
	▶ Consider oral vitamin K†
INR moderately elevated (eg, INR <5) and low risk of bleeding ^{1 32}	▶ Interrupt warfarin*
INR moderately elevated (eg, INR <5) and minor bleed or high risk of bleeding ^{1 32}	▶ Interrupt warfarin*
	▶ Administer oral vitamin K†
INR very high (eg, INR 5–9), but no bleeding or no clinically significant bleeding ^{1 32}	▶ Interrupt warfarin*
	▶ Administer oral vitamin K†
INR >9, but no bleeding or no clinically significant bleeding ^{1 32}	▶ Interrupt warfarin*
	▶ Administer oral vitamin K†
Clinically significant bleeding and/or INR >20 ³²	▶ Interrupt warfarin*
	▶ Administer:
	– Intravenous vitamin K†
	– Blood or blood products†
Life-threatening bleeding (eg, intracranial haemorrhage) or extreme warfarin overdose ^{1 4 32 61 62}	▶ Interrupt warfarin*
	▶ Administer:
	– Intravenous vitamin K†
	– Blood or blood products†
	– Prothrombin complex concentrate†

*For details on interrupting or stopping warfarin, see Ageno *et al*.⁴ and Hirsh *et al*.³²

†For details on dosage and administration of vitamin K, blood products, and so on, see Holbrook *et al*,¹ Ageno *et al*,^{4 61} Hirsh *et al*.³² and Morgenstern *et al*.⁶² INR, international normalised ratio.

not rapidly reverse the anticoagulated state.^{4 35} Emergency management of patients treated with warfarin is discussed in depth in many clinical guidelines that advise on interventions according to INR status, the need for invasive procedures and bleeding risk or severity; these are reviewed in [table 3](#). Vitamin K₁ (phytonadione), administered orally or intravenously, can be used to accelerate warfarin reversal to some extent by counteracting its effects on vitamin K-dependent coagulation factor synthesis.^{4 35 60 61} The effect of vitamin K₁ on reversal of VKA-based anticoagulation is not immediate but will progress over 18–24 h or more as the liver synthesises sufficient quantities of vitamin K-dependent coagulation proteins (factors II, VII, IX and X) to re-establish effective clotting, a process that takes even longer in the presence of liver disease or other metabolic or nutritional problems.¹

In patients who require urgent invasive procedures, in asymptomatic patients presenting with excessively elevated INR values, and in bleeding patients, therapeutic options include interruption of VKA treatment as well as the administration of vitamin K (usually vitamin K₁, phytonadione) and blood derivatives such as fresh frozen plasma and prothrombin complex concentrates (PCCs) and recombinant activated factor VII ([table 3](#)).^{4 61 62}

As the effects of the oral direct thrombin and FXa inhibitors on the coagulation pathway are independent of vitamin K, this traditional antidote is ineffective for reversing the effect of either class of NOACs.^{17 24 29 42} Antidotes for the new agents are in development.^{63 64} A recent study compared the effects of a four-factor PCC and a three-factor PCC lacking factor VII on PT and thrombin generation in healthy adult volunteers who had been treated with supratherapeutic doses of rivaroxaban for 4 days to achieve steady-state concentrations.⁶⁵ Both the four-factor and three-factor PCCs, administered on day 5, 4 h after rivaroxaban administration, shortened the PT. As the four-factor PCC more effectively reduced the mean PT, whereas the three-factor PCC more effectively reversed rivaroxaban-induced changes in endogenous thrombin potential, the authors suggested that the discrepant results might have reflected the presence of heparin in the four-factor PCC and the absence of factor VII in the three-factor PCC. Administration of both agents in the presence of rivaroxaban was well tolerated, with no signs of prothrombotic response.⁶⁵

Although no reversal agent is yet available for dabigatran, emergent dialysis may be considered in circumstances such as renal failure or overdose; as approximately 50–60% of the drug is removed during 4 h of haemodialysis.⁶⁶

No rapid reversal agent is currently available for apixaban; therefore, drug levels may persist for approximately 24 h after the last dose (ie, two half-lives). Use of procoagulant reversal agents such as PCC, activated PCC or recombinant factor VIIa may be considered, but this approach has not been evaluated in clinical trials. Neither FXa inhibitor is dialysable.^{29 42}

Treatment of bleeding emergencies

The currently approved NOACs demonstrated non-inferior or favourable major bleeding event profiles compared with warfarin in early pivotal trials including Randomized Evaluation of Long-Term Anticoagulation Therapy for dabigatran 150 mg once daily (3.11% vs 3.36%; $p=0.31$),¹⁵ Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation for rivaroxaban 20 mg once daily (3.6% vs 3.4%; $p=0.58$),⁶⁷ Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation for apixaban 5 mg twice daily (2.18% vs 3.19%; $p=0.75$)⁶⁸ and

Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation TIMI 60 mg once daily (2.75% vs 3.43%; $p<0.001$)⁶⁹ (NOAC vs warfarin, respectively).

The currently approved NOACs have half-lives of only several hours; therefore, withholding these drugs will lead to relatively quick reductions in both their plasma levels and their anticoagulation effect. In the event of a bleeding emergency, an important point to consider is that the majority of patients receiving NOAC therapy do not need to be ‘actively reversed’. In many cases, a bleeding event can be effectively managed simply by providing supportive therapy and withholding the NOAC in question (at least temporarily).

However, as an option for cases of severe bleeding events, specific anti-NOACs reversal agents are under clinical development. These new agents have demonstrated positive results in animal studies and in healthy human volunteers. These reversal agents are expected to give clinicians the option to respond quickly and effectively to the limited number of clinically significant bleeding events associated with these drugs. The new reversal agents include a novel fragment of an antigen-binding monoclonal antibody, idarucizumab, which binds dabigatran with high affinity, thereby preventing it from inhibiting thrombin.⁷⁰ It should be noted that idarucizumab has recently received a ‘Breakthrough Therapy’ designation from the US FDA, ensuring its rapid review.⁷¹ The second reversal agent is an engineered version of the human FXa protein (andexanet alfa), which lacks the direct catalytic activity of the native protein, but does bind FXa inhibitors with high affinity, thereby blocking their inhibition of FXa.⁷² This agent has also received ‘Breakthrough Therapy’ designation from the US FDA.⁷³ Key pharmacological parameters and general management recommendations for managing bleeding with the approved NOACs can be found in [table 4](#).

To help guide management, therefore, it is important to ascertain as accurately as possible when the last dose of a NOAC was taken because the drug exposure plasma profile is highly dependent on the rates of drug absorption and elimination. Determining the patient’s renal status also may be warranted as it can influence clearance of the NOACs,^{58 74–76} particularly of dabigatran, which is approximately 80% renally excreted.⁵⁸ Ensuring that adequate diuresis is maintained may be helpful in ensuring efficient dabigatran clearance.^{24 77} As clearance of NOACs is generally more rapid than that observed for warfarin, elimination from the plasma may play a larger role in determining treatment options for patients who are on the newer agents and experiencing a bleeding event than patients in a similar situation and receiving warfarin.

SUMMARY

In summary, the INR provides valuable information to guide the ED clinician when a patient anticoagulated with warfarin or another VKA is encountered. An INR test in a patient on one of the NOACs will give misleading information on coagulation status,^{17 22 24 26 28 29} and therefore *cannot* be relied upon to indicate whether coagulation activity has returned to a normal level.

Although routine anticoagulation monitoring is unnecessary with the NOACs, assays for determining the anticoagulant effect in emergency situations would be of considerable benefit in the cases of patients who require urgent invasive procedures, asymptomatic patients presenting with excessively elevated INR values and bleeding patients. Accurate, validated and clinically approved assays for use with the NOACs are expected to be available in the near future. Meanwhile, the aPTT test can be used to determine whether there is excessive anticoagulation with dabigatran.^{22–24 26}

Table 4 Key pharmacological parameters and bleeding management recommendations for approved NOACs

	Dabigatran ¹⁷	Rivaroxaban ¹⁸	Apixaban ¹⁹	Edoxaban ²¹
Pharmacodynamics	<ul style="list-style-type: none"> ▶ Dabigatran is a specific inhibitor of thrombin, leading to longer coagulation times in standard clinical tests, including thrombin time (TT), activated partial thromboplastin time (aPTT) and ecarin clotting time (ECT)¹⁷ 	<ul style="list-style-type: none"> ▶ Rivaroxaban is a selective inhibitor of FXa, demonstrating a dose-dependent prolongation of PT, the aPTT and the heparin clotting assay (HepTest[®])¹⁸ 	<ul style="list-style-type: none"> ▶ Apixaban is a specific inhibitor of FXa, which leads to prolongations of the prothrombin time (PT), the INR and aPTT¹⁹ 	<ul style="list-style-type: none"> ▶ Edoxaban is a selective inhibitor of FXa, resulting in the inhibition of free FXa, prothrombinase activity, and the inhibition of thrombin-induced platelet aggregation²¹
Pharmacokinetics (PK)	<ul style="list-style-type: none"> ▶ Dabigatran, and its active conjugates have similar PK profiles¹⁷ ▶ The PK of dabigatran are dose-dependent from 10 mg to 400 mg, with a half-life of 12–17 h in healthy subjects¹⁷ 	<ul style="list-style-type: none"> ▶ The elimination half-life of rivaroxaban ranges from 5 to 9 h in healthy subjects¹⁸ 	<ul style="list-style-type: none"> ▶ After oral administration, apixaban has a half-life of ~12 h ▶ The PK of apixaban are log-linear, with proportional increases in exposure for oral doses (up to 10 mg)¹⁹ 	<ul style="list-style-type: none"> ▶ After oral administration, the half-life of edoxaban is ~10–14 h²¹ ▶ In healthy subjects, edoxaban demonstrates approximately dose-proportional PK for doses from 15 to 150 mg, and from 60 to 120 mg following single and repeat doses, respectively²¹
Bioavailability	<ul style="list-style-type: none"> ▶ The dabigatran etexilate pro-drug is a substrate of the P-glycoprotein (P-gp) efflux transporter in the gut. Dabigatran's bioavailability after oral dosing is 3–7%¹⁷ ▶ While the presence of food does not alter the overall bioavailability dabigatran, it does alter the time to Cmax (1 h under fasting conditions, while dosing with a high-fat meal can delay the Cmax by ~2 h)¹⁷ 	<ul style="list-style-type: none"> ▶ The bioavailability of rivaroxaban is dose-dependent: at the 10 mg dose, 80–100% of the drug is bioavailable (and unaffected by food)¹⁸ ▶ At the 20 mg dose, the bioavailability is ~66%, and absorption is impacted by food (mean area under the curve and Cmax increase by 39% and 76%, respectively)¹⁸ 	<ul style="list-style-type: none"> ▶ Apixaban has a bioavailability of ~50% at doses up to 10 mg ▶ Food consumption has no known impact on the bioavailability or PK of apixaban¹⁹ ▶ Apixaban demonstrates proportional increases in bioavailability for doses up to 10 mg, and the Cmax is seen ~3–4 h after an oral dose¹⁹ 	<ul style="list-style-type: none"> ▶ The absolute bioavailability of edoxaban is 62%²¹ ▶ After oral dosing, peak plasma concentrations are measured within 1–2 h²¹ ▶ Consumption of food does not impact the overall systemic exposure to edoxaban²¹
Distribution	<ul style="list-style-type: none"> ▶ Approximately 35% of dabigatran is bound to human plasma proteins¹⁷ ▶ In healthy subjects, the apparent volume of distribution is 50–70 L¹⁷ 	<ul style="list-style-type: none"> ▶ Approximately 92–95% of rivaroxaban is bound to human plasma proteins¹⁸ ▶ In healthy subjects, the apparent volume of distribution at steady state is approximately 50 L¹⁸ 	<ul style="list-style-type: none"> ▶ Approximately 87% of absorbed apixaban is bound to plasma proteins¹⁹ ▶ The apparent volume of distribution of apixaban at steady state is ~21 L¹⁹ 	<ul style="list-style-type: none"> ▶ By in vitro assay, plasma protein binding of edoxaban is approximately 55%²¹ ▶ At steady state, the volume of distribution of edoxaban is 107 L²¹
Elimination	<ul style="list-style-type: none"> ▶ After intravenous dosing, the primary route of elimination for dabigatran is renal clearance, (~80% of total)¹⁷ ▶ Following oral dosing of dabigatran, only ~7% is recovered from the urine, with ~86% found in the faeces¹⁷ 	<ul style="list-style-type: none"> ▶ After an oral dose, ~33% of the absorbed drug is excreted unchanged in the urine ▶ The remainder of the absorbed dose, ~66%, is converted to inactive metabolites and excreted in the urine and faeces 	<ul style="list-style-type: none"> ▶ Excretion is by both the faeces and the urine (~27% of total clearance), with both biliary and direct intestinal excretion contributions ▶ Apixaban has a total clearance of ~3.3 L/h 	<ul style="list-style-type: none"> ▶ The primary route of elimination is for unmodified edoxaban to be excreted in the urine, for ~50% of the total clearance (22 L/h)²¹ ▶ The remaining fraction of edoxaban is excreted via metabolism and biliary/intestinal route²¹
Specific emergency reversal/bleeding management options	<ul style="list-style-type: none"> ▶ No specific agent currently available ▶ Idarucizumab, an investigational fully humanised antibody fragment under study as a specific reversal agent⁷⁸ ▶ Idarucizumab has received Breakthrough Therapy designation from the FDA⁷¹ 	<ul style="list-style-type: none"> ▶ No specific agent currently available ▶ Andexanet alfa is a recombinant, modified factor Xa molecule that is being developed as a direct reversal agent for FXa inhibitors⁷⁹ ▶ Andexanet alfa has received Breakthrough Therapy designation from the FDA⁷⁹ 	<ul style="list-style-type: none"> ▶ No specific agent currently available ▶ Andexanet alfa is a recombinant, modified factor Xa molecule that is being developed as a direct reversal agent for FXa inhibitors⁷⁹ ▶ Andexanet alfa has received Breakthrough Therapy designation from the FDA⁷⁹ 	<ul style="list-style-type: none"> ▶ A specific reversal agent for edoxaban is not available²¹ ▶ There is no established way to reverse the anticoagulant effects of edoxaban, which can be expected to persist for approximately 24 h after the last dose²¹
Supportive strategies for reversal of anticoagulation	<ul style="list-style-type: none"> ▶ Withhold dabigatran for two or more half-lives ▶ Coagulation factor concentrates, such as II, IX, or X, or aPCCs, for example, FEIBA or rFVIIa may be administered¹⁷ ▶ If a prolonged anticoagulant effect is anticipated, dialysis can be considered¹⁷ ▶ Administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used¹⁷ ▶ It is important to note that these agents/strategies have not been adequately evaluated in randomised clinical trials¹⁷ 	<ul style="list-style-type: none"> ▶ Withhold rivaroxaban for two or more half-lives ▶ Rivaroxaban is highly protein bound, therefore dialysis is of limited utility for removal of the drug¹⁸ ▶ The anticoagulant effect of rivaroxaban is not expected to be influenced by either protamine sulphate or vitamin K¹⁸ ▶ Modest reversal of the prolongation in the PTT has been reported in healthy volunteers following administration of PCCs¹⁸ ▶ Note: The use of either aPCC or rFVIIa has not been adequately evaluated in randomised clinical trials¹⁸ 	<ul style="list-style-type: none"> ▶ Withhold apixaban for two or more half-lives ▶ Dialysis is of limited utility due to high plasma protein binding of apixaban¹⁹ ▶ Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of apixaban¹⁹ ▶ Partial reversal of PTT prolongation has been seen after administration of PCCs in healthy volunteers¹⁹ ▶ Note: The use of other procoagulant reversal agents such as aPCC or rFVIIa has not been adequately evaluated in randomised clinical trials¹⁹ ▶ After overdose or accidental ingestion, doses of activated charcoal, provided at 2 and 6 h post ingestion may reduce the amount of drug absorbed into the blood¹⁹ 	<ul style="list-style-type: none"> ▶ Standard laboratory testing procedures cannot reliably assess the anticoagulant effect of edoxaban²¹ ▶ Haemodialysis cannot be relied on to significantly reduce plasma levels of edoxaban²¹ ▶ General agents such as tranexamic acid, vitamin K and protamine sulphate, vitamin K will not effectively reverse the anticoagulation effect of edoxaban²¹

aPCC, activated prothrombin complex concentrates; aPTT, activated partial thromboplastin time; FDA, US Food and Drug Administration; FEIBA, factor VIII inhibitor bypassing activity; INR, international normalised ratio; NOACs, non-warfarin oral anticoagulants; PCCs, prothrombin complex concentrates; PT, prothrombin time; rFVIIa, recombinant factor VIIa.

Appropriately calibrated PT assays and chromogenic FXa assays respond dose-dependently to rivaroxaban, although specific guidance on assays for clinical use is not yet available. Additionally, chromogenic FXa assays, while informative for surgeons, are likely to be of only limited use to ED clinicians.^{29 48 51 52} In the case of apixaban, although a responsive chromogenic FXa assay is available, neither this nor other coagulation assays are currently recommended for clinical use.⁴²

For patients with a bleeding emergency, ED clinicians need to identify the prescribed NOAC and, if possible, establish the time since the last dose was taken. ED clinicians also need to bear in mind the shorter half-lives, patients' renal status and support of renal clearance^{22-24 41 43 58 74 77} when considering the offset of action of these newer agents.

In conclusion, while accurate determination of current anticoagulant status (if any) would be ideal when an emergency situation arises, as a practical matter this will be problematic in most ED settings. Self-reporting of 'on-board' therapeutics will be difficult at best, and if the patient is unresponsive, identification via laboratory assays will be costly and time consuming, even if they are in widespread clinical use. It may be more productive to invite patients to wear a 'Medical Alert ID bracelet' that lists the identities and doses of any agents they are currently taking. This information could be very helpful in guiding selection of the appropriate management pathway for a given individual patient and ED environment.

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