Monitoring of new oral anticoagulants

Jonathan Douxfils, Anne Spinewine, Maximilien Gourdin, Anne-Sophie Dincq, Valérie Mathieux, Sarah Lessire, Christian Chatelain, Bernard Chatelain, François Mullier, Jean-Michel Dogné

March 27th, 2012
Introduction

Monitoring of NOACs
  Why?
    Dabigatran etexilate
    PD properties
    PK properties
  Rivaroxaban
    PD properties
    PK properties
  When?
  How?
    Dabigatran etexilate
    Rivaroxaban

Discussion

Conclusion
Introduction
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- Introduction
- Monitoring of NOACs
  - Why?
    - Dabigatran etexilate
      - PD properties
      - PK properties
    - Rivaroxaban
      - PD properties
      - PK properties
  - When?
  - How?
    - Dabigatran etexilate
    - Rivaroxaban
- Discussion
- Conclusion
The promise of new oral anticoagulants

- Simplified dosing regimen
- No dietary restrictions
- Predictable anticoagulation and no need for routine coagulation monitoring
- Can be given at fixed doses

Reduced potential for food and drug interactions

- Less labour-intensive
- Less impact on patients’ daily life
- Improved compliance
- Improved quality of life
- Improved efficacy and safety
- Reduced administrative costs

Content

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- Conclusion
Monitoring of NOACs

Pradaxa®: dabigatran etexilate
Monitoring of NOACs: Why?
Dabigatran etexilate PD properties

- Dabigatran etexilate
  - Primary pharmacodynamic properties
    - Inhibits:
      - Thrombin: Ki = 4.5nM
      - Fibrin-bound thrombin
      - Thrombin-induced platelet aggregation
    - AT – Independent inhibitor
    - Synthetic, non-peptidic

Adapted from Spyropoulos AC. *Expert Opin Investig Drugs* 2007;16:431–440
Monitoring of NOACs: Why?
Dabigatran etexilate PK properties

- Dabigatran etexilate
  - Pharmacokinetic properties
    - Pro-drug (double esterification)
Monitoring of NOACs: Why?
Dabigatran etexilate PK properties

- Dabigatran etexilate
  - Pharmacokinetic properties

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct IIa inhibitor</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>Yes</td>
</tr>
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<td>Bioavailability (%)</td>
<td>3–7</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>35</td>
</tr>
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<td>Half-life (h)</td>
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<td>Elimination</td>
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</tr>
<tr>
<td>Route of elimination</td>
<td>Urine: ~80%</td>
</tr>
<tr>
<td></td>
<td>Feces: ~20%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Fixed, twice daily</td>
</tr>
<tr>
<td>Substrate of CYP enzymes</td>
<td>No</td>
</tr>
<tr>
<td>Substrate of drug transporters: P-gp</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Low…

⇒ with a very large interindividual variability of PK parameters (C\text{max}, AUC).

⇒ the **inter-individual** variability of C\text{max} and AUC expressed as CV was high i.e. approximately 80%.

⇒ In healthy volunteers the **intra-individual** variability was close to 30%.

E Nutescu et al. ; J Thromb Thrombolysis 2011; 31: 326-343
Monitoring of NOACs: Why?

Dabigatran etexilate PK properties

- Dabigatran etexilate
- Pharmacokinetic properties

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Low...</th>
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<tr>
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⇒ with a very large interindividual variability of PK parameters (Cmax, AUC).

⇒ Risks of underdosage (thrombosis) or overdosage (bleeding)

⇒ Importance of monitoring and individual follow-up

E Nutescu et al.; J Thromb Thrombolysis 2011; 31: 326-343
Monitoring of NOACs: Why?
Dabigatran etexilate PK properties

- Dabigatran etexilate
  - Pharmacokinetic properties

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Moderate renal insufficiency (CrCL between 30 – 50 ml/min): 2.7-fold AUC increase</th>
</tr>
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<td>Route of elimination</td>
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Monitoring of NOACs: Why?

Dabigatran etexilate PK properties

- Dabigatran etexilate
  - Pharmacokinetic properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct IIa inhibitor</td>
</tr>
<tr>
<td>Pro-drug</td>
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<td>Route of elimination</td>
<td>Urine: ~80%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Fixed, twice daily</td>
</tr>
<tr>
<td>Substrate of CYP enzymes</td>
<td>No</td>
</tr>
<tr>
<td>Substrate of drug transporters</td>
<td>P-gp</td>
</tr>
</tbody>
</table>

Severe renal deficiency
(CrCL between 10 – 30 ml/min): 6-fold AUC increase
=> **CONTRAINDICATED**

E Nutescu et al.; J Thromb Thrombolysis 2011; 31: 326-343
Who said no monitoring?

EMA public assessment report (2008):

Pradaxa in the prevention of Venous Thromboembolism (VTE) in patients following elective knee or hip replacement surgery

Conclusion on balance benefit-risk in the indication

“It is important to underline that the PK characteristics of DAB i.e low bioavailability (6.5%) with a very large interindividual variability, the concentration-effect relationship and the bleeding risks strongly suggest that drug monitoring is needed”.

Based on the above balance the benefits associated with the proposed use of DE are considered to outweigh the risks.
Monitoring of NOACs

Xarelto®: rivaroxaban
Monitoring of NOACs: Why? Rivaroxaban PD properties

- Rivaroxaban
  - Primary pharmacodynamic properties
    - Inhibits:
      - FXa: Ki = 0.4 nM
      - Clot-bounds FXa and prothrombinase activity
    - AT – Independent inhibitor
    - Synthetic, non-peptidic

Adapted from Spyropoulos AC. Expert Opin Investig Drugs 2007;16:431–440
Monitoring of NOACs: Why?
Rivaroxaban PK properties

- Rivaroxaban
  - Pharmacokinetic properties
    - Not a pro-drug (opposite to dabigatran etexilate)
Rapidly absorbed: $C_{\text{max}}$ within 2–4 hours of oral administration

Rapidly absorbed without accumulation

Multiple rivaroxaban doses
Healthy volunteers

Monitoring of NOACs: Why?
Rivaroxaban PK properties

- Rivaroxaban
- Pharmacokinetic properties

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct IIa inhibitor</td>
<td>Direct Xa inhibitor</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>3–7</td>
<td>80</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>35</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>14–17</td>
<td>5–9</td>
</tr>
<tr>
<td>Elimination</td>
<td>~100% unchanged drug</td>
<td>~50% unchanged drug</td>
</tr>
<tr>
<td></td>
<td>and active metabolites</td>
<td>50% inactive metabolites</td>
</tr>
<tr>
<td>Route of elimination</td>
<td>Urine: ~80%</td>
<td>Urine: ~70%</td>
</tr>
<tr>
<td></td>
<td>Feces: ~20%</td>
<td>Feces: ~30%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Fixed, twice daily</td>
<td>Fixed, once daily</td>
</tr>
<tr>
<td>Substrate of CYP</td>
<td>No</td>
<td>Yes (CYP3A4, CYP2J2)</td>
</tr>
<tr>
<td>enzymes</td>
<td></td>
<td>Major DI</td>
</tr>
<tr>
<td>Substrate of drug</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>transporters: P-gp</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contraindicated in patient with hepatic disease associated with coagulopathy and an increase of bleeding risks.

Is to be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy.

Risk of hemorrhage.

E Nutescu et al.; J Thromb Thrombolysis 2011; 31: 326-343
Influence of CYP3A4 and P-gp inhibitors on rivaroxaban plasma concentration

<table>
<thead>
<tr>
<th>Rivaroxaban +</th>
<th>CYP3A4 inhibition</th>
<th>P-gp inhibition</th>
<th>AUC x-fold increase</th>
<th>C\text{max} x-fold increase</th>
<th>Clinically relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole 400 mg o.d.</td>
<td>Strong</td>
<td>Strong</td>
<td>2.6</td>
<td>1.7</td>
<td>YES*</td>
</tr>
<tr>
<td>Ritonavir 600 mg b.i.d.</td>
<td>Strong</td>
<td>Strong</td>
<td>2.5</td>
<td>1.6</td>
<td>YES*</td>
</tr>
<tr>
<td>Clarithromycin 500 mg b.i.d.</td>
<td>Strong</td>
<td>Moderate</td>
<td>1.5</td>
<td>1.4</td>
<td>No</td>
</tr>
<tr>
<td>Erythromycin 500 mg t.i.d.</td>
<td>Moderate</td>
<td>Moderate</td>
<td>1.3</td>
<td>1.3</td>
<td>No</td>
</tr>
</tbody>
</table>

*For full details please see the rivaroxaban summary of product characteristics.
Monitoring of NOACs: Why? Rivaroxaban PK properties

**Mild renal impairment:**
(\(\text{Cl}_{\text{Cr}}\) between 50 to 79ml.min\(^{-1}\))
AUC increase by 44%

No recommendation

**Moderate renal impairment:**
(\(\text{Cl}_{\text{Cr}}\) between 30 to 49ml.min\(^{-1}\))
AUC increase by 52%

No recommendation, but **care is to be taken** in patient concomitantly receiving medicinal products which increase rivaroxaban plasma concentration

Is to be used with **caution**

and **not recommended** in patient with \(\text{Cl}_{\text{Cr}}<15\text{mL/min}\)

➔ **Risk of bleeding**
Monitoring

- **Why? Situation at risk?**
  - EMA (SmPC) recommendations:
    - "caution" ➔ what is the meaning?
    - "closely monitor patients for decrease effect of rivaroxaban"
      - Lack of effectiveness is of major concern
      - Risk of thrombosis
      - How to "closely monitor"?
      - What are the risk minimizations?
      - Educational material for HCPs and patients?
Monitoring

- **Opinion of the regulator agencies**

- EMA (CHMP Report EMEA/543519/2008)

  “There is a **need** to develop a **laboratory test for detecting increased exposure** or pharmacodynamic activity. The Applicant has, as a follow-up measure, undertaken to validate modified commercially available tests for estimations of the pharmacodynamic activity of rivaroxaban that could be used in routine clinical setting.”
Monitoring

Why? Situation at risk?
- Interest of biological monitoring of rivaroxaban

- Risk of **overdose**
  - Bleedings

- Risk of **underdose**
  - Lack of effectiveness!!!
  - Thrombosis
Summary

- **Introduction**
- **Monitoring of NOACs**
  - Why?
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      - PD properties
      - PK properties
    - Rivaroxaban
      - PD properties
      - PK properties
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  - How?
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- **Discussion**
- **Conclusion**
Situations requiring a biological monitoring

- Interest of biological monitoring of rivaroxaban

- Clinical trials
  - Safe and protected environment
Situations requiring a biological monitoring

Interest of biological monitoring of rivaroxaban

- Clinical trials
  - Safe and protected environment
  - Monitoring not necessary
Situations requiring a biological monitoring

- Interest of biological monitoring of rivaroxaban

Clinical trials
Safe and protected environment

Monitoring not necessary

Real world…
Situations requiring a biological monitoring

- Interest of biological monitoring of rivaroxaban

Clinical trials
Safe and protected environment

Monitoring not necessary

Real world...

Monitoring to minimize the risks of bleedings and identify non responders (lack of effectiveness)
Monitoring

- When?
  - At the instauration of the treatment
  - In the case of a switch from AVK to rivaroxaban
  - Relapse of thrombosis or stroke
  - Bleedings complications
  - To assess compliance
Summary

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How to monitor?

- APTT: Activated Partial Thromboplastin Time
- PT: Prothrombin Time
- dPT: Dilute Prothrombin Time
- TT: Thrombin Time
- PiCT: Prothrombinase induced Clotting Time
- ECT: Ecarin Clotting Time
- ECA-T: Ecarin Chromogen Assay
- ACT: Activated Clotting Time
- Hemoclot® Thrombin Inhibitor assay (Hyphen BioMed)
- HepTest
- antiXa chromogenic assays (StaChrom and Rotachrom/ Liquid anti Xa)
- Thrombin Generation test (TGT)
- Thromboelastogram (TEG)
Dabigatran etexilate
Dabigatran: APTT

Douxfils J. Mullier F et al. Thrombosis and hemostasis *in press.*
Hemoclot Thrombin Inhibitor ® assay (HTI)

SmPC:

**HTI Ctrough**

If the dTT is used, dabigatran concentrations above 200 ng/ml, measured at trough after 150 mg twice daily dosing (10-16 hours after the previous dose), are associated with an increased risk of bleeding

Douxfils J. Mullier F et al. Thrombosis and hemostasis *in press.*
How to monitor?

- **Dabigatran**
  - aPTT could be used for the monitoring of dabigatran and as screening test for the risk of overdose.
  - because of its higher sensitivity, good reproducibility, excellent linear correlation at all doses, its simplicity of use, and possibilities of automation, HTI should be considered as the gold-standard
Practical approach

- aPTT > cut-off $\rightarrow$ HTI.

- As aPTT and HTI are global assays, it is also necessary for the clinical biologist to know which anticoagulant is administrated to choose the adequate assay with accurate normal ranges.

- Validation in patients receiving Pradaxa®. Indeed, it is currently unknown how coagulation tests are predictive of the bleeding risks.
In patients at high risk of bleeding a reduction in dabigatran dose may be necessary. A diluted Thrombin Time test (dTT) is commercially available and can be used to identify patients at increased risk because of excessive exposure to dabigatran, e.g. when renal function could be impaired [...].
Rivaroxaban
Rivaroxaban: PT

Douxfils J., Mullier F. et al. *In redaction*
Rivaroxaban: Biophen DiXaI

Douxfls J., Mullier F. et al. In redaction
How to monitor?

- Rivaroxaban
  - PT can be used as screening test to assess the risk of bleeding
  - More specific and sensitive assay such as Biophen DiXaI using calibrators should be used to determine correctly the concentration of rivaroxaban in plasma

  - Biophen DiXaI is a specific assay for the measurement of direct factor Xa inhibitors thanks to Tris-EDTA-NaCl buffer at pH 7.85
Practical approach

- PT > cut-off → Biophen DiXaI

- Thanks to Tris-EDTA-NaCl buffer Biophen DiXaI may be used in case of bridging therapy to assess to plasmatic concentration of rivaroxaban since it is insensitive to VKA and heparinoid.

- Validation in patients receiving Xarelto®. Indeed, it is currently unknown how coagulation tests are predictive of the bleeding risks.

Douxfils J. Mullier F et al. Thrombosis and Haemostasis. In redaction
Case report
Summary

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- Monitoring of NOACs
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- Discussion
- Conclusion
Discussion
Discussion

- There is a need for widely available tests, giving rapid informations (without the necessity of calibration curve and control) about the anticoagulation in case of emergency.

- Thus, we propose:
  1. A screening functional test with routinely and widely available coagulation assay (aPTT and PT).
  2. If the value of these coagulation assays exceed a cut-off (to be determined in each lab depending on the reagent used), a confirmation test based on more specific procedure should be performed.
Nevertheless, some points are to be considered: limitations for the interpretations!

- Reagents differences
- No cut-off data (risk of bleeding)
- Importance of standardizing the time between the intake of NOACs and the time of blood collection.
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Conclusion
Biological monitoring

Invited Editorial Focus

Monitoring new oral anticoagulants, managing thrombosis, or both?

Hugo ten Cate¹,²
¹Department of Internal Medicine and Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, the Netherlands; ²Maastricht Anticoagulation Clinic, Maastricht, the Netherlands

Issues with the absence of monitoring:

1. One should not abolish the opportunity to further improve the efficacy and safety of new anticoagulants in practice, e.g. by searching for the optimal dose in the individual patient (tailored medication). This may, eventually, require laboratory based dose adjustment.
Biological monitoring

Invited Editorial Focus

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**Issues with the absence of monitoring:**

2. By not monitoring, there is a risk of losing track of the patient during long-term (often lifelong) treatment. In the majority of patients with AF, there is no need for long-term follow up by the cardiologist, hence continuation of medication is maintained by prescription of the drug by the general practitioner. In the absence of a structured organisation, there will be no routine check on side effects, tolerance and adherence, while it is known that in unmonitored conditions medication adherence levels are not better than 50%.
Biological monitoring

Issues with the absence of monitoring:

3. There are many possible acute situations where one would like to measure the anticoagulant’s effect, by some assay. Such situations involve suspected under- or overdosing, comorbidity, potential interactions interventions like surgery and cardioversion, renal failure (not typically the chronic slow progressive form but also rapid changes in clearance in situations such as dehydration, use of antibiotics etc) and other morbidity that is frequent in the elderly.
Conclusion on monitoring

- At the present time, neither directly measured plasma concentrations nor PT or aPTT prolongation predict bleeding in an individual patient treated with rivaroxaban and dabigatran, respectively.

- There is no rationale (guideline) for changing the timing of administration or the dosing based on laboratory coagulation tests in the routine clinical setting.
Thank you for you attention