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DANISH MEDICINES AGENCY

Feedback from the EMA

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Is There a Role For Pharmacokinetic/Pharmacodynamics Guided Dosing For Novel Anticoagulants?

CSRC Meeting, Washington D.C., December 3, 2015

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Declaration of Interests

- Employment: No interests
- Consultancy: No interests
- Strategic Advisory Role: No interests
- Financial Interests: No interests
- Principal investigator: No interests
- Investigator: No interests

Cover page,
the BMJ,
July 2014

Approved indications in the EU

	Dabigatran etexilate	Riva-roxaban	Apixaban	Edoxaban
Prevention of VTE in patient undergoing hip/knee replacement surgery	X	X	X	
Prevention of stroke and systemic embolism in non-valvular AF	X	X	X	X
Treatment of DVT and PE	X	X	X	X
Prevention of recurrent DVT and PE	X	X	X	X
Prevention of atherothrombotic events after ACS		X		

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Posology in the EU

	Dabigatran etexilate	Riva-roxaban	Apixaban	Edoxaban
Prevention of VTE in patient undergoing hip/knee replacement surgery	220 mg OD or 150 mg OD	10 mg OD	2.5 mg BID	
Prevention of stroke and systemic embolism in non-valvular AF	150 mg BID or 110 mg BID	20 mg OD or 15 mg OD	5 mg BID or 2.5 mg BID	60 mg OD or 30 mg OD
Treatment of DVT and PE	150 mg BID or 110 mg BID	Day 1-21 15 mg BID Day 22- 20 mg OD or 15 mg OD	Day 1-7 10 mg BID Day 8- 5 mg BID	60 mg OD or 30 mg OD
Prevention of recurrent DVT and PE	150 mg BID or 110 mg BID	20 mg OD or 15 mg OD	2.5 mg BID	60 mg OD or 30 mg OD
Prevention of atherothrombotic events after ACS		2.5 mg BID		

OD = once daily, BID = twice daily

Main characteristics

	Dabigatran etexilate	Riva-roxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Key sources of PK variability	Low oral BA, P-gp substrate, predominant renal elimination	P-gp and CYP3A4 substrate, some renal elimination	Moderate (~50%) oral BA, P-gp and CYP3A4 substrate, some renal elimination	Moderate (~62%) oral BA, P-gp substrate, substantial (~50%) renal elimination
Measures of anticoagulant activity	dTT, ECT, aPTT	Calibrated quantitative anti-factor Xa assay	Calibrated quantitative anti-factor Xa assay	Calibrated quantitative anti-factor Xa assay
Antidote available	Idarucizumab	In development	In development	In development

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What is in the current Product Information?
Dabigatran etexilate

Pradaxa does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution (see section 5.1).

Table 2 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding (see section 5.1)

Table 2: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding.

Test (trough value)	Indication	
	pVTEp orthopaedic surgery	SPAF and DVT/PE
dTT [ng/mL]	> 67	> 200
ECT [x-fold upper limit of normal]	No data	> 3
aPTT [x-fold upper limit of normal]	> 1.3	> 2
INR	Should not be performed	Should not be performed

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What is in the current Product Information?
Rivaroxaban, apixaban and edoxaban

Although treatment with [factor X inhibitor] does not require routine monitoring of exposure, [factor X inhibitor] levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of [factor X inhibitor] exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see sections 5.1 and 5.2).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 October 2015
EMA/681537/2015
Human Medicines Evaluation Division

Programme - Workshop on the role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants

23 November 2015 at the European Medicines Agency, 30 Churchill Place, Canary Wharf, London, UK, meeting room 3A

General objectives

At this workshop we will bring together experts and stakeholders to discuss the utility of PK and PD measurements in the clinical use of the direct oral anticoagulants (DOACs). The objectives are to improve the understanding of:

1. Problems related to the use of DOACs in clinical practice, in the overall population of patients, in subgroups of patients at particular risk of bleeding or underexposure, and in patients presenting with a major bleeding or with a need for acute surgery or other invasive interventions
2. Need to further guide clinical decision-making on dose adjustment during routine use, when major bleedings occur, or when the need for acute surgery emerges
3. Recommendations regarding PK and PD measurements that can be implemented based on the current data
4. Gaps in the knowledge on PK and PD measurements of DOACs
5. Analytical methods, their validity, availability in the European Union and current use
6. Priorities in future research in the field of PK/PD measurements of DOACs

Scope

The scope of the workshop is to discuss the current knowledge and clinical experience in the use of the direct oral anticoagulants (DOACs) authorised in the European Union in particular aspects related to measurement of anticoagulant activity in view of available PK and PD data.

The medicinal products currently authorised in the EU are Pradaxa (dabigatran etexilate), Xarelto (rivaroxaban), Eliquis (apixaban) and Lixiana (edoxaban).

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Send a question via our website www.ema.europa.eu/contact

Took place in London, England, on November 23, 2015

EMA Workshop objectives

Improve the understanding of

- Problems related to the use of DOACs in clinical practice
  - in the overall population of patients
  - in subgroups of patients
- Need to further guide clinical decision-making on dose adjustment
  - during routine use
  - when major bleedings occur
  - when the need for acute surgery emerges

EMA Workshop objectives

Improve the understanding of

- Recommendations regarding PK and PD measurements that can be implemented based on the current data
- Gaps in the knowledge on PK and PD measurements of DOACs
- Analytical methods, their validity, availability in the European Union and current use
- Priorities in future research in the field of PK/PD measurements of DOACs

EMA Workshop attended by

- Regulators: EMA and its scientific committees CHMP and PRAC, FDA
- Academia
- Clinicians, other healthcare professional representatives
- Patient representatives
- Pharmaceutical industry representatives

Workshop agenda

Session 1: The oral anticoagulant landscape - setting the scene

- Patient perspective
- Clinician perspective

Session 2: Session 2: What can we do now and what are the gaps in our knowledge?

- The direct thrombin inhibitor (dabigatran etexilate)
- The direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Workshop agenda

Session 3: The analytical part

- The direct thrombin inhibitor (dabigatran etexilate)
- The direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Session 4: Future perspectives. What could be done?

- Academic perspective
- Industry perspective
- Panel discussion

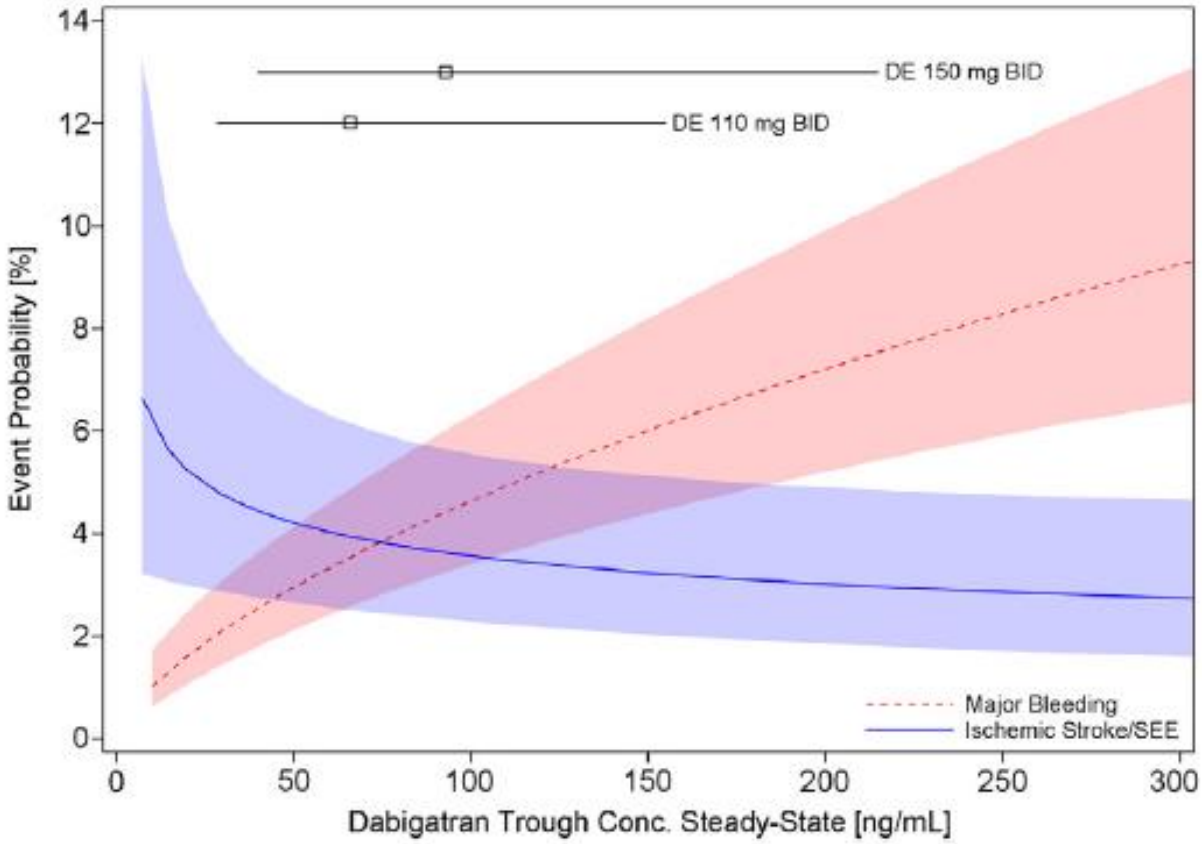
Views expressed at the meeting

- Many patients are worried because a monitoring scheme with NOACs is rarely offered
  - Would my therapy be safer if the extent of anticoagulation would be controlled?
  - Is my anticoagulation within the desired therapeutic range?
- Widespread view that high age, renal impairment, many comorbidities and many co-medications pose challenges with regard to the interplay between thromboembolic risk, bleeding risk and effects and side effects of NOACs
- However, thromboembolic events or major bleedings also occur in seemingly uncomplicated patients treated with NOACs

Views expressed at the meeting

- A wealth of PK/PD data is already available which may/may not allow recommendations for monitoring in routine use
  - It was noted that PK/PD data is available from huge clinical outcome studies with dabigatran etexilate and edoxaban

Graph showed many times during the meeting



- Probability of major bleeding event and ischaemic Stroke/SEE vs. trough plasma concentration of dabigatran

Reilly PA et al. J Am Coll Card. 2014 Feb 4;63(4):321-8

Views expressed at the meeting

- The most widely available coagulation tests are not very useful for NOACs
  - APTT
  - PT
- The best tests lack widespread availability
  - dTT
  - Anti-Xa chromogenic assays
- Criticism was raised about the current wording in the EU Product Information for the NOACs

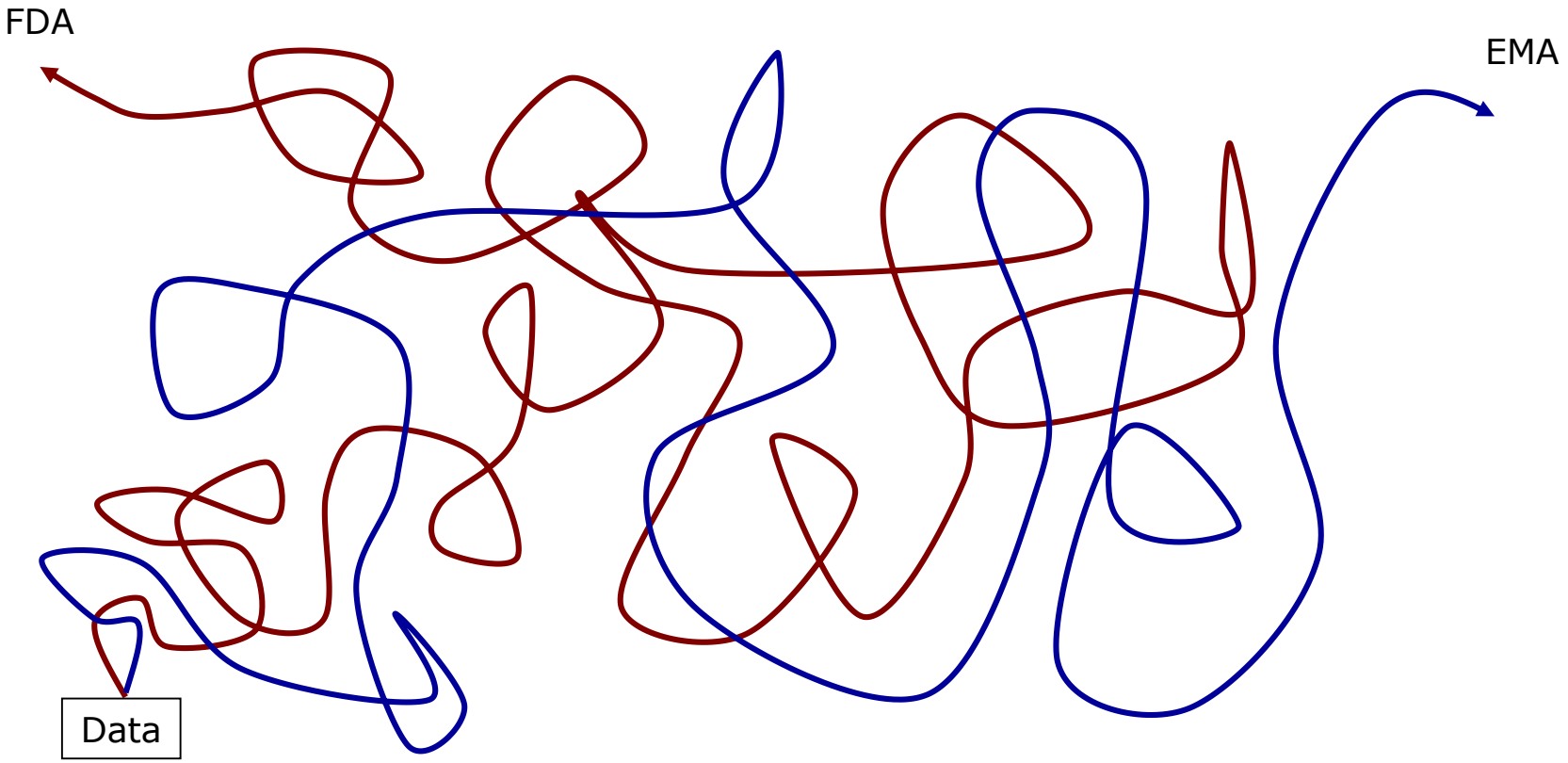
Conclusions of the meeting

- Agreement that tests for anticoagulant activity may be warranted in urgent situations
  - Bleedings
  - Need for urgent surgery or other invasive interventions
- General agreement that the benefit-risk balance was positive for all four NOACs – even without requirements for routine monitoring
- The controversial issue was whether the benefit-risk balance could be further enhanced by implementation of routine monitoring

Conclusions of the meeting

- No clear consensus emerged in terms of recommendations for routine monitoring in non-urgent situations
- On one side, there were scepticism from a number of experts about the utility of monitoring
- One the other side, there were several who felt that it may very well be possible to develop sound recommendations on monitoring based on the currently available data
- Next steps?

Transatlantic harmony



Thank you for your attention