

## Vascular medicine

# Non-vitamin-K oral anticoagulants and laboratory testing: now and in the future

## Views from a workshop at the European Medicines Agency (EMA)

Tomas Salmonson<sup>1</sup>, Jean-Michel Dogné<sup>2</sup>, Heidi Janssen<sup>3</sup>, Juan Garcia Burgos<sup>4</sup>, and Paul Blake<sup>5\*</sup>

<sup>1</sup>Committee Chair, Committee for Medicinal Products for Human Use, EMA, London E14 5EU, UK; <sup>2</sup>Committee Member, Pharmacovigilance Risk Assessment Committee, EMA, London E14 5EU, UK; <sup>3</sup>Head of Office, Endocrinology, Metabolism & Cardiovascular Office, EMA, London E14 5EU, UK; <sup>4</sup>Head of Service, Medical and Health Information Service, EMA, London E14 5EU, UK; and <sup>5</sup>Scientific Officer, Medical and Health Information Service, EMA, London E14 5EU, UK

Received and revised on 4 October 2016; accepted 5 October 2016

In contrast to vitamin K antagonists, no routine coagulation monitoring is required in patients taking non-vitamin-K oral anticoagulants (NOACs). However, dosing must take into account factors such as patient age, renal function, and accompanying haemorrhagic risk. There has been considerable debate about when laboratory measurement might be appropriate and which tests should be used. A workshop at the European Medicines Agency recently discussed the evidence about laboratory measurement from formal studies, clinical experience, and the multiple perspectives on NOAC treatment, and considered how our knowledge might be further enhanced.

### Keywords

DOACs • Direct Oral Anticoagulants • Non-vitamin-K oral anticoagulants • NOACs • Anticoagulation • Coagulation tests

## Introduction

Unlike vitamin K antagonists (VKAs) such as warfarin that reduce hepatic synthesis of various clotting factors, non-vitamin-K oral anticoagulants (NOACs, also called direct oral anticoagulants, DOACs) act on specific factors within the coagulation cascade; dabigatran (given as the prodrug dabigatran etexilate, Pradaxa) inhibits thrombin while apixaban (Eliquis), edoxaban (Lixiana), and rivaroxaban (Xarelto) inhibit factor Xa.<sup>1–4</sup> (see *Table 1*)

In contrast to VKAs, no routine coagulation monitoring is required in patients taking NOACs.<sup>1–4</sup> This relieves both patients and health services of the burden of regular blood tests. However, dosing of NOACs must take into account factors such as patient age, renal function and accompanying haemorrhagic risk.<sup>1–5</sup> Efficacy and safety using this dosing paradigm have been shown in a series of large clinical trials which found that the risk of intracranial bleeding

was lower with NOACs than with warfarin. Evidence from these studies is reflected in recommendations in major cardiovascular guidelines.<sup>6–8</sup>

However, clinical experience suggests fear of bleeding complications may lead to the selection of low doses in practice, even at the risk of decreased efficacy and so a greater thrombotic risk. There has been considerable debate on whether laboratory measurement might therefore be appropriate not only in emergency situations or overdose but even in routine management. There is also a continuing need for guidance about which tests should be used.

A workshop<sup>9</sup> at the European Medicines Agency, attended by patient representatives, clinicians, academics, regulators and participants from the pharmaceutical industry, recently discussed the evidence about laboratory measurement from formal studies, clinical experience, and the multiple perspectives on NOAC treatment, and considered how our knowledge might be further enhanced.

\* Corresponding author. Tel: +44 (0)20 3660 6000, Fax: +44 (0)20 3660 5555, Email: [paul.blake@ema.europa.eu](mailto:paul.blake@ema.europa.eu)

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## Which tests are available?

Experimental data show that drug concentrations of NOACs correlate with their activity. Although the pharmacokinetics of the licensed NOACs differ (see *Table 1*), unlike warfarin they have relatively short half-lives of around 5–15 h under normal circumstances, and the steep decline in plasma concentration after the peak makes measurements very sensitive to the time of sampling with respect to the last dose. This can make interpretation difficult. Mass spectrometry is the most reliable way of measuring drug concentration but is almost never used in routine practice.<sup>10</sup>

The classical coagulation tests can be misleading for determining NOAC activity.<sup>11,12</sup> Product information for all these medicines warns against use of INR. Activated partial thromboplastin time (aPTT) or prothrombin time (PT) also cannot be used to quantify their activity precisely: changes in clotting measures are

generally small and depend on the reagents used, and patients with normal values may have levels of NOAC that produce a significant anticoagulant effect.

In contrast, specific assays (dTT—diluted thrombin time, or ecarin-based assays such as ecarin chromogenic assay (ECA) for dabigatran, chromogenic factor Xa assays for the factor Xa inhibitors, see *Table 2*) correlate well with plasma concentrations<sup>11,12</sup> although they may be less reliable at very low concentrations and require product-specific calibration.

## When might measurements be useful?

With increasing use of NOACs, patients in the pivotal clinical trials may not be representative of those being treated in clinical practice;

**Table 1** Non-vitamin-K oral anticoagulants

	<b>Apixaban (Eliquis)</b>	<b>Dabigatran etexilate (Pradaxa)</b>	<b>Edoxaban (Lixiana)</b>	<b>Rivaroxaban (Xarelto)</b>
Date authorized in the EU	18 May 2011	18 March 2008	19 June 2015	30 September 2008
Indications in adults <sup>a</sup>	Prevention of stroke and systemic embolism with non-valvular atrial fibrillation with additional risk factors; Treatment of deep-vein thrombosis and pulmonary embolism and prevention of recurrence of these conditions; Prevention of thromboembolism following total hip or total knee replacement surgery	Prevention of stroke and systemic embolism with non-valvular atrial fibrillation with additional risk factors; Treatment of deep-vein thrombosis and pulmonary embolism and prevention of recurrence of these conditions; Prevention of thromboembolism following total hip or total knee replacement surgery	Prevention of stroke and systemic embolism with non-valvular atrial fibrillation with additional risk factors; Treatment of deep-vein thrombosis and pulmonary embolism and prevention of recurrence of these conditions	Prevention of stroke and systemic embolism with non-valvular atrial fibrillation with additional risk factors; Treatment of deep-vein thrombosis and pulmonary embolism and prevention of recurrence of these conditions; Prevention of thromboembolism following total hip or total knee replacement surgery; Adjunct for prevention of atherothrombotic events after acute coronary syndrome
Target:	Factor Xa	Thrombin	Factor Xa	Factor Xa
Bioavailability (%):	50%	3-7%	62%	80–100% for 2.5 and 10 mg doses; 66% for 15 and 20 mg doses
Prodrug:	No	Yes—activated by esterase (CES1)	No	No
Half-life (hours):	8–15	11–13	10–14	5–13
Tmax (hours):	3–4	0.5–2	1–2	2–4
Renal clearance:	25%	80%	50%	33%
Substrate of:	P-gp; CYP3A4/5, CYP1A2, CYP2J2	P-gp	P-gp; CYP3A4/5	P-gp; CYP3A4, CYP2J2
Protein binding:	87%	35%	55%	>90%
Effects of food:	Tmax delayed; Cmax & AUC unchanged	Tmax delayed; Cmax & AUC unchanged	Food increases peak exposure to a varying extent, but has minimal effect on total exposure.	Tmax delayed; Cmax and AUC unchanged at the 2.5 mg and 10 mg dose, less marked decrease than fasting state at higher doses (the 15 and 20 mg doses should be given with food to increase availability)

<sup>a</sup>Abbreviated wording of authorized indications; refer to the summary of product characteristics for the full indications

**Table 2** Coagulation tests that can be used to estimate plasma concentrations of NOACs or to estimate the relative intensity of anticoagulation<sup>a,b</sup>

Test	Molecule(s)	Utility	Sensitivity/ Specificity	Dependence of the reagent	External quality control	Cut-off for a risk of bleeding (Unit(s) of expression)
LC-MS/MS	Dabigatran/ Rivaroxaban / Apixaban / Edoxaban	Proven: Accurately estimates the plasma concentrations— results expressed in ng/ mL	LoD and LoQ around 1 and 3 ng/mL	Not applicable	No	Yes: Depends on the indication (ng/mL) for dabigatran (i.e. 200 ng/mL at trough in AF) Not established for direct factor Xa inhibitors
APTT	Dabigatran	Limited: Poorly reflect the inten- sity of anticoagulation	±100 ng/mL / No	Yes	Yes	Yes: Depends on the indication and the reagent (specific values are not presented since they depend on the reagent)
TT	Dabigatran	Limited: Only to exclude the presence of dabiga- tran. Useful in the peri-operative setting	Too sensitive (lower LoD below 0.025 ng/mL with some methodolo- gies) / No	Yes	Yes	Not established
dTT	Dabigatran	Proven: Accurately estimates the plasma concentrations— results expressed in ng/ mL	±10 ng/mL / No	No	Yes	Yes: Depends on the indication (ng/mL)
ECT	Dabigatran	Limited: Standardization and vali- dation required	±15 ng/mL / No	Probably not but an inter- lot variability has been reported	No	Yes: Depends on the indication (ratio: 3xULN and sec- onds: >103 seconds)
ECA	Dabigatran	Proven: Accurately estimates the plasma concentrations— results expressed in ng/ mL	±10 ng/mL / No	No	Yes	Yes: Depends on the indication (ng/mL) (i.e. 200 ng/mL at trough in AF)
PT	Rivaroxaban/ (Edoxaban)	Limited: Poorly reflect the inten- sity of anticoagulation	from ±100 to >500 ng/mL (depending on the reagent) / No	Yes	Yes	Not established
Chromogenic anti-Xa assays	Rivaroxaban / Apixaban / Edoxaban	Proven: Accurately estimates the plasma concentrations— results expressed in ng/mL	±10 ng/mL / Yes–No (depend on the anti-Xa assay)	No	Yes	Not established

<sup>a</sup>Based on presentations and discussions during the workshop, and information summarized in<sup>7,15</sup> of this article.

<sup>b</sup>None of these tests are able to discriminate between therapies. Thrombin specific tests can easily identify dabigatran but other direct thrombin inhibitors such as argatroban or hirudin can influence them. For direct factor Xa inhibitors, only the Biophen<sup>®</sup> Direct Factor Xa Inhibitor can discriminate between heparins and direct FXa inhibitors but fail to differentiate between direct FXa inhibitors.

LoD, limit of detection; LoQ, limit of quantification; ULN, upper limit of normal.

real-life patients prescribed NOACs are often older, have reduced renal function and other comorbidities, and may be taking medicines that affect P-glycoprotein transporter or CYP3A4 activity—all factors that can affect plasma concentrations of NOACs and potentially increase the risk of bleeding or thrombosis.<sup>1–4</sup>

Regular clinical evaluation<sup>5</sup> of patients treated with NOACs, for example to monitor renal function, is required. It may be important, too, in supporting adherence, particularly as patients used to monitoring for VKAs may be concerned by the lack of monitoring when switched to a NOAC.<sup>9</sup> Existing thrombosis services and coagulation clinics may play an important role in such management.

So can specific drug assays offer a significant safety improvement over the present dose adjustment by age, renal function, and haemorrhagic risk factors? Importantly there are no established, evidence-based therapeutic ranges for plasma concentrations of these medicines, although on-therapy ranges are available from some of the large studies and have been taken into account in the EU product information.<sup>1–4</sup> However, these on-therapy drug concentrations vary with the indication for NOAC use and with patient characteristics. No single plasma concentration range provides optimal benefit-risk for all patients.<sup>9</sup> Specific assays are used in some centres to identify outliers—patients with extremes of drug concentration—and so decide if the selected treatment is appropriate,<sup>9</sup> but the blood concentration is only one factor in determining bleeding risk.

This limits the usefulness of routine measurements of drug concentration, and on the basis of presentations to the workshop, the large-scale clinical trials that would be needed to establish a series of

evidence-based therapeutic ranges for each subgroup of patients taking these medicines seem unlikely to be forthcoming.

However, testing may be useful to confirm exposure in specific clinical situations such as patients who are bleeding, thought to be overdosed or who require invasive procedures, or where other factors (particularly in combination) may affect exposure (summarized in *Table 3*).<sup>9,13</sup> There may also be a role for assays in monitoring the effect of the specific antidotes which have begun to become available (idarucizumab now licensed in the EU as Praxbind, andexanet alfa in development).<sup>9</sup> The SmPC for Praxbind recommends using test results (using aPTT, dTT, or ECT) as one of the criteria to determine the need for repeat dosing,<sup>14</sup> but an initial dose should not be delayed while awaiting the results of clotting time tests.

Workshop participants heard that, critically, there is no evidence to support doses outside the licensed dose range for a given NOAC; if a patient cannot be managed within the recommended range it may be better to consider an alternative anticoagulant.<sup>9</sup>

## What are the challenges in practice?

Anticoagulant therapy requires the patient, together with the doctor, to determine the acceptability of the risk of major bleeding on the one hand and of thrombotic events on the other. After decades of using VKAs, adoption of NOACs into clinical practice inevitably requires a shift in the approach to oral anticoagulation for both

**Table 3** Situations in which coagulation testing for NOACs may be helpful

Situation	Comment
Bleeding (spontaneous or traumatic) When emergency surgery or invasive procedures are required In perioperative management Before thrombolytic treatment	For example in patients requiring elective surgery in whom the medicine may still be active
During bridging from one anticoagulant to another Patients suspected of being overdosed To assess efficacy or adherence	Note: there is no evidence to support titration outside the licensed doses For example if new thrombosis develops during treatment with the anticoagulant
Patients with deteriorating renal function Patients taking other medications that affect the pharmacokinetics	Renal function is an important determinant of NOAC dosing Although NOACs are less sensitive to drug-drug interactions than warfarin, product information warns that dabigatran etexilate and edoxaban are substrates for P-glycoprotein (P-gp) and that apixaban and rivaroxaban pharmacokinetics are affected both by P-gp and cytochrome CYP3A4. Some combinations with inhibitors or inducers of these pathways are contraindicated or discouraged in the relevant SmPCs but even those inhibitors/inducers which do not normally produce clinically significant changes may be significant in combination with other factors
Patients at extremes of bodyweight	Edoxaban requires a dose reduction for patients with very low body weight; extremes of body weight may be significant for other NOACs in combination with other factors
Patients who have received an initial dose of a specific antidote	Initial administration of a specific antidote should not be delayed to await test results if it is clinically indicated, but testing may be helpful in determining the need for subsequent doses
Patients with some combination of the above factors	Patients not uncommonly exhibit a combination of factors (such as poor renal function, low body weight and co-administration of potentially interacting medications) that could combine to affect NOAC activity

prescribers and patients. Critical points on the safe use of VKAs—such as INR monitoring and care over diet to avoid changes in vitamin K intake—do not apply to NOACs. Health professionals do, however, need to recognize NOACs on a patient's medication history to avoid mishaps and assess anticoagulation appropriately.

Although the evidence supports use of specific quantitative tests rather than prothrombin time tests,<sup>9,11</sup> the specific tests are still not routinely available in many centres.<sup>9,15</sup> Even where available, they need relevant expertise which may not be available around the clock, and so are often not requested, even in an emergency. Moreover, they require drug-specific calibration, and, in the absence of international calibration standards for the assays, there are considerable variations between laboratories.<sup>9,12</sup> In practice, therefore, clinicians report that they often use aPTT or PT for screening, even though these tests cannot quantify activity precisely and may sometimes give normal results despite effective anticoagulation. International standardization of the specific tests is required, and rapid, point-of-care tests for use in emergency situations would be desirable.

Information on appropriate testing is already included in the NOAC product information but guidance on selection and interpretation of the tests can be refined to provide the most appropriate information to health professionals. However, while regulators should ensure product information is clear, individual judgement on the circumstances for testing must rest with the clinician.

## Where do we go from here?

Non-vitamin-K oral anticoagulants are effective medicines whose approval in the EU and elsewhere reflects a consistent regulatory assessment that their benefits outweigh their risks. Their product information already contains information to allow decisions on dose selection and the use of available assays. Nonetheless, further knowledge to support best use of these medicines and dose selection in particular subgroups is desirable.

Large-scale randomized trials in patient subgroups are probably not feasible, but other avenues are being explored. Many patients requiring anticoagulation also have comorbidity and deteriorating renal function, so smaller studies on subgroups such as haemodialysis patients could be useful to understand the relevance of measurements in specific populations; some studies (such as NCT01896297) are under way, and others, such as a study of apixaban in atrial fibrillation patients on dialysis, are planned.<sup>9</sup> Structured follow-up of real life patients can also help provide further evidence. Re-analysis of existing study data may be important to clarify our knowledge of relationships between drug levels and efficacy/bleeding risk and thereby strengthen recommendations. Such clarification can only further improve the safety and efficacy of NOAC use in the wider population, and might help to assuage those concerns of physicians and patients regarding bleeding risks that can lead to sub-optimal use of these medicines.

However, education and dissemination of the relevant information is equally important to allow prescribers, patients and others to use these medicines as safely as possible.<sup>9</sup> Many hospitals have local

protocols for dose adjustment, while for non-specialists a variety of regularly updated guidelines are available<sup>5–8</sup> and may be helpful, but it is important that these are based on the latest evidence.<sup>11</sup> Product information is regularly reviewed and should be updated to refine available guidance as new information emerges.

## Acknowledgements

The authors would also like to acknowledge the particularly valuable contribution to the text of Anna Baczynska, Catherine Drai, Giampiero Mazzaglia, and Dinesh Mehta, scientific officers at the European Medicines Agency and of Jens Heisterberg, clinical pharmacologist and former CHMP member and Chief Medical Officer of the Danish Medicines Agency, who also chaired one of the sessions of the workshop. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

**Conflict of interest:** The authors have read and understood journal policy on declaration of interests and have no relevant personal interests to declare; Prof. Dogné is also a member of the Thrombosis and Hemostasis Center of the University of Namur, which has received a grant from Bayer Pharmaceuticals to support general research in thrombosis and haemostasis.

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