Clinical application of Thrombin Generation for new oral anticoagulants

François Mullier, Jonathan Douxfils, Christian Chatelain, Bernard Chatelain, Jean-Michel Dogné

August 2012, 29th
• New oral anticoagulants (NOACs) have been recently approved by the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) for the prevention of thromboembolism in total hip replacement or total knee replacement and to prevent stroke in patients with non-valvular atrial fibrillation.

• The treatment of acute deep-vein thrombosis is an additional indication approved by the EMA (Future: Acute coronary syndrome).

• New oral anticoagulants include anti-IIa agents (dabigatran etexilate) and anti-Xa agents (rivaroxaban, apixaban and edoxaban).
No head-to-head comparisons between apixaban, rivaroxaban and dabigatran have been performed in a randomised clinical trial setting. The information in this table is based on the SmPCs for apixaban, rivaroxaban and dabigatran. Please refer to the SmPCs for further information.

<table>
<thead>
<tr>
<th></th>
<th>Apixaban&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Dabigatran&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct factor Xa inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td><strong>Absolute availability</strong></td>
<td>~50%</td>
<td>80–100%</td>
<td>3-7%</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Pro-drug</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Food effect</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>~27%</td>
<td>~33 %</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Mean half-life (t&lt;sub&gt;1/2&lt;/sub&gt;)</strong></td>
<td>~12 h</td>
<td>7–11 h</td>
<td>14–17 h</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>3-4 h</td>
<td>2–4 h</td>
<td>0.5–2 h</td>
</tr>
</tbody>
</table>
• NOACs do not require monitoring nor frequent dose adjustment.

• However, point measurement may be useful in some situations.
Background: Why is monitoring of dabigatran sometimes required? (I)

- Pro-drug (double esterification)
Low…

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

⇒ the **interindividual** variability of $C_{\text{max}}$ and AUC expressed as CV was high i.e. approximately 80%.

⇒ In healthy volunteers the **intraindividual** variability was close to 30%.
Low…

⇒ 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
**Background: Why is monitoring of dabigatran sometimes required? (IV)**

<table>
<thead>
<tr>
<th>Table: Dabigatran Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
</tr>
<tr>
<td>Pro-drug</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
</tr>
<tr>
<td>Protein binding (%)</td>
</tr>
<tr>
<td>Half-life (h)</td>
</tr>
<tr>
<td>Elimination</td>
</tr>
<tr>
<td>Route of elimination</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Dosing</td>
</tr>
<tr>
<td>Substrate of CYP enzymes</td>
</tr>
<tr>
<td>Substrate of drug transporters: P-gp</td>
</tr>
</tbody>
</table>

**Moderate renal insufficiency** (CrCL between 30 – 50 ml/min): 2.7-fold AUC increase

⇒ Pradaxa should be used with caution

⇒ A **close clinical surveillance** (looking for signs of bleeding or anemia)
### Background: Why is monitoring of dabigatran sometimes required? (V)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct IIa inhibitor</td>
</tr>
<tr>
<td><strong>Pro-drug</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>3–7</td>
</tr>
<tr>
<td><strong>Protein binding (%)</strong></td>
<td>35</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>14–17</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>~100% unchanged drug and active metabolites</td>
</tr>
<tr>
<td><strong>Route of elimination</strong></td>
<td>Urine: ~80%</td>
</tr>
<tr>
<td></td>
<td>Feces: ~20%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Fixed, twice daily</td>
</tr>
<tr>
<td><strong>Substrate of CYP enzymes</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Substrate of drug transporters: P-gp</strong></td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### Severe renal deficiency

(CrCL between 10 – 30 ml/min): 6-fold AUC increase

=> **CONTRAINDICATED**
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.
### Background: Why is monitoring of rivaroxaban sometimes required? (I)

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

**Contraindicated** in patients 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.

ıldığı CYP3A4, CYP2J2 major DI

➤ **Risk of bleedings**

E Nutescu et al. ; J Thromb Thrombolysis 2011; 31: 326-343
Background: Why is monitoring of rivaroxaban sometimes required? (II)

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&lt;sub&gt;max&lt;/sub&gt; 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.
**Background: Why is monitoring or rivaroxaban sometimes required? (III)**

**Mild renal impairment:**  
(\(\text{Cl}_{\text{Cr}}\) between 50 to 79 ml.min\(^{-1}\))  
AUC increase by 44%  
No recommendation

**Moderate renal impairment:**  
(\(\text{Cl}_{\text{Cr}}\) between 30 to 49 ml.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 bleedings**

**Severe renal impairment:**  
(\(\text{Cl}_{\text{Cr}}\) <30 ml.min\(^{-1}\))  
AUC increase by 54%  
Is to be used with **caution**  
and **not recommended** in patient with \(\text{Cl}_{\text{Cr}}<15\text{mL/min}\)  
⇒ **Risk of bleedings**
• **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.”
**Background: Why is monitoring of apixaban sometimes required? (I)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pharmacokinetic (PK) profile of apixaban</th>
<th>Apixaban SmPC recommendation¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal impairment</strong></td>
<td>In individuals with mild, moderate and severe renal impairment, apixaban AUC was increased 16, 29, and 44% respectively, vs. individuals with normal creatinine clearance (CrCl).¹</td>
<td>No dose adjustment necessary in mild (CrCl 51-80 mL/min) or moderate (CrCl 30-50 mL/min) renal impairment. <strong>Caution:</strong> Patients with severe renal impairment (CrCl 15-29 mL/min) <strong>Not recommended:</strong> Patients with CrCl &lt;15 mL/min or in patients undergoing dialysis</td>
</tr>
<tr>
<td><strong>Hepatic impairment</strong></td>
<td>Apixaban exposure was comparable between subjects with mild or moderate hepatic impairment and healthy subjects²</td>
<td><strong>Caution:</strong> patients with mild or moderate hepatic impairment (Child Pugh A or B)</td>
</tr>
</tbody>
</table>

¹EliquisTM SmPC 2011
### Background: Why is monitoring of apixaban sometimes required? (II)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect on CYP3A4</th>
<th>Effect on P-gp</th>
<th>Impact on apixaban $C_{\text{max}}$</th>
<th>Impact on apixaban AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>+++</td>
<td>+++</td>
<td>↓ 42%</td>
<td>↓ 54%</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>- - -</td>
<td>- - -</td>
<td>↑ 1.6-fold</td>
<td>↑ 2-fold</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>- -</td>
<td>-</td>
<td>↑ 1.3-fold</td>
<td>↑ 1.4-fold</td>
</tr>
<tr>
<td>Naproxen</td>
<td>No effect</td>
<td>- -</td>
<td>↑ 1.6-fold</td>
<td>↑ 1.5-fold</td>
</tr>
</tbody>
</table>

**Caution with:**
- **Strong inducers of both CYP3A4 and P-gp**, e.g. rifampicin, phenytoin, carbamazepine, phenobarbital and St. John’s Wort
- **NSAIDS** including aspirin

**Not recommended with:**
- **Strong inhibitors of both CYP3A4 and P-gp** –azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir)

+++ = strong induction  
- - - = strong inhibition  
- - = moderate inhibition  
- = weak inhibition

*Eliquis™ SmPC 2011*
Real world is not as safe and protected as clinical trials...
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.
Issues with the absence of monitoring:

2. By not monitoring, there is a risk of losing track of the patient during long-term (often life-long) 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%.
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-(recurrence) or overdosing (bleeding), 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.

+ bridging, drug interactions, infants, pregnant women or in extreme body weights
The topic of (the lack of) an antidote has recently been highlighted in the *New England Journal of Medicine* in a letter to the editor: http://www.nejm.org/doi/full/10.1056/NEJMc1111095. The letter suggests that patients treated with dabigatran who experience injury/trauma are at increased risk of serious bleedings, including fatal bleedings.
• Recent studies have shown that aPTT, HTI and ECT could be used to monitor dabigatran whereas PT and anti-Xa chromogenic assays could be used to monitor anti-Xa agents, while standardizing the time between the last intake of rivaroxaban and the sampling is mandatory.

• However, their performances varied depending on the reagent.
Background: Dabigatran: APTT

Auspar:
At Ctrough when DAB was given 150mg bid, an aPTT greater than 80 sec is associated with a higher risk of bleeding.

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.

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.

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 [...].
Background: Dabigatran: APTT

- We also proposed cut-off associated with a bleeding or thrombosis risk based on pharmacokinetic studies but further investigation in the field and confirmation are required (aPTT > cut-off → HTI).

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Local normal values</th>
<th>Baseline time</th>
<th>Clotting time corresponding to a sub-therapeutic level in AF at C_{trough} (i.e. 43 ng/ml) (8)†</th>
<th>Clotting time corresponding to a sub-therapeutic level in AF at C_{max} (i.e. 113 ng/ml) (8)†</th>
<th>Clotting time corresponding to mean C_{trough} in AF (i.e. 80 ng/ml) (8)</th>
<th>Clotting Time corresponding to mean C_{max} in AF (i.e. 254 ng/ml) (8)</th>
<th>Clotting time corresponding to a risk a bleeding in AF at C_{trough} (i.e. 200 ng/ml) (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actin FS®</td>
<td>25.8–33.2</td>
<td>30.3</td>
<td>44.4</td>
<td>1.46</td>
<td>51.0</td>
<td>1.68</td>
<td>46.3</td>
</tr>
<tr>
<td>Cephascreen®</td>
<td>N.D.</td>
<td>27.4</td>
<td>33.7</td>
<td>1.23</td>
<td>40.8</td>
<td>1.49</td>
<td>37.5</td>
</tr>
<tr>
<td>CKPrest®</td>
<td>26.7–37.6</td>
<td>30.5</td>
<td>37.6</td>
<td>1.23</td>
<td>45.0</td>
<td>1.48</td>
<td>41.6</td>
</tr>
<tr>
<td>PTT-A®</td>
<td>28.0–39.0</td>
<td>33.2</td>
<td>41.1</td>
<td>1.24</td>
<td>49.5</td>
<td>1.49</td>
<td>45.2</td>
</tr>
<tr>
<td>Synhasil®</td>
<td>25.8–33.2</td>
<td>27.5</td>
<td>34.2</td>
<td>1.24</td>
<td>41.3</td>
<td>1.50</td>
<td>38.0</td>
</tr>
<tr>
<td>Hemoclot Thrombin Inhibitor®</td>
<td>N.D.</td>
<td>33.3</td>
<td>38.5</td>
<td>1.16</td>
<td>45.7</td>
<td>1.37</td>
<td>42.3</td>
</tr>
</tbody>
</table>

† Sub-therapeutic level in AF is defined as mean-2*standard deviation; for C_{trough} and C_{max} (8).
PT can be used as screening test to assess the concentration of rivaroxaban.
More specific and sensitive assay such as Biophen DiXa should be used to determine correctly the concentration of rivaroxaban in plasma.

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

Douxfils J. Mullier F et al. Thrombosis Research. In revision
Background: Rivaroxaban: practical approach

- PT > cut-off $\rightarrow$ Biophen DiXal

- Thanks to Tris-EDTA-NaCl buffer Biophen DiXal may be used in case of bridging therapy to assess the plasmatic concentration of rivaroxaban since it is insensitive to VKA and heparinoid
Classical coagulation assays measure only the initiation phase of the coagulation cascade (i.e. the lag time) but not all new oral anticoagulants act mainly through this way.

In addition, most of these studies have been performed by using spiked normal pooled plasma samples.

Thus inter-individual variation must be investigated with the recommended assays.
• Moreover these results should be validated in patients receiving these NOAC.

• Indeed, it is currently unknown how coagulation tests are predictive of the bleeding risks.
In the early 2000, the thrombin generation (TG) method was introduced by Hemker and coll. as a global assay able to measure the initiation, the propagation, the amplification and the termination of the coagulation assay.
Some years ago, it was shown that the calibrated automated thrombin (CAT) generation test could be used in monitoring unfractionated heparin (UFH) and low molecular weight heparin (LMWH) that it could also be more sensitive than the traditional tests.
• Moreover, procedures to measure TG in whole blood and at the point of care are under development.

• In addition, when antidotes will be available for these new oral anticoagulants, it will be important to have reliable test to confirm whether the anticoagulant effects are persisting in case of bleedings.
Objectives

• To compare traditional coagulation assays with thrombin generation assay to assess the impact of new oral anticoagulants (rivaroxaban, dabigatran, apixaban) on haemostasis.

• To study the impact of dabigatran and rivaroxaban in patients by thrombin generation assay compared to other traditional coagulometric and chromogenic assays.
Material and methods

• Five patients under dabigatran (4 on treatment, 1 initiation) and 5 patients under rivaroxaban (3 on treatment, 2 initiations) for atrial fibrillation were included in this study.

• Blood samples were taken at different intervals: at Ctrough, 2h and 3h after drug administration.

• All the tests were calibrated by spiking rivaroxaban or dabigatran at increasing concentrations in pooled citrated normal human platelet poor plasma (PPP).
Material and methods

- **Rivaroxaban:**
  - Prothrombin Time (PT): Triniclot PT Excel S® and Innovin®,
  - Thrombin Generation Assay (TGA): PPP-Reagent and PPP-Reagent High
  - Biophen Direct Factor-Xa Inhibitor® (DiXal).

- **Dabigatran:**
  - Activated Partial Thromboplastin Time (aPTT): CK-Prest® and Synthasil®
  - Hemoclot Thrombin Inhibitor® (HTI)
  - Thrombin Generation Assay (TGA) using PPP-Reagent and PPP-Reagent Low.
Apixaban:
The pharmacodynamic effect of apixaban among a range of routine (APTT, PT) or specific tests (antiXa assays, thrombin generation assay) will also be presented.
Results: rivaroxaban: comparison in vitro-ex vivo

As PT is a global assay, there is some limitation with concentration determination based on NPP calibration.
• The PPP-reagent Low does not allow resolving TGA profiles with different rivaroxaban concentrations. Consequently, PPP-Reagent and PPP-Reagent High were only tested ex vivo.

• The low sensitivity of the lag time explains the lack of sensitivity of PT, even with the more sensitive reagent (i.e. Triniclot PT Excel S®).
Results: rivaroxaban

- The Peak and mVRI were the most sensitive CAT parameters with a high sensitivity:
  - Peak IC50: 3ng/mL (PPP-Reagent Low and PPP-Reagent)
    14ng/mL with PPP-Reagent High;
  - mVRI IC50: 1ng/mL (PPP-Reagent Low and PPP-Reagent)
    3ng/mL (PPP-Reagent High)

- Both reagent showed a low variability (CV<1.0%).
Impact of rivaroxaban on the different CAT parameters using PPP-Reagent and comparison with the plasma drug concentration in patients with non-valvular atrial fibrillation
Impact of rivaroxaban on the different CAT parameters using PPP-Reagent-high and comparison with the plasma drug concentration in patients with non-valvular atrial fibrillation
The 5 patients have the same time-dependent profile with interindividual variations in concentration and TGT parameters.
Results: rivaroxaban: PPP-reagent

Similar profile for similar rivaroxaban concentrations?
Results: rivaroxaban: PPP-reagent-High

The 5 patients have the same time-dependent profile with interindividual variations in concentration and TGT parameters.

- Patient 1: Initiation of the treatment
- Patient 2: On treatment: Steady state
- Patient 3: Initiation of the treatment
- Patient 4: On treatment: Steady state
- Patient 5: On treatment: Steady state
Results: rivaroxaban: PPP-reagent-High

Similar profile for similar rivaroxaban concentrations?
• Similar concentrations of rivaroxaban in different patients provided with Biophen DiXal® are associated with small differences in TGA profile.

• Therefore, Biophen DiXal® and TGA should be compared to propose cut-off associated with a bleeding or thrombosis risk.

• This illustrates the interest to have tests able to evaluate the entire thrombin generation process to propose cut-off associated with a bleeding or thrombosis risk.
• The PPP-reagent High is less sensitive in comparison to PPP-Reagent and PPP-Reagent Low.

• Dabigatran mainly delayed the initiation phase with a strong dose-dependent increase of lag time and Tmax and a slight dose-dependent decrease of Cmax, ETP and mVRI.
Impact of dabigatran on the different CAT parameters using PPP-Reagent and comparison with the plasma drug concentration in patients with non-valvular atrial fibrillation.
Results: dabigatran: PPP-reagent-low

The concentration in dabigatran needed to double the lag time was 70 ng/mL.

Absence of correlation!

Impact of dabigatran on the different CAT parameters using PPP-Reagent-low and comparison with the plasma drug concentration in patients with non-valvular atrial fibrillation.
Results: dabigatran: PPP-reagent

The 5 patients have different time-dependent profile with interindividual variations in concentration and TGT parameters.
Results: dabigatran: PPP-reagent

Different profile for similar dabigatran concentrations
The 5 patients have different time-dependent profile with interindividual variations in concentration and TGT parameters.

PPP-reagent is the most useful reagent (PPP-reagent LOW is associated with lack of resolution).
Results: dabigatran: PPP-reagent LOW

Different profiles for similar dabigatran concentrations
Results: Ex vivo: dabigatran

- As the lag time is the most sensitive parameter, this could decrease the interest of TGA to detect over or underdosage.

- Similar concentrations of dabigatran in different patients provided with HTI are associated with differences in TGA profile.

- This illustrates the interest to have tests able to evaluate the entire thrombin generation process to propose cut-off in one or more parameters associated with a bleeding or thrombosis risk.
Results: Apixaban: PT

In contrast with rivaroxaban, PT is practically not influenced by apixaban.

The sensitivity is not strong enough to allow quantitative measurement of plasma apixaban concentration.
Results: Apixaban: aPTT

aPTT is very slightly influenced but the relation is curvilinear and showed a plateau from 100ng/mL.

The sensitivity is not strong enough to allow quantitative measurement of plasma apixaban concentration.
Results: Apixaban: antiXa chromogenic assays

Chromogenic anti-Xa assays were very sensitive to apixaban depending on the reagent and the methodology. Thus, for the routine lab measurement, chromogenic anti-Xa seemed to be the best assays to perform a quantitative measurement of plasma drug concentration.
Results: Apixaban: Thrombin generation assay

As for rivaroxaban, the most influenced TGA parameters are the peak and the mVRI.

The sensitivity depends on the reagent: PPP-Reagent Low and PPP-Reagent are the most sensitive reagents.
Results: Apixaban: Thrombin generation assay

As for rivaroxaban, the most influenced TGA parameters are the peak and the mVRI.

The sensitivity depends on the reagent: PPP-Reagent Low and PPP-Reagent are the most sensitive reagents.
Results: Apixaban: Thrombin generation assay

Tailoring effect for high apixaban concentrations with PPP-reagent LOW

→ Lack of resolution in high apixaban concentrations with PPP-Reagent Low
Conclusions:

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

• Thrombin generation assay could be superior to traditional coagulometric and chromogenic assays to monitor new oral anticoagulants in terms of prediction of bleeding or thrombosis risk.
Thank you for your attention
Thank you....

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