Laboratory testing of NOAC

NOAC – **N**on vitamin K **o**ral **a**nti**c**oagulants
DOAC – **D**irect **o**ral **a**nti**c**oagulants
ODI – **O**ral **D**irect **I**nhibitors

Dr Kate Talks

October 2014

EMA approved Use of NOACs

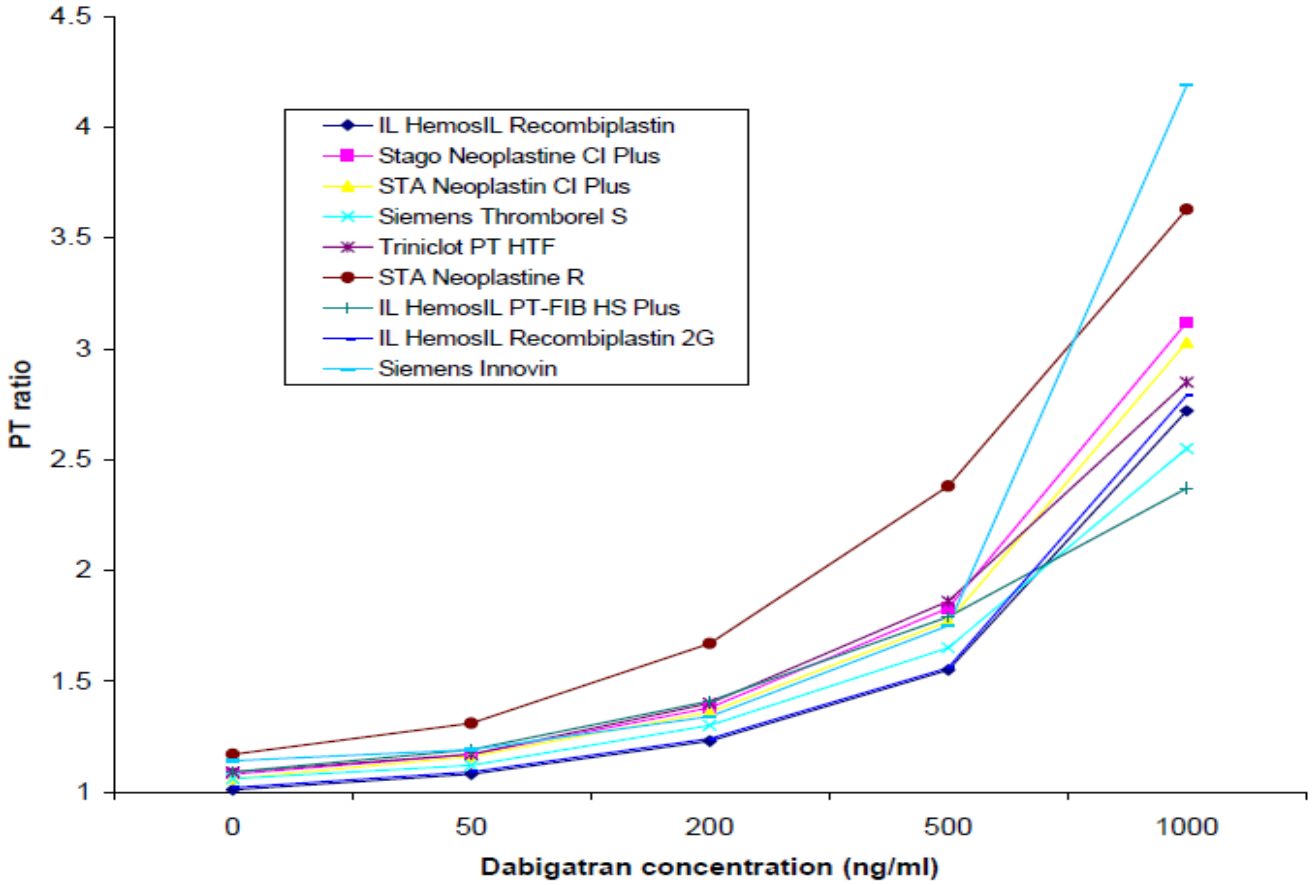
	Dabigatran IIa inhibitor	Rivaroxaban Xa inhibitor	Apixaban Xa inhibitor
Orthopaedic thromboprophylaxis	+	+	+
General thromboprophylaxis	-	-	-
AF	+	+	+
DVT	+	+	+
PE	+	+	+

Other Xa inhibitors in development: Edoxaban, Betrixaban, Otamixaban

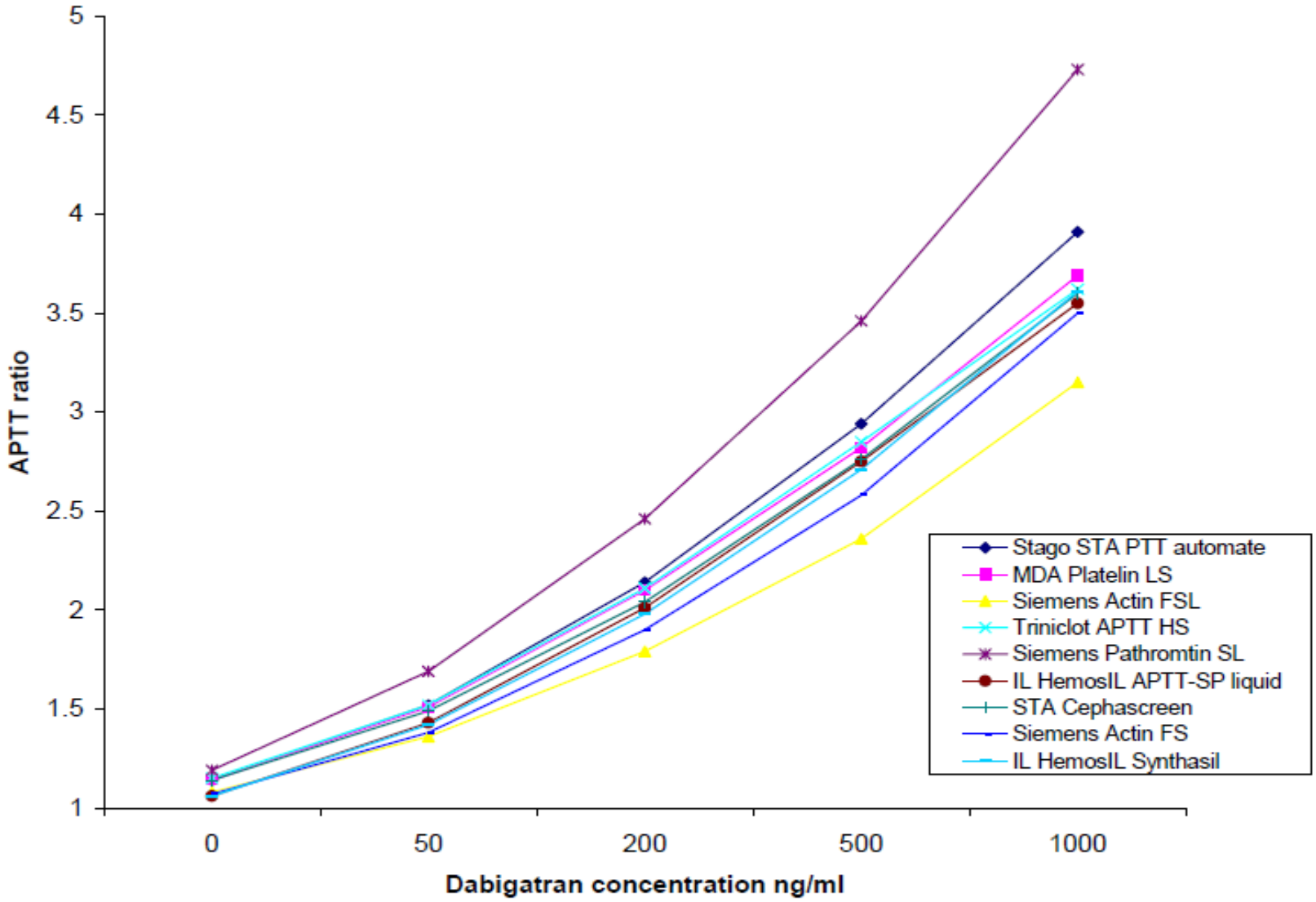
Lab tests and NOAC

- ‘Routine’ laboratory coagulation test results are influenced by the NOAC (PT, APTT, TT, Fib)
- But results do not provide direct information on drug level
- The prolongation of individual tests varies with different reagents and analysers
- To interpret coagulation tests meaningfully and ensure the correct tests are done an accurate information on drug history is needed by the lab

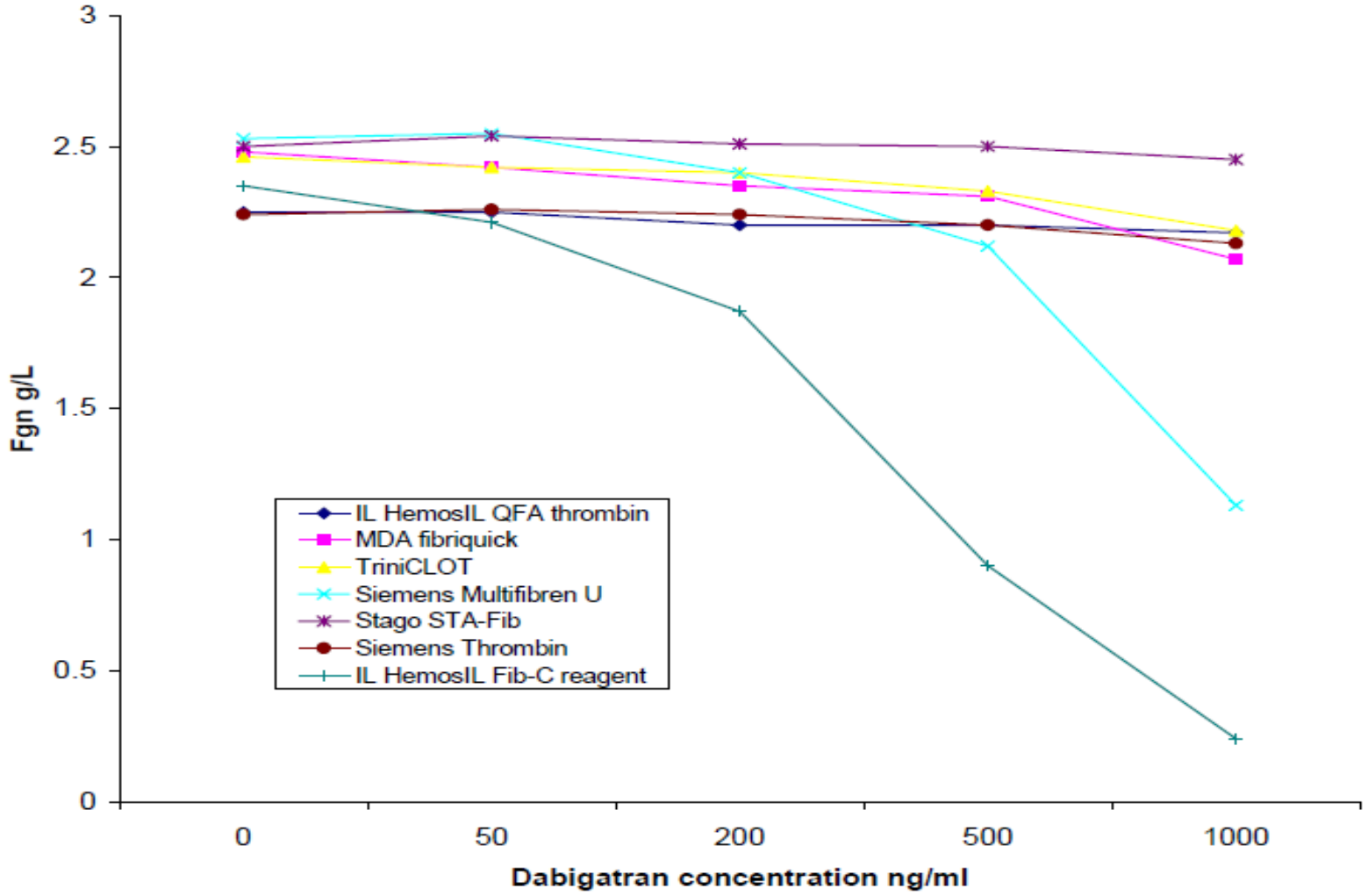
Effect of Dabigatran on PT



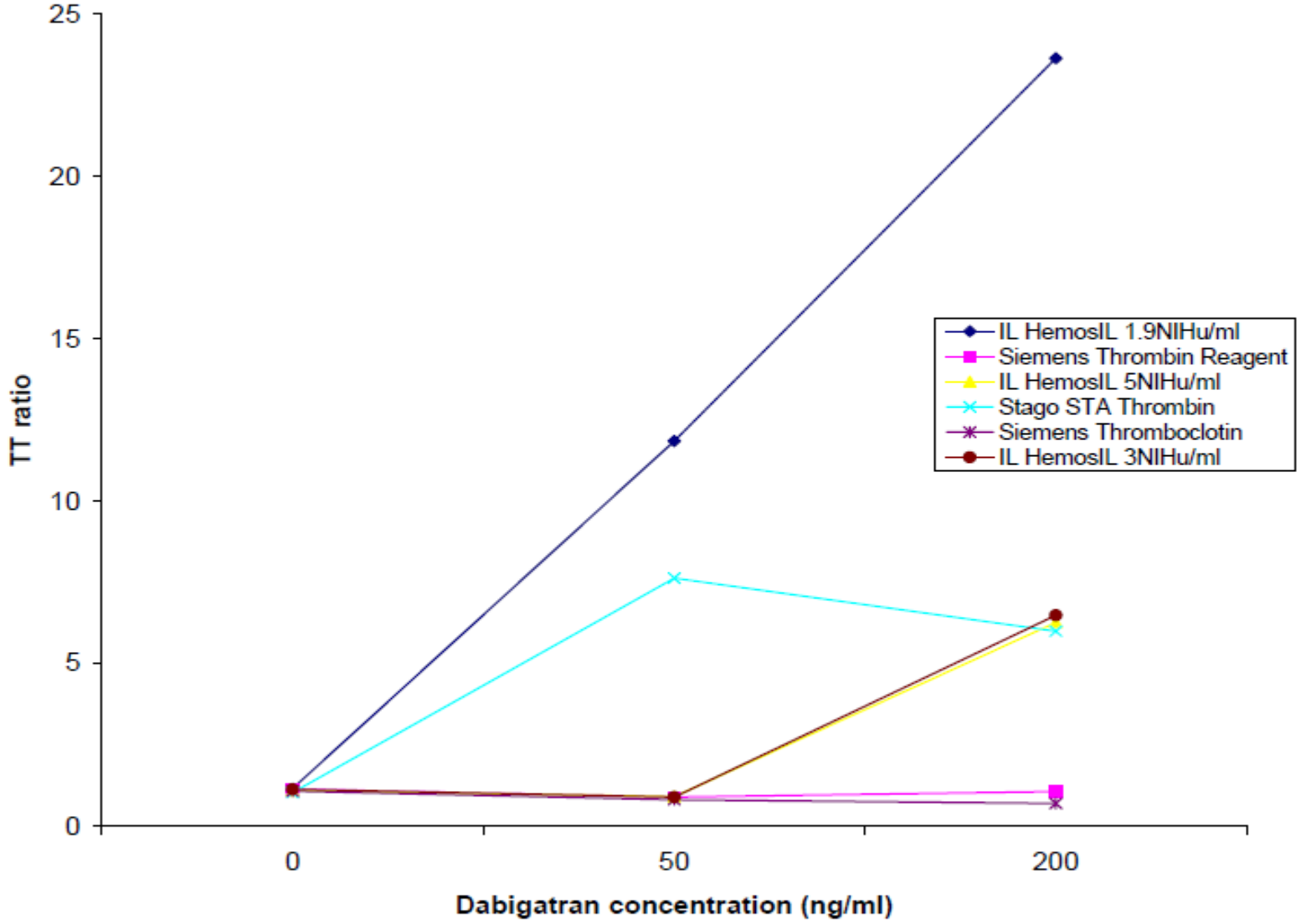
Effect of Dabigatran on APTT



Effect of Dabigatran on CFib



Effect of Dabigatran on Thrombin



Effects of anticoagulants on routine coagulation tests

Anticoagulant	PT	APTT	Fib	TT	DDimer
Warfarin	+++	+			Low
Unfractionated heparin	+	+++		+++	Low
LMWH		+			Low
Dabigatran	+	++	-/+	+++	Low
Rivaroxaban	++	+			Low
Apixaban	-/+	-/+			Low

Why test drug levels?

- Drug monitoring to optimize dosing or increase efficacy and/or safety eg. differentiate treatment failure/ compliance in event of recurrent VTE
- Establish level is in the therapeutic range if potential drug interaction (Pgp and CYP3A4 inhibitors) or patient factors associated with a high bleeding risk
- If emergency/ urgent surgery required levels may inform relative bleeding risk and timing of procedure / use of an antidote

Why test?

- Monitoring not required when anticoagulant is used for prophylaxis or when the anticoagulant effect is predictable and drugs administered at a fixed weight based dose eg. LMWH
- NOAC apixiban, dabigatran and rivaroxaban introduced WITHOUT intention of routine monitoring

BUT

- Clinical trials often exclude patients with impaired renal function, children, the very elderly, those with an increased bleeding risk and those at the extremes of body weight.
- The lack of a need to monitor demonstrated in the trials may therefore not be applicable to groups excluded from trial entry

- assumed similarity in pharmacokinetic and pharmacodynamic responses between individuals within a relatively wide therapeutic window.
- It has been estimated that the same dose of direct inhibitors of thrombin and activated factor X (Xa) can have up to 30% difference in thrombin generation inhibition

Does this matter?

thebmj

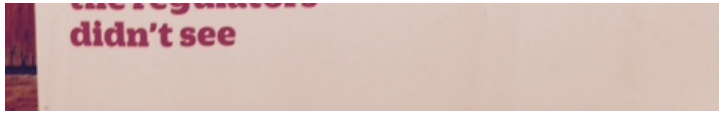
BMJ 2014;349:g4517 doi: 10.1136/bmj.g4517 (Published 23 July 2014)

Table

Table 1| Major bleeds in RE-LY trial defined by different criteria*

	No (%) taking dabigatran		
	110 mg twice daily	150 mg twice daily	No (%) taking warfarin (dose adjusted)
Major bleeds	377	460	451
Hospital admission required	275 (73)	358 (78)	345 (77)
Transfusion ≥2 units	229 (61)	304 (66)	238 (53)
Gastrointestinal bleed	150 (40)	209 (45)	132 (29)
Symptomatic intracranial bleed	31 (8)	36 (8)	85 (19)
Surgical intervention required	35 (9)	56 (12)	62 (14)
Died	26 (7)	28 (6)	39 (9)

*Excerpted from EMA Rapporteur Day 80 critical assessment report[13]



believed its actions might slightly improve the efficacy of dabigatran in preventing stroke. The EMA, by contrast, showed continuing concerns about reducing the risk of bleeding and pursued multiple risk reduction policies. But neither agency insisted on the most effective step to reduce bleeding risk—optimising the drug's anticoagulant effect in each patient.

room visits, symptomatic gastrointestinal bleeding that didn't require a two unit transfusion, and some emergency admissions.[4] In the RE-LY trial, major and minor bleeds occurred in 18.5% of warfarin patients each year and 16.4% of patients taking dabigatran 150 mg twice daily.

Correspondence to: T J Moore tmoore@tlamp.org

Clinical Research: Antithrombotic Therapy | February 2014

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

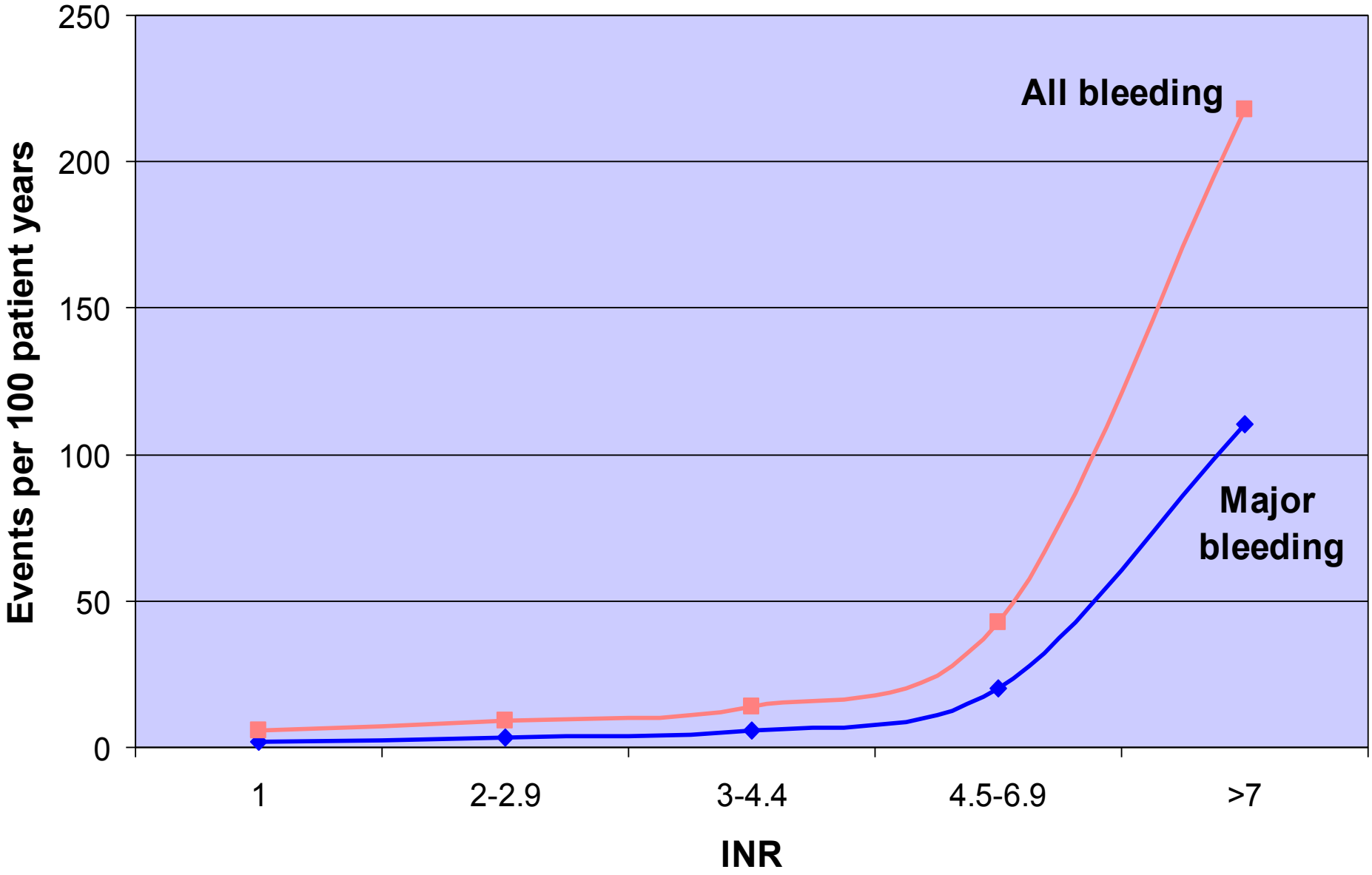
Paul A. Reilly, PhD[*]; Thorsten Lehr, PhD[†]; Sebastian Haertter, PhD[†]; Stuart J. Connolly, MD[§]; Salim Yusuf, MD, DPhil[§]; John W. Eikelboom, MB BS[§]; Michael D. Ezekowitz, MD, PhD[‖]; Gerhard Nehmiz, PhD[†]; Susan Wang, PhD[*]; Lars Wallentin, MD, PhD[¶]

[+] Author Information

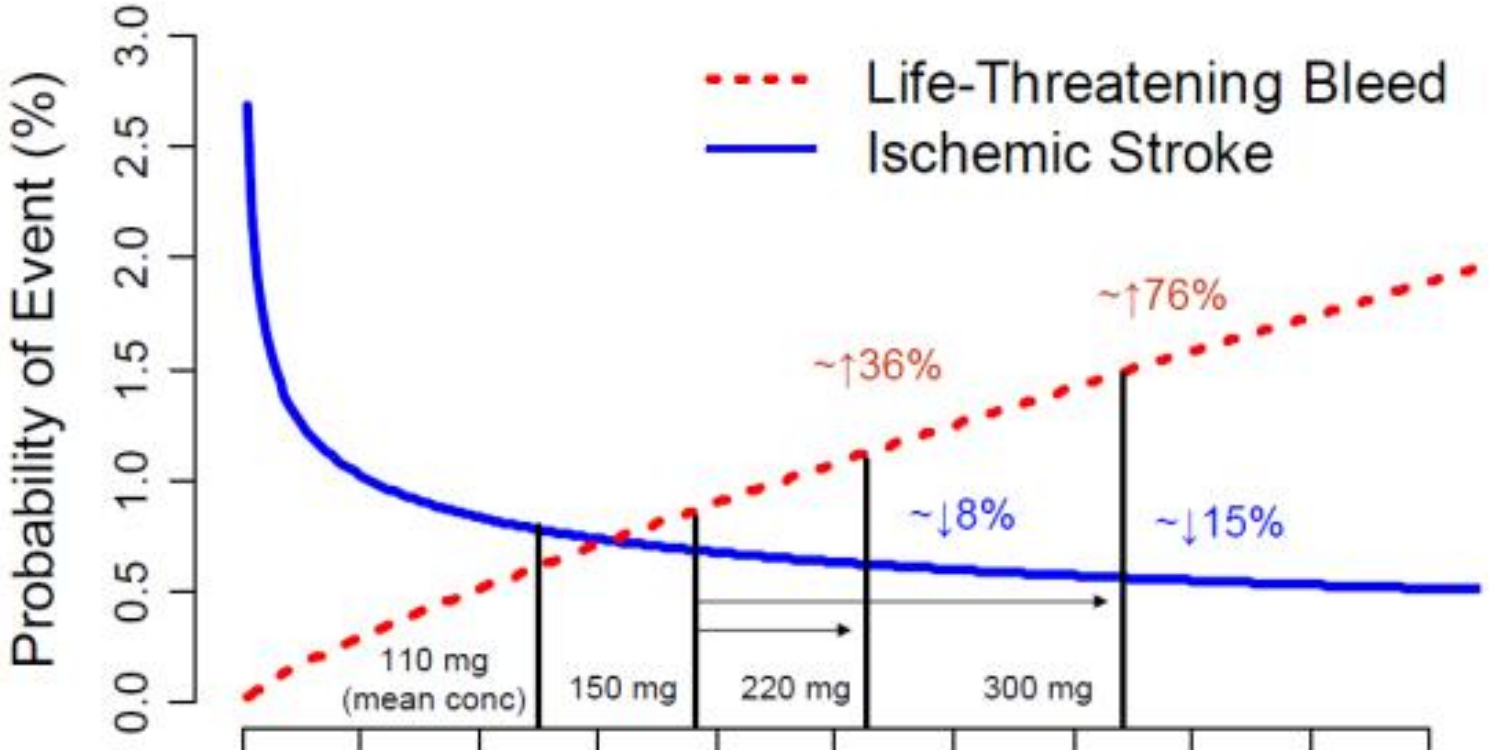
J Am Coll Cardiol. 2014;63(4):321-328. doi:10.1016/j.jacc.2013.07.104

- **Results** Plasma concentrations were obtained from 9,183 patients, with 112 ischemic strokes/systemic emboli (1.3%) and 323 major bleeds (3.8%) recorded. Dabigatran levels were dependent on renal function, age, weight, and female sex, but not ethnicity, geographic region, ASA use, or clopidogrel use.
- A multiple logistic regression model (c-statistic 0.657, 95% confidence interval [CI]: 0.61 to 0.71) showed that the risk of ischemic events was inversely related to trough dabigatran concentrations ($p = 0.045$), with age and previous stroke (both $p < 0.0001$) as significant covariates. Multiple logistic regression (c-statistic 0.715, 95% CI: 0.69 to 0.74) showed major bleeding risk increased with dabigatran exposure ($p < 0.0001$), age ($p < 0.0001$), ASA use ($p < 0.0003$), and diabetes ($p = 0.018$) as significant covariates.
- **Conclusions** Ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations. Age was the most important covariate. Individual benefit–risk might be improved by tailoring dabigatran dose after considering selected patient characteristics.

INR and bleeding risk (Palareti et al 1996)



Does Benefit/Risk Support Exploration of Higher Doses of Dabigatran?



Relationship of dose to bleeding risk dabigatran

- The EMA examined a subset of spontaneously reported deaths from bleeding in which dose was known.
- It concluded that 23.1% of deaths occurred in patients receiving the 150 mg dose who would have received a lower dose under its guidelines.
- FDA review 134 000 patients >65 on anticoagulants warfarin and dabigatran. Found lower risk of strokes, IC haemorrhage and death with dabigatran

Need to consider risk/benefit of different anticoagulants and follow guidance in spc when selecting drug dose

N Engl J Med. 2013 Sep 26;369(13):1206-14. doi: 10.1056/NEJMoa1300615. Epub 2013 Aug 31.

Dabigatran versus warfarin in patients with mechanical heart valves. RE-ALIGN study

- Study used dose adjustment aiming for a minimum trough of 50ng/ml
- at least 8% of participants had plasma levels below the 50 ng/mL target even when prescribed double the maximum approved dose—up to 300 mg twice daily
- Study terminated early as associated with increased rates of thromboembolic and bleeding complications

Clinical studies are needed to establish benefit of dose adjustment to plasma levels

- No evidence for benefit of routine monitoring of plasma concentrations
- Don’t know how information could be used to dose adjust
- Readily available clinical information eg age, renal function, co-administration of anti-platelet therapy should be used for dose selection
- Clinical studies of NOAC demonstrate non-inferiority in stroke/ VTE with less bleeding than warfarin

Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban: Guidance from the British Committee for Standards in Haematology

Trevor Baglin,[1,*] David Keeling[2] and Steve Kitchen[3]

[1]*Addenbrooke's Hospital, Cambridge, UK,* [2]*Oxford University Hospitals, Oxford, UK and* [3]*Royal Hallamshire Hospital, Sheffield, UK*

Keywords: anticoagulants, anticoagulation, laboratory haematology.

Oral direct inhibitors of thrombin and activated factor X (factor Xa) are now approved as anticoagulant drugs. The first two drugs to complete phase III clinical trials are dabigatran etexilate and rivaroxaban, which are given at fixed dose and do not require monitoring. In most circumstances both have predictable bioavailability, pharmacokinetic and pharmacodynamic effects, however, there will be clinical circumstances when urgent assessment of the anticoagulant effect of these drugs will be required. The effects of dabigatran and rivaroxaban on laboratory tests have been determined *in vitro* by spiking normal samples with a known concentration of active compound or *ex vivo* using plasma samples from volunteers and patients. To date there are few data on the sensitivity of different reagents and so only general guidance as to the effect and interpretation of a test result can be given at present. Laboratories should be aware of the sensitivity of their own assays to each drug, which can be achieved using commercially available dabigatran and rivaroxaban calibrants.

Dabigatran etexilate is an oral prodrug that is hydrolysed in the liver to the direct thrombin inhibitor dabigatran. Doses recommended for clinical use are 150 mg od, 220 mg od, 110 mg bd and 150 mg bd. Peak plasma levels are reached 2 to 3 h after ingestion. Dabigatran is 80% renally excreted with a half-life of approximately 13 h with a glomerular filtration rate (GFR) of >80 ml/min, and 18 h with a GFR of 30–50 ml/min. There is a dose-dependent effect of dabigatran on laboratory clotting tests (Wienen *et al*, 2007; van Ryn *et al*, 2010; Freyburger *et al*, 2011; Lindahl *et al*, 2011).

Rivaroxaban is an oral direct inhibitor of factor Xa. Doses recommended for clinical use are 10 mg od and 20 mg od (15 mg bd for first 3 weeks of treatment of DVT). Peak plasma levels are reached 2 to 3 h after ingestion. Rivaroxaban is 33% renally excreted and has a half-life of 9 h in patients with normal renal function. There is a dose-dependent effect of rivaroxaban on laboratory clotting tests (Samama *et al*, 2010; Freyburger *et al*, 2011; Hillarp *et al*, 2011).

For both drugs, peak plasma concentrations are in the range of 100 to 400 ng/ml. Trough concentrations are in the range of 20 to 150 ng/ml.

Clinicians require knowledge as to how routine coagulation tests are affected because many patients having a 'coagulation screen' will be taking these drugs. They also need to know if and how the degree of anticoagulation can be assessed using routine coagulation tests.

Urgent assessment of the degree of anticoagulation may be required

- before surgery or invasive procedure when a patient has taken a drug in the previous 24 h (or longer if creatinine clearance <50 ml/min),
- when a patient is bleeding,
- when a patient has taken an overdose,
- when a patient has developed renal failure,
- when a patient has thrombosis on treatment (to assess whether there is failure of therapy or lack of adherence).

In this situation a test must be readily available, easily performed and provide a result within 30 to 60 min. The result of the test can indicate whether anticoagulation is supratherapeutic, therapeutic or subtherapeutic, but cannot be used to determine the plasma concentration of the drug.

The test results are dependent on when the last dose of drug was taken and therefore require interpretation with reference to the dose, anticipated half-life and factors that influence pharmacokinetics.

Activated partial thromboplastin time

- The APTT shows a curvilinear dose-response to dabigatran with a steep increase at low concentrations and linearity

*Correspondence: Dr Trevor Baglin, c/o BCSH Secretary, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
E-mail: bsh@b-s-h.org.uk

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Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology

Steve Kitchen,[1] Elaine Gray,[2] Ian Mackie,[3] Trevor Baglin[4] and Mike Makris[1,5] on behalf of the BCSH committee

[1]*Sheffield Haemophilia and Thrombosis Centre, Sheffield Teaching Hospitals NHS Trust, Sheffield,* [2]*Haemostasis section, Biotherapeutics Group, National Institute for Biological Standards and Control, Potters Bar,* [3]*Haemostasis Research Unit, Department of Haematology, University College London, London,* [4]*Department of Haematology, Addenbrooke's Hospital, Cambridge, and* [5]*Department of Cardiovascular Science, University of Sheffield, Sheffield, UK*

Keywords: Monitoring/measuring anticoagulation, Xa inhibitors, IIa inhibitors, heparin, low molecular weight heparin.

The guideline group was selected to include UK-based medical, scientific and laboratory representatives. Publications known to the writing group were supplemented with additional papers identified by searching MEDLINE/Pubmed using the keywords direct thrombin inhibitors (DTI), direct Xa inhibitors, apixaban, argatroban, bivalirudin, dabigatran, fondaparinux, rivaroxaban, in combination with measurement, monitoring, coagulation assays, haemostasis assays and laboratory tests.

The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH). The BCSH GRADE system was not applied to this guideline as it is inappropriate for laboratory studies. The guideline was then reviewed by a sounding board of *c.* 50 UK haematologists, the BCSH and British Society for Haematology (BSH) Committee and comments were incorporated where appropriate.

The objective of this guideline is to provide healthcare professionals with clear guidance on the clinically important issues regarding the laboratory assessment of currently used non-coumarin anticoagulants and their impact on laboratory tests of haemostasis.

A short summary of the effects of rivaroxaban and dabigatran on routine coagulation screens and assessment of anticoagulation intensity on behalf of the BCSH (Baglin *et al*, 2012) and international recommendations related to measurement of oral direct inhibitors (Baglin *et al*, 2013) have recently been published.

The sections on heparin and low molecular weight heparin (LMWH) represent an update of the previously issued guidance (Baglin *et al*, 2006).

Anticoagulants in use in the UK

The most common anticoagulants in use in hospitals in the UK are vitamin K antagonists, of which warfarin predominates. Recent BCSH guidelines have addressed warfarin management (Keeling *et al*, 2011) and this is not discussed in this document. Non-coumarin anticoagulants licensed for use in the UK at the time of writing are listed in Table I.

Drug monitoring aims to use laboratory testing to optimize dosing to increase efficacy and/or safety. Monitoring of anticoagulants, other than warfarin, is primarily indicated for the intravenously administered drugs, such as unfractionated heparin (UFH), danaparoid, argatroban and bivalirudin. Monitoring is not required when anticoagulants are used for prophylaxis, where the anticoagulant effect is predictable and the drugs can be administered at a fixed weight-based dose. The efficacy of this approach has been established by the experience with the subcutaneously administered low molecular dose heparin (LMWH) and fondaparinux. More recently, the oral anticoagulants dabigatran, rivaroxaban and apixaban have been introduced without the intention of routine monitoring. These drugs have been shown in randomized trials to be effective and safe without monitoring (Connolly *et al*, 2009; Schulman *et al*, 2009; EINSTEIN Investigators, 2010; Patel *et al*, 2011). Arguments for and against laboratory monitoring of the new anticoagulants have been published (Bounameaux & Reber, 2010; Mismetti & Laporte, 2010).

The lack of a need for monitoring is based on the assumed similarity in pharmacokinetic and pharmacodynamic responses between individuals within a relatively wide therapeutic window. It has been estimated that the same dose of direct inhibitors of thrombin and activated factor X (Xa) can have up to 30% difference in thrombin generation inhibi-

*Correspondence: BCSH Secretary, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK.
E-mail: bsh@b-s-h.org.uk

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bjh guideline

Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology

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Keywords: Monitoring/measuring anticoagulation, Xa inhibitors, IIa inhibitors, heparin, low molecular weight heparin.

The sections on heparin and low molecular weight heparin (LMWH) represent an update of the previously issued guidance (Baglin *et al*, 2006).

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Expected peak and trough plasma conc of ODI

Table III. Expected plasma concentrations of Oral Direct Inhibitors.

Drug	Dose	Peak levels mean and range	Trough levels mean and range	References
Apixaban	2·5 mg bd	0·062 mg/l (CV 37%)	0·021 mg/l (CV 17%)	Frost *et al* (2013)
Apixaban	5 mg bd	0·128 mg/l (CV 10%)	0·050 mg/l (CV 20%)	Frost *et al* (2013)
Dabigatran	150 mg bd	0·184 mg/l (95% CI 0·064–0·443)	0·090 mg/l (0·031–0·225)	Van Ryn *et al* (2010)
Rivaroxaban	10 mg od	0·125 mg/l (0·091–0·195)	0·009 mg/l (0·001–0·038)	Mueck *et al* (2008)
Rivaroxaban	20 mg od	0·223 mg/l (0·16–0·36)	0·022 mg/l (0·004–0·096)	Mueck *et al* (2008)

CV, coefficient of variation; 95% CI, 95% confidence interval.

Baseline information to consider interpreting levels

- Which drug the patient is taking and dose regime (age)
- The time the last dose was taken
- The renal (e-GFR) and hepatic function of the patient

If the patient is bleeding it is essential to consider other factors that could contribute to bleeding ie platelet count/ use of anti-platelet drugs, DIC

Potential lab tests to measure NOAC

Drug	Major mode of mechanism	Potential Lab tests
Dabigatran Direct thrombin inhibitor DTI	Inhibition of FII	Anti-IIa, Thrombin Clotting Time, ECT
Rivaroxaban	Inhibition of FX	Anti-Xa
Apixiban	Inhibition of FX	Anti-Xa

BCSH recommendations measurement dabigatran 2014

- Dilute thrombin-based assays, ecarin-based assays or chromogenic anti-IIa assays (in the absence of heparin) are suitable for determination of plasma concentrations of dabigatran.
- Assays to determine anticoagulant concentration should be calibrated with drug-specific calibrators.
- Prothrombin time (PT) and activated partial thromboplastin time (APTT) should not be used to measure the plasma concentration of dabigatran

Drug	PT	APTT	Fibrinogen	TT
Dabigatran	Less marked INR<1.5 * 29% normal at peak Caution POCT	Usually prolonged even at trough 18% normal at peak	Depends on amount thrombin in test	>10x prolongation at peak Do NOT normalise at trough with some reagents

A normal TT excludes the presence of any dabigatran

Table V. Effects of Dabigatran on specialist tests of haemostasis.

Test	Effects	Comments	References
FII, FV, FVII, FVIII, FIX, FX, FXI assays	Underestimation by clot-based assays	FII clot-based assay particularly affected. Chromogenic FVIII assay unaffected	Freyburger *et al* (2011) Adcock *et al* (2013)
APCR	Elevated ratios	False normal APCR in presence of FV Leiden >0·1 mg/l drug	Lindahl *et al* (2011) Adcock *et al* (2013)
ATǀ	Overestimation	If using thrombin-based assay (Xa-based assays unaffected)	Lindahl *et al* (2011) Douxfils *et al* (2012) Adcock *et al* (2013)
PC assay	Overestimation for clot-based assay	False normal results may be possible with clot-based assays. Chromogenic assays unaffected	Adcock *et al* (2013)
PS assay	Overestimation for clot-based assay	Free PS antigen unaffected	Adcock *et al* (2013)
FVIII Inhibitor	False positive Bethesda >0·2 mg/l		Adcock *et al* (2013)
ACT	Normal at <0·05 mg/l, normal or prolonged at 0·05–0·2 mg/l, prolonged at >0·2 mg/l	*Ex vivo* samples. Method studied- Hemochron ACT-LR	Hawes *et al* (2013)
DRVVT	False positive at 0·05 mg/l and in *ex vivo* samples	Standard or Normalized ratios affected	Halbmayer *et al* (2012) Martinuzzo *et al* (2013)

FII, factor II; FV, factor V; FVII, factor VII; FVIII, factor VIII; FIX, factor IX; FX, factor X; FXI, factor XI; APC, activated protein C; APCR, activated protein C resistance; AT, antithrombin; PC, protein C; PS, protein S; ACT, activated clotting time; ACT-LR, Low Range Activated Clotting Time; DRVVT, Dilute Russell viper venom time.

BCSH recommendation on measurement of oral anti-Xa inhibitors

- Anti-Xa chromogenic assays should be used to determine plasma concentration of direct FXa inhibitors.
- Product-specific calibrator should be used and results should be expressed in mass concentration.
- LMWH reference standards should not be used as calibrators for direct FXa inhibitors.
- PT and APTT should not be used to measure the plasma concentration of Xa inhibitors.

Effects of rivaroxaban and apixaban on tests of haemostasis

- Each laboratory should know the sensitivity of its own PT and APTT tests to rivaroxaban and apixaban and advise on interpretation.
- The PT or APTT can be used with most reagents for a crude estimation of the relative intensity of anticoagulation due to rivaroxaban but some patients with therapeutic concentrations will have a normal PT or APTT.
- For rivaroxaban the PT is usually more sensitive than the APTT but cannot be used to determine the drug concentration.
- For apixaban both the PT and APTT are insensitive and patients may have normal coagulation times despite therapeutic concentrations.
- Clotting factor assays performed in the presence of Xa inhibitors should include multiple test plasma dilutions and an assessment of parallelism.

Table VII. Effects of rivaroxaban on routine coagulation tests.

Test	Peak or trough	Test result	References
PT	Peak	PT ratio 1·3–1·6 (7 methods)	Samama *et al* (2010) Hillarp *et al* (2011)
PT	Trough	Usually normal	Samama *et al* (2010) Hillarp *et al* (2011)
APTT	Peak	APTT ratio 1·4–1·6. Prolonged, 5 to10 s	Samama *et al* (2010) Hillarp *et al* (2011) Asmis *et al* (2012)
APTT	Trough	Normal	Mani *et al* (2011)
Thrombin time	Peak or trough	Unaffected	Asmis *et al* (2012) Mani *et al* (2011)
Clauss fibrinogen assay	Peak or trough	Unaffected	Asmis *et al* (2012) Mani *et al* (2011)
DDimer	Peak or trough	Unaffected	Mani *et al* (2013)

PT, prothrombin time; APTT, activated partial thromboplastin time.

Table VIII. Effects of rivaroxaban on specialist coagulation tests.

Test	Effects	Comments	References
One stage assay of FII, FV, FVII, FVIII, FIX, FX or FXI	Under estimation	Higher test dilutions less affected	Mani *et al* (2013)
DRVVT	False prolongation	*In vitro* and *ex vivo* samples	Samama and Guinet (2011) Merriman *et al* (2011) Mani *et al* (2013) Martinuzzo *et al* (2013)
APCR	Elevated ratios in one assay No effect in another		Hillarp *et al* (2011)
AT	Overestimation	If using Xa in assay (IIa-based assays unaffected)	Hillarp *et al* (2011) Mani *et al* (2011)
PC and PS assays	Potential for overestimation using clot-based assays	False normal results may be possible	Mani *et al* (2013)

FII, factor II; FV, factor V; FVII, factor VII; FVIII, factor VIII; FIX, factor IX; FX, factor X; FXI, factor XI; DRVVT, Dilute Russell viper venom time; APCR, activated protein C resistance; AT, antithrombin; PC, protein C; PS, protein S.

Circumstances when measurement of anticoagulant concentration may be useful. (1)

- In the presence of spontaneous or traumatic haemorrhage
- Following suspected overdose
- When patients are taking another interacting drug
- To monitor efficacy in patients presenting with new thrombosis whilst on the anticoagulant
- When emergency surgery is required
- In patients due to have neuraxial anesthesia for elective or emergency procedures or surgery

Circumstances when measurement of anticoagulant concentration may be useful. (2)

- In patients requiring elective surgery and in whom the drug may still be present
- In patients with renal impairment
- When bridging from one anticoagulant to another
- To assess compliance
- At the extremes of body weight
- In subjects with prior intestinal surgery where it is unclear if absorption will be affected
- Trough levels may be useful to assess potential accumulation in very elderly patients

Conclusion

- Labs need to be aware of the sensitivity of their local reagent/ analyser to NOAC's and potential for interference with routine and more specialized coagulation tests
- Users need to be aware of NOAC's and the limitations of current information on plasma concentrations and lack of data on dose adjustment and consider when initiating anticoagulation treatment
- In the management of a bleeding patient drug levels are unlikely to influence the initial management; routine coagulation tests may be of some limited value in confirming presence/ absence of drug