Non-vitamin K antagonist oral anticoagulants (NOACs): a view from the laboratory

A. D. BLANN
University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH

Accepted: 17 October 2014

ABSTRACT

Disadvantages with traditional anticoagulants (vitamin K antagonists and heparinoids) have led to the development on non-vitamin K antagonist oral anticoagulants (NOACs). These agents are set to replace the traditional anticoagulants in situations such as following orthopaedic surgery, in atrial fibrillation, and in the prevention and treatment of venous thromboembolism. Although superior to vitamin K antagonists and heparinoids in several aspects, NOACs retain the ability to cause haemorrhage and, despite claims to the contrary, may need monitoring. This review aims to summarise key aspects of the NOACs of relevance to the laboratory.

KEY WORDS: Apixaban.
Dabigatran.
Edoxaban.
Heparin.
Heparin, low-molecular-weight.
NOAC.
Oral anticoagulation.
Rivaroxaban.

Introduction

Thrombosis is the major common end-point in most human disease. In the coronary circulation, occlusive thrombi and/or the rupture of atherosclerotic plaque cause myocardial infarction: in the cerebral circulation thrombosis causes ischaemic stroke.[1] Antiplatelet drugs such as aspirin and clopidogrel are the primary therapy for reducing the risk of coronary and cerebrovascular thrombosis.[2]

Venous thromboembolism (VTE), manifesting clinically as pulmonary embolus (PE) and deep vein thrombosis (DVT), is a frequent complication among hospital in-patients and contributes to longer hospital stays and to increased morbidity and mortality.[3] However, in contrast to arterial thrombosis, pharmacotherapy of VTE is aimed not at the platelet but at the coagulation pathway.[4] As a leading cause of thrombotic stroke and systemic embolism, atrial fibrillation (AF) also demands antithrombotic treatment. However, although AF concerns the left side of the heart, and thrombi are carried in the arterial circulation, anticoagulation (as opposed to antiplatelet therapy) provides better protection.[5]

Until perhaps five years ago, heparinoids (unfractionated heparin, low molecular weight heparin [LMWH] and fondaparinux) and vitamin K antagonists (VKAs; warfarin, acenocoumarol, phenocoumarol) were options for the prevention of thrombotic stroke in AF, and of VTE in general.[6–8] Although effective, several practical, management and clinical disadvantages (Table 1) prompted the search for better drugs, now collectively known as non-vitamin K antagonist oral anticoagulants (NOACs), although they may also be known as new oral anticoagulants, direct oral inhibitors or direct oral anticoagulants.[8–10] These agents are steadily replacing the heparinoids and VKAs in both in-patient and out-patient prevention and treatment of VTE, and of thrombotic stroke in AF. Indications for the use of VKAs are shown in Table 2.[11,12] Figure 1 summarises the mode of action of anticoagulants on the coagulation pathway.

The purpose of this review is to summarise the current position regarding laboratory issues with the use of the NOACs.[8–10] In order to identify relevant publications, PubMed was searched using the key words NOACs, dabigatran, rivaroxaban, apixaban and edoxaban.

Correspondence to: Dr. A. D. Blann
Email; a.blann@bham.ac.uk

Non-vitamin K antagonist oral anticoagulants

Non-vitamin K antagonist oral anticoagulants may be classified by mode of action: dabigatran is a direct thrombin inhibitor, while rixaroxaban, apixaban and edoxaban all target coagulation factor Xa.[13–16]

Dabigatran

This agent possesses various qualities that make it potentially an attractive and promising OAC with its predictable pharmacokinetics and pharmacodynamics.[13] It is rapidly absorbed (within two hours) and distributed with estimated half-lives of eight to 10 hours and 14–17 hours for single and multiple dose administrations, respectively. Nearly 80% of the pro-drug (dabigatran etexilate) is excreted unchanged by the kidney with average bioavailability of 6.5%, so high doses are needed to maintain adequate plasma concentrations. Phase II and III clinical trials have been conducted to assess dosages, efficacy and tolerability in numerous indications (e.g., prevention of secondary VTE, DVT, stroke and embolism due to AF).[17–20]

Rivaroxaban

With favourable pharmacokinetic characteristics and a bioavailability of 60–80%, rivaroxaban achieves peak plasma

levels in three hours and has a half-life of nine hours in healthy, young subjects, and about 12 hours in elderly subjects.[14] It is metabolised by the liver via CYP3A4, with up to two-thirds of the drug being eliminated by the kidney.[21] Caution in the use of rivaroxaban in patients with renal impairment is required because of its renal clearance. It does not interact significantly with platelet function in preclinical studies, and has a bleeding risk comparable to that of enoxaparin. Rivaroxaban has also been trialled for the prevention of secondary VTE, DVT, stroke and embolism due to AF.[22–26]

Apixaban

This drug also has a good bioavailability (more than 50%, and a similar half-life of between nine and 14 hours). With fixed twice-daily dosing and metabolism in the liver via CYP3A4, about 25% is excreted by the kidney and the remainder by the intestine.[15] It has been shown to be safe and well tolerated in initial testing in volunteers, and its anticoagulant effects closely correlate to plasma concentration of the drug. Apixaban has also been trialled for the prevention of secondary VTE, DVT and stroke due to AF.[27–31]

Edoxaban

Like others agents in its class, edoxaban also shows promise in terms of efficacy and safety compared to VKAs.[16] It has a bioavailability of 66%, plasma levels peak one to two hours after ingestion, has minimal hepatic metabolism, and 50% is excreted via the kidney. It has been trialled in the prevention of secondary VTE, DVT, stroke and embolism due to AF, but as yet is unlicensed in the UK.[32–34]

Table 2. Indications for the use of VKAs, and recommended duration of anticoagulation.

Indication	Duration
Pulmonary embolus	Six months
Distal DVT due to temporary risk factors (eg orthopaedic surgery, pregnancy)	Three months
Proximal DVT or DVT of unknown cause or those associated with on-going risk factors	Six months
VTE associated with malignancy	Six months then review
Recurrence of VTE (while NOT on warfarin)	Long term
Recurrence of VTE (while ON warfarin)	Long term
Atrial fibrillation (AF)	Long term
AF: patient due for cardioversion (CV)	Four weeks pre-CV, minimum four weeks post-CV
Cardiomyopathy	Long term
Mural thrombus	Three months
Rheumatic mitral valve disease	Long term
Mechanical prosthetic heart valves (aortic)	Long term
Mechanical prosthetic heart valves (mitral)	Long term
Antiphospholipid syndrome (venous)	Long term
Antiphospholipid syndrome (arterial)	Long term
Thrombophilia	Depends on circumstances

Table 1. Disadvantages of traditional anticoagulants.

Vitamin K antagonists
• Regular blood tests (perhaps four-weekly, hence expensive and inconvenient to manage)
• Narrow therapeutic window
• Interactions with many other drugs and lifestyle choices
• Teratogenic to the embryo
• Long-half life (hence insensitive to need for a rapid change)
Unfractionated heparin
• Need to be injected
• Unreliable pharmacokinetic and pharmcodynamics, hence requirement for monitoring with activated partial thromboplastin time
• Small risk of heparin-induced thrombocytopenia
Low molecular weight heparin
• Need to be injected
• Very small risk of heparin-induced thrombocytopenia
NB: list not intended to be exhaustive.

In the UK, the National Institute for Health and Care Excellence (NICE) publishes opinions and guidelines on the value of pharmaceuticals. A summary of these with regard to the NOACs is presented in Table 3. Although it may be expected that NOACs could gain licences in all the indications listed in Table 2, in practice there may never be rigorous trials of these agents in those indications that are less common. Accordingly, in the absence of robust NOAC data, there may always be a place of VKAs in less-frequent conditions.

Table 3. NICE documents and the NOACs.

Indication	NOAC	NICE document
VTE following hip and knee orthopaedic surgery	Dabigatran	TA157
	Rivaroxaban	TA170
	Apixaban	TA245
Stroke and systemic embolism in atrial fibrillation	Dabigatran	TA249
	Rivaroxaban	TA256
	Apixaban	TA275
	Edoxaban	ID624
Prevention and treatment of VTE after acute DVT	Dabigatran	ID483
	Rivaroxaban	TA261
	Apixaban	ID726
	Edoxaban	ID622

VTE: venous thromboembolism;
DVT: deep vein thrombosis;
TA: technology appraisal;
ID: in development.

See www.nice.org.uk

Clinical use of the NOACs

A disadvantage of VKAs is the many drug interactions that frustrate management. Similarly, NOAC are sensitive to different co-medications via P-glycoprotein and cytochrome metabolic pathways, leading to recommendations that the dose of the particular NOAC be reduced (Table 4) or not used (as in most triazole antifungals).[35] Other factors possibly leading to the need to reduce the dose include the use of antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy and steroids, gastrointestinal bleeding, recent surgery on a critical organ, or thrombocytopenia. Other factors leading to higher plasma NOAC levels include increasing age (generally <75) and low weight (e.g., ≤60 kg). Renal function must be considered because as function deteriorates so the effective half-life of the drug increases and thus the dose of the NOAC should be reduced (Table 5).[35–37]

Table 4. Selected drug interactions with NOACs.

Drug	Dabigatran	Apixaban	Rivaroxaban
Atorvastatin	+18%	No data yet	No effect
Verapamil	+12–80%*	No data yet	Minor effect†
Quinidine	+50%*	No data yet	+50%*
Diltiazem	No effect	+40%*	Minor effect†
Amiodarone	+12–60%*	No data yet	Minor effect†
Clarithromycin, erythromycin	+15–20%*	No data yet	+30–54%*

*Reduce the dose of the NOAC;
†Use with caution if creatinine clearance 15–50 mL/min.

Modified from references 35 (which has more interactions and recommendations), 52 and 65 and elsewhere.

NB: This list is not intended to be exhaustive.

An NOAC or a VKA?

Those advocating prudent economics point to the higher pharmaceutical cost of NOACs compared to the VKAs. However, NOACs are not routinely monitored, and the cost of monitoring VKAs is considerable, and the cost of the strokes and other endpoints saved by using NOACs should be taken into account.

Perhaps patients who are very stable on a VKA, and so have a high time in therapeutic range (TTR),[38] implying good management involving monitoring only every three months, are very cost-effective for the NHS, and therefore should remain on their VKA. Conversely, the NHS may benefit from those patients who are difficult to manage, with a low TTR deriving from regular and frequent visits to the oral anticoagulant clinic, being transferred to an NOAC.

The importance of this was demonstrated in a study of 595 patients undergoing VKA prophylaxis after orthopaedic surgery. Only 37% of hip arthroplasty patients were in international normalised ratio (INR) range, and 13% never reached their target. These data on a poor TTR argue in favour of an alternative to a VKA, that being an LMWH or an NOAC.[39]

A scoring system (SAMe-TT_2R_2) has been developed to help predict the likelihood of achieving good anticoagulation control with a VKA in newly-diagnosed AF patients.[40] If an individual's SAMe-TT_2R_2 score is 0 or 1, then a VKA (probably warfarin) is recommended. For those with SAMe-TT_2R_2 score ≥2, an NOAC is recommended. Notably, those with a poor TTR are at risk both of thrombosis (when the INR is below the target range) and haemorrhage (when above the target range).[41–43] However, the SAMe-TT_2R_2 score cannot be used in a decision to move an AF patient from a VKA to an NOAC, and the model is not yet validated in other groups requiring long-term oral anticoagulation (such as those with heart valve disease or a thrombophilia) (Table 2).

Haemorrhage

The major problem with all anticoagulants (VKAs, NOACs and the heparins) is that inappropriate use may seriously impair the coagulation pathway so that an ineffective thrombus is formed (if at all), leading to haemorrhage. However, the extent of haemorrhage is variable and may not always call for active treatment.[44,45] Such haemorrhage may be classified (Table 6) and the practitioner must make a clinical decision as to the severity. Laboratory involvement includes blood transfusion and the correction of abnormal haemostasis with blood products such as factor VII and prothrombin complex concentrate.[35,46–49]

Table 5. Renal function and the NOACs.

	Dabigatran	Apixaban	Rivaroxaban
Fraction of absorbed dose that is renally excreted	80%	27%	35%
Half-life when CrCl >60 mL/min	~14 hours	No data	~8.5 hours
Half-life when CrCl 30–60 mL/min	~18 hours	No data	~9 hours
Half-life when CrCl 15–30 mL/min	~28 hours	No data	~9.5 hours
Not recommended if CrCl <…	30 mL/min	15 mL/min	15 mL/min
Dosing recommendation when creatinine clearance is falling	CrCl 30–49 mL/min: reduce dose (e.g., from 150 to 110 mg bd)	CrCl 15–29 mL/min: reduce dose (e.g., from 5 to 2.5 mg bd)	CrCl 15–49 mL/min: reduce dose (e.g., from 20 to 10 mg qd)

CrCl: creatinine clearance.

Modified from references 35, 36, 59, 60 and elsewhere.

NB: Ensure the correct equation is used as eGFR according to the Modification of Diet in Renal Disease equation gives different results to the creatinine clearance as estimated by the Cockcroft and Gault equation.[95]

In the face of haemorrhage, the time of the last dose of the NOAC should be determined and the half-life estimated from the estimated glomerular filtration rate (eGFR)/creatinine clearance (Table 5).[49–52] When bleeding is not severe, temporary drug withdrawal may be the only requirement. However, when bleeding is more severe, active treatment is likely and may consist of blood components.[49,53,54] In these cases there will be regular laboratory monitoring and a root cause analysis inquest. Table 7 summarises key aspects regarding response to haemorrhage on an NOAC, many of which also apply to haemorrhage on a VKA.

Monitoring

Despite the view that NOACs need not routinely be monitored, there are several instances where knowledge of the precise anticoagulant status of an individual is needed (Table 8), and thus a blood test required. Although the patient can most likely be relied upon to provide a recent history of their compliance, this may not always be accurate, and, as there is marked variation in absorbance and metabolism of each NOAC, may not reflect the degree of anticoagulation of their blood.[35] The actual molar concentration of a particular NOAC in the plasma may be determined by complex methods such as high-performance liquid chromatography (HPLC) and tandem mass spectrometry.[54–58] However, these techniques are unlikely to be available to most routine laboratories, which are most likely to have prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) in regular use, and to some extent these may provide limited use in certain circumstances.[46,59]

Nevertheless, there are more sensitive, specific and tailored assays for the effects of the NOACs that will be present in high-throughput and reference laboratories. These include the reptilase time, antithrombin, tests of thrombin generation, thrombelastography, the ecarin clotting time (ECT), the Hemoclot thrombin inhibitor assay, and anti-factor Xa assays such as the HepTest.[54,57–60] Despite the availability of these methods, there remains variability between them and each NOAC, which is in direct contrast to the simplicity of the INR.

Dabigatran

Under experimental (non-clinical) conditions, high doses of dabigatran will prolong the PT, but at clinical levels this test has unacceptably low sensitivity and is strongly dependent on the characteristics of the particular thromboplastin reagent.[61,62] Accordingly, the PT (or INR) is not recommended for monitoring the effects of dabigatran. However, a variant of the PT, using a lower concentration of thromboplastin (hence dilute PT), may be better as it is likely to have improved sensitivity.[60] The APTT shows a more appropriate curvilinear response to dabigatran, and at a result greater than two times the upper limit of normal (perhaps 90 seconds) is suggestive of over anticoagulation, and thus an excess risk of haemorrhage. At the peak of plasma levels, one of the standard low doses (110 mg twice daily) sees the APTT ratio often prolonged at 1.4–1.7, while at 150 mg twice daily the ratio may be in the region 1.5–1.8.[13,63,64]

Table 6. Degrees of haemorrhage.

Level	Typical clinical picture
1	Relatively minor and localised bruising, especially at sites of trauma
2a	Extensive bruising caused by trauma
2b	Extensive spontaneous bruising in the (claimed/presumed) absence of trauma
3	Actual bleeding, such as epistaxis, and bleeding from gums and wounds
4	Haematuria, vomiting blood, bleeding per vagina, per rectum
5	Major bleeding: from or into a critical organ (e.g., intracranial, intraspinal, gastrointestinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular) and/or a fall in Hb >20 g/L, or leading to the transfusion of two or more units of whole blood or red cells (ISTH criteria).[44]

Table 7. Summary of potential actions in the face of haemorrhage with an NOAC.

• Act based on clinical picture, determine time and strength (mg) of the last dose.
• Stop NOAC, maintain diuresis with fluids (oral/intravenous as required)
• If bleeding modestly, treat locally (e.g., compression). Consider fluid, red blood cell replacement (if necessary) and platelet replacement (if thrombocytopenia <50), fresh frozen plasma (as plasma expander, not to maintain haemostasis), tranexamic acid and desmopressin.
• If bleeding severely, all of the above, and: For Xa-inhibitors, consider prothrombin complex concentrate (PCC; 25 U/kg: may be repeated once or twice), activated PCC (e.g., FEIBA, 40–80 U/kg, maximum 200 u/kg/day), recombinant factor VIIa (e.g., 90 μg/kg). For dabigatran, as for Xa-inhibitors, but also consider concentrates of coagulation factors II, IX and X. Consider oral charcoal and dialysis.
• After an appropriate period, determine likelihood of the return of haemostasis with ECT/dilute TT/APTT for dabigatran and an anti-factor Xa assay/modified PT for factor Xa inhibitors.
• Determine cause of haemorrhage and reinforce patient education.
• Recommence anticoagulation after a suitable period.
Opinion pooled from references 35, 46, 49, 52, 82–84 and elsewhere.

Table 8. Instances where the precise anticoagulation status of a named patient is required.

• Prior to emergency surgery or other invasive procedure
• In the face of evident or suspected haemorrhage
• Where there is suspicion of overdose
• If in acute thrombosis, or renal, liver or heart failure
• For proof of compliance
• In potential drug-drug interactions
• In trauma, acute medical disease, malignancy

The preferred tests of the effects of dabigatran are based on thrombin: the 'standard' TT, a modified dilute TT (commercially available as the Hemoclot thrombin inhibitor assay, which can be used to determine the drug concentration) and the ECT.[13,46,58,62] In one study of 120 plasma samples from 52 patients on dabigatran, levels of the drug correlated poorly with the INR (r^2=0.49) and the APTT (r^2=0.54), moderately with the thrombin time (r^2=0.70), but the strongest correlation was with the dilute thrombin time (r^2=0.95).[63] In another, using spiked normal plasma, the correlation coefficients were 0.84, 0.85, 0.86 and 0.92, respectively.[62] Thus, both studies point to the superiority of the dilute thrombin time. A TT result >65 seconds implies an excessive risk of bleeding: a normal TT means drug levels are low.[46,64] A result for the ECT greater than three times the upper limit of normal also suggests increased risk of haemorrhage.[35,59,65] and this test may be suitable for assessing the reversal of haemorrhage with the use of prothrombin complex concentrate.[54]

Factor Xa inhibitors

Rivaroxaban, apixaban and edoxaban all influence the coagulation pathway to varying extents. The relationship between the APTT and rivaroxaban is curvilinear,[59] but is strongly influenced by reagents and analysers: in some cases, a prolonged APTT indicates supratherapeutic levels, whereas, in other cases, the anticoagulant effect is underestimated, hence preferred use of the PT over the APTT (Figs. 2 and 3).[60,66] However, although the relationship between rivaroxaban and the PT is linear, this test cannot be used to determine plasma levels of the drug, but it may be modified by diluting the plasma (hence dilute PT), which gives better results.[66–68] The importance of the thromboplastin reagent is demonstrated by the report of correlation coefficients between a PT ratio and plasma levels of rivaroxaban that vary between 0.66 and 0.94.[69]

Tests of anti-factor Xa activity (e.g., HepTest), as may be used to monitor the effects of LMWHs, may be modified to assess rivaroxaban.[70–72] However, the choice of a test may

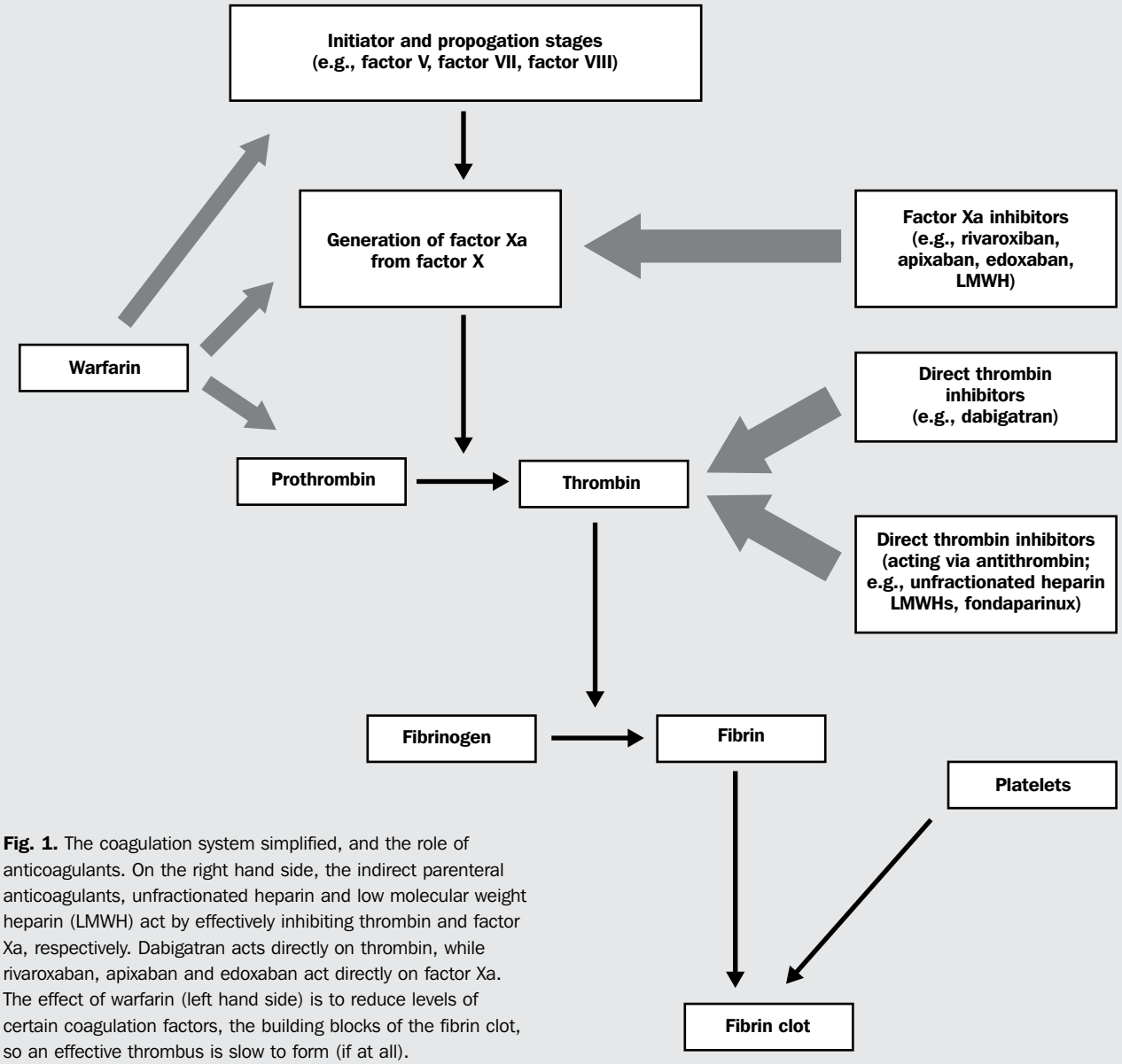

Fig. 1. The coagulation system simplified, and the role of anticoagulants. On the right hand side, the indirect parenteral anticoagulants, unfractionated heparin and low molecular weight heparin (LMWH) act by effectively inhibiting thrombin and factor Xa, respectively. Dabigatran acts directly on thrombin, while rivaroxaban, apixaban and edoxaban act directly on factor Xa. The effect of warfarin (left hand side) is to reduce levels of certain coagulation factors, the building blocks of the fibrin clot, so an effective thrombus is slow to form (if at all).

depend on the indication: if a qualitative assessment of the effect of the drug is required, then a PT with calibrated reagents maybe better, whereas for a determination of the amount of drug in the blood, a chromogenic anti-factor Xa test is preferred.[67,72] There may be a place for the use of a test based on Russell's viper venom in assessing the effect of rivaroxaban.[73]

Both apixaban and edoxaban can prolong the PT and the APTT, depending on reagents, but clotting and (preferably) chromogenic factor Xa assays give satisfactory results, and so may be preferable (Figs. 4 and 5),[74–80] although there may be a place for a modified PT.[79] Correlation coefficients between the expected and observed apixaban levels in spiked plasma were better than 0.99 in four different anti-Xa assays.[74] Another study reported a correlation coefficient of 0.88–0.89 between the spiked plasma concentration of apixaban and its ability to influence factor Xa, while the correlation between plasma apixaban and the PT/INR (r=0.36) was poor.[77]

Cuker *et al*. emphasised the inferiority of the PT/INR (correlation coefficient 0.36–0.41) compared to anti-FXa assay (correlation coefficient 0.88–0.97) in determining the plasma level of apixaban.[80] Unlike rivaroxaban (which seems to interact with the LA-1 low phospholipid reagent) and dabigatran, apixaban is less likely to produce false-positive lupus anticoagulant results.[74,81] Comparable data to the above for the effect of edoxaban in a clinical setting is awaited.

Emergency settings

As discussed, the ECT or dilute TT for dabigatran, and an anti-factor Xa assay for factor Xa inhibitors should be considered appropriate in an emergency setting, such as a patient on an NOAC presenting to accident and emergency in frank haemorrhage or after trauma such as a road traffic accident. However, in the absence of first-line tests, an APTT for dabigatran and a PT for the factor Xa inhibitors are (with caveats) recommended.[76,82–86] Table 9 summarises aspects of the laboratory monitoring of the NOACs.

Conclusions

The NOACs are an exciting new class of drugs that, as a whole, provide at least as good protection from thrombosis as their condition-specific comparator (VKA or LMWH), but also have better safety profiles. However, there are differences between them in AF and in orthopaedic surgery, and formal guidelines and recommendations are becoming available[35,59,82,85–87] that describe relevant blood tests. The purpose of the monitoring may be relevant, as a test for determining plasma levels of the drug may not be the best for determining anticoagulant effect.[59,60] For example, in determining whether or not clinically relevant below on-therapy levels of dabigatran are present, a standard TT may be preferred. Conversely, in seeking to determine if above on-therapy levels of dabigatran are present, a dilute TT or ecarin-based assay may be better.[80] Despite the above, a constant recommendation is that all laboratories invest in their methodology and determine which sets of commercial reagent and analysers they find to be most reliable both in clinical and laboratory terms.

With increasing confidence in the use of these agents, it is likely that their use will extend to other conditions where

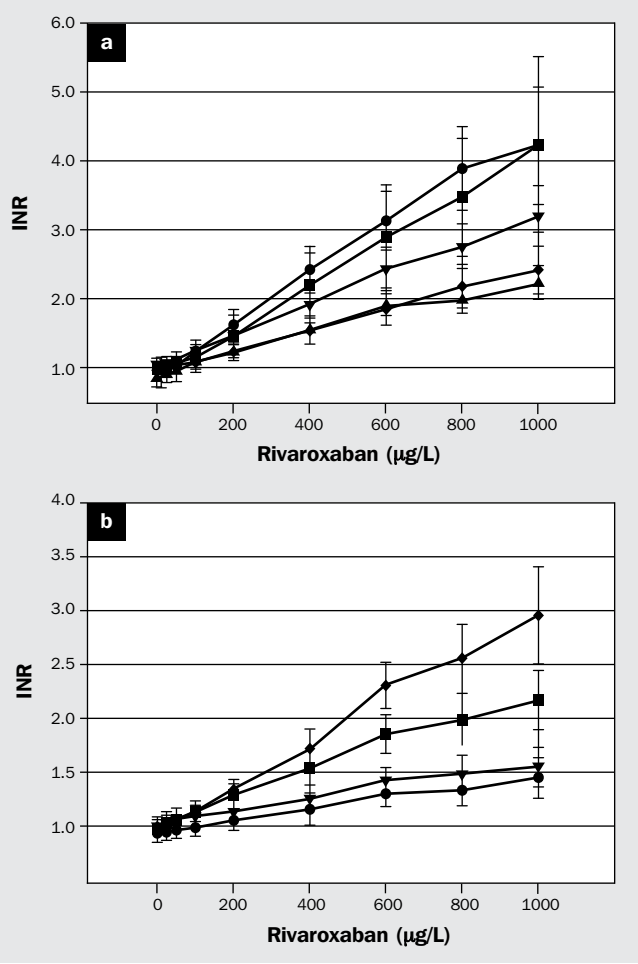

Fig. 2. Effect of rivaroxaban on the prothrombin time expressed as an INR. **a)** Analysis using five different plain thromboplastin reagents. **b)** Analysis using four different rabbit thromboplastin reagents. Note the marked differences in the dose-response lines indicating variable sensitivity (reproduced from reference 66 with permission).

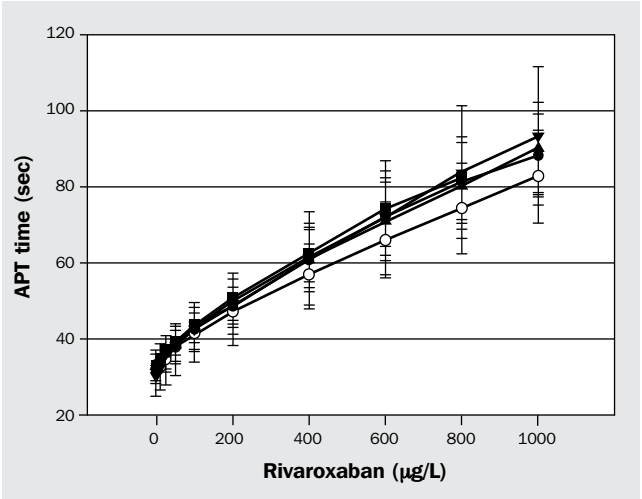

Fig. 3. Effect of rivaroxaban on the APTT using five different reagents plotted against the plasma drug levels. Note the curvilinear relationship and differences in the dose-response lines indicating variable sensitivity (reproduced from reference 66 with permission).

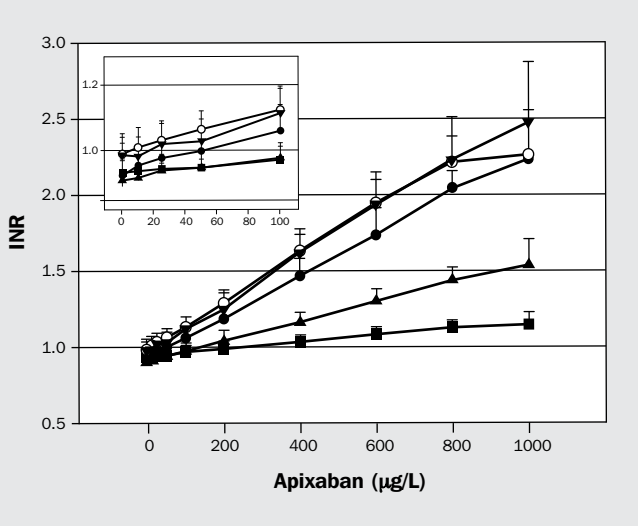

Fig. 4. Effect of apixaban on the prothrombin time expressed as an INR using five different plain thromboplastin reagents. Note the marked differences in the dose-response lines indicating variable sensitivity (reproduced from reference 74 with permission).

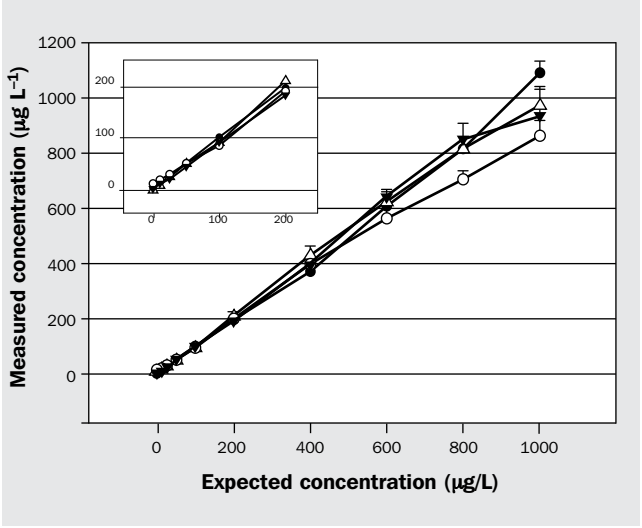

Fig. 5. Determination of the apixaban plasma concentration by four different anti-Xa assays. In each, the correlation coefficient (r^2) exceeds 0.99 (reproduced from reference 74 with permission).

VKAs and/or LMWHs are partially effective, are inconvenient and/or are contraindicated, such as in acute coronary syndromes.[88] Furthermore, additional NOACs are in development,[89] as is a new VKA.[90] Despite the apparent success of the NOACs, there is at least one instance (mechanical heart valves) where they fail to provide a better outcome than is available with a VKA.[91] In cancer, meta-analyses of recurrent VTE found that, as a whole, NOACs were equivalent in efficacy and safety to VKAs.[92,93] However, recent guidance on prevention of VTE in hospitalised medical cancer patients from the International Society on Thrombosis and Haemostasis fails to mention NOACs.[94] Nevertheless, oral anticoagulant will continue to be an important and rapidly developing area for at least the coming five, possibly 10 years. □

Note added in proof

In the USA, the Food and Drug Administration has granted breakthrough therapy designation for the development of an antidote to dabigatran (http://clinicaltrials.gov/ct2/show/NCT02028780?term=idarucizumab&rank=2). A formal publication will appear in 2015.

Table 9. Laboratory monitoring of NOACs.

NOAC	Preferred method(s)	Alternative
Dabigatran	1. ECT 2. Dilute thrombin time (e.g., Hemoclot)	APPT (standard or modified)
Rivaroxaban	Anti-factor Xa (e.g., HepTest)	PT (standard or modified)
Apixaban	Anti-factor Xa (e.g., HepTest)	Dilute PT
Edoxaban	Little firm data: possibly anti-Factor Xa	Little firm data

Refer to the text. Opinion pooled from references 35, 59, 60, 79, 80, 86 and elsewhere.

Dr Blann declares hospitality, speaker fees and research funds from Pfizer, Bayer, Daiichi-Sankyo and Boehringer Ingleheim. The University Department of Medicine at City Hospital recruits into anticoagulant trials. The author also thanks Dr G. Moore and Dr I. Jennings for their comments.

References

1 Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; **362** (6423): 801–9.
2 Hennekens CH. Aspirin in the treatment and prevention of cardiovascular disease. *Annu Rev Public Health* 1997; **18**: 37–49.
3 ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. *J Thromb Haemost* 2014: **12** (10): 1580–90.
4 Blann AD, Lip GY. Venous thromboembolism. *BMJ* 2006; **332** (7535): 215–9.
5 Lip GY, Tse HF, Lane DA. Atrial fibrillation. *Lancet* 2012; **379** (9816): 648–61.
6 Buller HR, Sohne M, Middeldorp S. Treatment of venous thromboembolism. *J Thromb Haemost* 2005; **3** (8): 1554–60.
7 Turpie AG, Chin BS, Lip GY. Venous thromboembolism: pathophysiology, clinical features and prevention. *BMJ* 2002; **325** (7369): 887–90.
8 Blann AD, Khoo CW. The prevention and treatment of venous thromboembolism with LMWHs and new anticoagulants. *Vasc Health Risk Manag* 2009; **5**: 693–704.
9 Gross PL, Weitz JI. New anticoagulants for treatment of venous thromboembolism. *Arterioscler Thromb Vasc Biol* 2008; **28**: 380–6.
10 Husted S, De Caterina R, Andreotti F *et al.*; ESC Working Group on Thrombosis Task Force on Anticoagulants in Heart Disease. Non-vitamin K antagonist oral anticoagulants (NOACs): no longer new or novel. *Thromb Haemost* 2014; **111**: 781–2.
11 Keeling D, Baglin T, Tait C *et al.*; British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin – 4th edn. *Br J Haematol* 2011; **154** (3): 311–24.
12 Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists:

the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; **126** (3 Suppl): 204S–233S.
13 Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007; **64** (3): 292–303.
14 Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* 2005; **78** (4): 412–21.
15 Wong PC, Crain EJ, Xin B *et al*. Apixaban, an oral, direct and highly selective factor Xa inhibitor: *in vitro*, antithrombotic and antihemostatic studies. *J Thromb Haemost* 2008; **6** (5): 820–9.
16 Ogata K, Mendell-Harary J, Tachibana M *et al*. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010; **50** (7): 743–53.
17 Eriksson BI, Dahl OE, Rosencher N *et al*.; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. *Lancet* 2007; **370** (9591): 949–56.
18 Eriksson BI, Dahl OE, Rosencher N *et al*.; RE-MODEL Study Group. Oral dabigatran etexilate *vs.* subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; **5** (11): 2178–85.
19 Connolly SJ, Ezekowitz MD, Yusuf S *et al*.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361** (12): 1139–51.
20 Wallentin L, Yusuf S, Ezekowitz MD *et al*.; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010; **376** (9745): 975–83.
21 Perzborn E, Strassburger J, Wilmen A *et al*. *In vitro* and *in vivo* studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct factor Xa inhibitor. *J Thromb Haemost* 2005; **3** (3): 514–21.
22 Kakkar AK, Brenner B, Dahl OE *et al*.; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled study. *Lancet* 2008; **372** (9632): 31–9.
23 Lassen MR, Ageno W, Borris LC *et al*.; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; **358** (26): 2776–86.
24 Agnelli G, Gallus A, Goldhaber SZ *et al*.; for the ODIXa-DVT Study Investigators. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT study. *Circulation* 2007; **116** (2): 180–7.
25 Patel MR, Mahaffey KW, Garg J *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365** (10): 883–91
26 Prins MH, Lensing AW, Bauersachs R *et al*.; EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; **11** (1): 21.
27 Botticelli Investigators, Writing Committee, Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *J Thromb Haemost* 2008; **6** (8): 1313–8.
28 Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010; **375** (9717): 807–15.
29 Pineo GF, Gallus AS, Raskob GE *et al*. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. *J Thromb Haemost* 2013; **11** (3): 444–51.
30 Granger CB, Alexander JH, McMurray JJ *et al*.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365** (11): 981–92.
31 Wallentin L, Lopes RD, Hanna M *et al*. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation* 2013; **127** (22): 2166–76.
32 Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA *et al*. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; **369** (15): 1406–15.
33 Giugliano RP, Ruff CT, Braunwald E *et al*.; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369** (22): 2093–104.
34 Raskob G, Cohen AT, Eriksson BI *et al*. Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. A randomised double-blind dose-response study. *Thromb Haemost* 2010; **104** (3): 642–9.
35 Heidbuchel H, Verhamme P, Alings M *et al*.; European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013; **15** (5): 625–51.
36 Rachidi S, Aldin ES, Greenberg C, Sachs B, Streiff M, Zeidan AM. The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery. *Expert Rev Hematol* 2013; **6** (6): 677–95.
37 Harenberg J, Weiss C. Clinical trials with new oral anticoagulants. Additive value of indirect comparisons also named network meta-analyses. *Hamostaseologie* 2013; **33** (1): 62–70.
38 Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; **69** (3): 236–9.
39 Barnes GD, Kaatz S, Golgotiu V *et al*. Use of warfarin for venous thromboembolism prophylaxis following knee and hip arthroplasty: results of the Michigan Anticoagulation Quality Improvement Initiative (MAQI2). *J Thromb Thrombolysis* 2013; **35** (1): 10–4.
40 Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. *Chest* 2013; **144** (5): 1555–63.
41 Wan Y, Heneghan C, Perera R *et al*. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes* 2008; **1** (2): 84–91.
42 Witt DM, Delate T, Clark NP *et al*. Non-adherence with INR monitoring and anticoagulant complications. *Thromb Res* 2013; **132** (2): e124–30.
43 Lip GY, Haguenoer K, Saint-Etienne C, Fauchier L. Relationship of the SAME-TT_2R_2 score to poor quality anticoagulation, stroke, clinically relevant bleeding and mortality in patients with atrial fibrillation. *Chest* 2014; **146** (3): 719–26.

44 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihaemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3** (4): 692–4.

45 Schulman S, Beyth RJ, Kearon C, Levine MN; American College of Chest Physicians. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). *Chest* 2008; **133** (6 Suppl): 257S–298S.

46 Baglin T. Clinical use of new oral anticoagulant drugs: dabigatran and rivaroxaban. *Br J Haematol* 2013: **163** (2); 160–7.

47 Keeling D, Baglin T, Tait C *et al.*; British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin – 4th edn. *Br J Haematol* 2011; **154** (3): 311–24.

48 Kearon C, Akl EA, Comerota AJ *et al*. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis (9th edn): American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 Suppl): e419S–94S.

49 Fawole A, Daw HA, Crowther MA. Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban. *Cleve Clin J Med* 2013; 80 (7): 443–51.

50 Holster IL, Hunfield NG, Kuipers EJ, Kruip MJ, Tjwa ET. On the treatment of new oral anticoagulant-associated gastrointestinal hemorrhage. *J Gastrointestin Liver Dis* 2013: **22** (2); 229–31.

51 Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. *Best Pract Res Clin Haematol* 2013; **26** (2): 191–202.

52 Schulman S. New oral anticoagulant agents – general features and outcomes in subsets of patients. *Thromb Haemost* 2014; **111** (4): 575–82.

53 Steiner T, Bohm M, Dichgans M *et al*. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs) apixaban, dabigatran and rivaroxaban. *Clin Res Cardiol* 2013; **102** (6): 399–412.

54 Dinkelaar J, Patiwael S, Harenberg J, Leyte A, Brinkman HJ. Global coagulation tests: their applicability for measuring direct factor Xa- and thrombin inhibition and reversal of anticoagulation by prothrombin complex concentrate. *Clin Chem Lab Med* 2014; **52** (11): 1615–23.

55 Rohde G. Determination of rivaroxaban – a novel, oral, direct factor Xa inhibitor–in human plasma by high-performance liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008; **872** (1–2): 43–50.

56 Clemens A, van Ryn J, Sennewald R *et al*. Switching from enoxaparin to dabigatran etexilate: pharmacokinetics, pharmacodynamics, and safety profile. *Eur J Clin Pharmacol* 2012; **68** (5): 607–16.

57 Antovic JP, Skeppholm M, Eintrei J *et al*. Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma. *Eur J Clin Pharmacol* 2013; **69** (11): 1875–81.

58 Douxfils J, Dogné JM, Mullier F *et al.* Comparison of calibrated dilute thrombin time and aPTT tests with LC-MS/MS for the therapeutic monitoring of patients treated with dabigatran etexilate. *Thromb Haemost* 2013; **110** (3): 543–9.

59 Baglin T, Keeling D, Kitchen S. Effects on routine coagulation screens and assessment of anticoagulation intensity in patients taking oral dabigatran or rivaroxaban: guidance from the British Society for Standards in Haematology. *Br J Haematol* 2012; **159** (4): 427–9.

60 Samama MM, Guinet C. Laboratory assessment of new anticoagulants. *Clin Chem Lab Med* 2011: **49** (5): 761–72.

61 Lindahl TL, Baghaei F, Blixter IF *et al.*; Expert Group on Coagulation of the External Quality Assurance in Laboratory Medicine in Sweden. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. *Thromb Haemost* 2011; **105** (2): 371–8.

62 van Ryn J, Stangier J, Haertter S *et al*. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010; **103** (6): 1116–27.

63 Chin PK, Patterson DM, Zhang M *et al*. Coagulation assays and plasma fibrinogen concentrations in real-world patients with atrial fibrillation treated with dabigatran. *Br J Clin Pharmacol* 2014; **78** (3): 630–8. doi: 10.1111/bcp.12366.

64 Hapgood G, Butler J, Malan E, Chunilal S, Tran H. The effect of dabigatran on the activated partial thromboplastin time and thrombin time as determined by the Hemoclot thrombin inhibitor assay in patient plasma samples. *Thromb Haemost* 2013; **110** (2): 308–15.

65 Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clemens A. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost* 2012; **107** (5): 838–47.

66 Hillarp A, Baghaei F, Fagerberg Blixter I *et al*. Effects of the oral, direct factor Xa inhibitor rivaroxaban on commonly used coagulation assays. *J Thromb Haemost* 2011; **9** (1): 133–9.

67 Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. *Blood Coagul Fibrinolysis* 2012; **23** (2): 138–43.

68 Samama MM, Martinoli JL, LeFlem L *et al*. Assessment of laboratory assays to measure rivaroxaban – an oral, direct factor Xa inhibitor. *Thromb Haemost* 2010; **103** (4): 815–25.

69 Arachchillage DR, Efthymiou M, Lawrie AS, Machin SJ, Mackie IJ, Cohen H. Comparative sensitivity of commonly used thromboplastin to *ex vivo* therapeutic rivaroxaban levels. *Thromb Haemost* 2014; **112** (2): 421–3.

70 Douxfils J, Mullier F, Loosen C, Chatelain C, Chatelain B, Dogné JM. Assessment of the impact of rivaroxaban on coagulation assays: laboratory recommendations for the monitoring of rivaroxaban and review of the literature. *Thromb Res* 2012; **130** (6): 956–66.

71 Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct Factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005; **61** (12): 873–80.

72 Samama MM, Contant G, Spiro TE *et al.*; Rivaroxaban Anti-Factor Xa Chromogenic Assay Field Trial Laboratories. Evaluation of the anti-factor Xa chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. *Thromb Haemost* 2012; **107** (2): 379–87.

73 Altman R, Gonzalez CD. Simple and rapid assay for effect of the new oral anticoagulant (NOAC) rivaroxaban: preliminary results support further tests with all NOACs. *Thromb J* 2014; **12** (1): 7.

74 Hillarp A. Gustafsson KM, Faxalv L *et al.* Effects of the oral, direct factor Xa inhibitor apixaban on routine coagulation assays and anti-Xa assays. *J Thromb Haemost* 2014; **12** (9): 1545–53.

75 Frost C, Nepal S, Wang J *et al*. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. *Br J Clin Pharmacol* 2013; **76** (5): 776–86.

76 Lippi G, Ardissino D, Quintavalla R, Cervellin G. Urgent monitoring of direct oral anticoagulants in patients with atrial fibrillation: a tentative approach based on routine laboratory tests. *J Thromb Thrombolysis* 2014; **38** (2): 269–74.

77 Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory

measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay. *Thromb Haemost* 2010; **104** (6): 1263–71.

78 Gouin-Thibault I, Flaujac C, Delavenne X *et al*. Assessment of apixaban plasma levels by laboratory tests: suitability of three anti-Xa assays. A multicentre French GEHT study. *Thromb Haemost* 2014; **111** (2): 240–8.

79 Barrett YC, Wang Z, Knabb RM. A novel prothrombin time assay for assessing the anticoagulant activity of oral factor Xa inhibitors. *Clin Appl Thromb Hemost* 2013; **19** (5): 522–8.

80 Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the target-specific oral anticoagulant drugs. *J Am Coll Cardiol* 2014; **64** (11): 1128–39.

81 Martinuzzo ME, Barrera LH, D'adamo MA, Otaso JC, Gimenez MI, Oyhamburu J. Frequent false-positive results of lupus anticoagulant tests in plasmas of patients receiving the new oral anticoagulants and enoxaparin. *Int J Lab Hematol* 2014; **36** (2): 144–50.

82 Cushman M, Lim W, Zakai NA. Clinical practice guide on antithrombotic drug dosing and management of anti-thrombotic drug-associated bleeding complications in adults. February 2014 Edition (www.hematology.org/Clinicians/Guidelines-Quality/Quick-Ref/2869.aspx).

83 Alikhan R, Rayment R, Keeling D *et al*. The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran. *Emerg Med J* 2014; **31** (2): 163–8.

84 Siegal DM, Crowther MA. Acute management of bleeding in patients on novel oral anticoagulants. *Eur Heart J* 2013; **34** (7): 489–500.

85 Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring oral direct inhibitors (ODIs) of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the ISTH. *J Thromb Haemost* 2013; 11: 756–60.

86 Kitchen S, Gray E, Mackie I, Baglin T, Makris M. Measurement of non-coumarin anticoagulants and their effects on tests of haemostasis: Guidance from the British Committee for Standards in Haematology. *Br J Haematol* 2014; **166** (6): 830–41.

87 Blann AD, Lip GY. Laboratory monitoring of the non-vitamin K oral anticoagulants (NOACs). *J Am Coll Cardiol* 2014; **64** (11): 1140–2.

88 Ganetsky VS, Hadley DE, Thomas TF. Role of novel and emerging oral anticoagulants for secondary prevention of acute coronary syndromes. *Pharmacotherapy* 2014; **34** (6): 590–604.

89 Ahrens I, Peter K, Lip GY, Bode C. Development and clinical applications of novel oral anticoagulants. Part II. Drugs under clinical investigation. *Discov Med* 2012; **13** (73): 445–50.

90 Ellis DJ, Usman MH, Milner PG, Canafax DM, Ezekowitz MD. The first evaluation of a novel vitamin K antagonist, tecarfarin (ATI-5923), in patients with atrial fibrillation. *Circulation* 2009; **120** (12): 1029–35.

91 Eikelboom JW, Connolly SJ, Brueckmann M *et al*.; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013; **369** (13): 1206–14.

92 van der Hulle T, den Exter PL, Kooiman J, van der Hoeven JJ, Huisman MV, Klok FA. Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. *J Thromb Haemost* 2014; **12** (7): 1116–20.

93 Gerotziafas GT, Mahe I, Elalamy I. New orally active anticoagulant agents for the prevention and treatment of venous thromboembolism in cancer patients. *Ther Clin Risk Manag* 2014; **10**: 423–36.

94 Di Nisio M, Carrier M, Lyman GH, Khorana AA. Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2014; **12** (10): 1746–9.

95 Wood S, Petty D, Fay M, Lewington A. Assessing kidney function in oral anticoagulant prescribing: an aid for safer drug and dose choices. *Br J Cardiol* 2013; 20 (2): 61–4.