How do I prevent massive bleeding due to new oral anticoagulants?

Mullier François

Expert meeting « Severe bleeding »
Brussels,
28 November 2013
## Disclosures of François Mullier

<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
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<tr>
<td>Employment</td>
<td>No conflict of interest to disclose</td>
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<td>Research support</td>
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<td>Scientific advisory board</td>
<td>No conflict of interest to disclose</td>
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<tr>
<td>Consultancy</td>
<td>No conflict of interest to disclose</td>
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<tr>
<td>Speakers bureau</td>
<td>Speakers fees from Bayer Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb and Sanofi Aventis</td>
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<tr>
<td>Major stockholder</td>
<td>No conflict of interest to disclose</td>
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<td>Patents</td>
<td>No conflict of interest to disclose</td>
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<td>Honoraria</td>
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<tr>
<td>Travel support</td>
<td>No conflict of interest to disclose</td>
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<td>Other</td>
<td>No conflict of interest to disclose</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: N/A

This presentation is not sponsored by any company.
NOACs indications

- Pulmonary embolism (PE)
  - 500,000 deaths per year in Europe
- Deep venous thrombosis (DVT)
  - 1 event every 12 seconds
- Elective hip replacement surgery
  - DVT risk: 42–57%
- Elective knee replacement surgery
  - DVT risk: 41–85%

Ischemic Stroke
15% due to atrial fibrillation

SPAFe

Unstable angina and myocardial infarction
1 death every 17 seconds

ACS
Rates of major bleeding in NVAF

- In comparison to warfarin:
  - Dabigatran etexilate, rivaroxaban and apixaban are associated with a decreased risk of intracranial haemorrhage,
  - Apixaban and dabigatran etexilate (110 mg twice daily) are associated with a decreased risk of major bleeding into any site.
  - Dabigatran etexilate, rivaroxaban and apixaban are associated with an increased risk of major GI bleeding

Clinical trials are different from real life

Clinical trials

Real Life
Clinical trials are different from real life

- Carefully controlled
- Careful patient selection
- Translation into clinical practice?
- Postmarketing registers currently recruiting
- Safety in clinical practice: limited data with reporting bias
- Major bleeding rates in clinical practice do not exceed the rates reported in the pivotal trials

EMA 2013
Southworth MR NEJM 2013
Comparion of clinical trials is difficult

- Patients may differ in biographic, renal function, exclusion criteria and additional risk factors

- Open (RE-LY) or double blind design (ROCKET AF, ARISTOTLE) with warfarin

- Time in therapeutic range (TTR) of INR values,

- Differences in the reporting of the defined endpoints, in particular for the bleeding events \(\rightarrow\) bias that may influence the result of the meta-analysis.

# Pharmacology of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor IIa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Tmax (h)</strong></td>
<td>1.5 - 3.0</td>
<td>2.0 - 4.0</td>
<td>3.0 - 4.0</td>
</tr>
<tr>
<td><strong>Distribution volume (L)</strong></td>
<td>60 – 70</td>
<td>± 50</td>
<td>23</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>dabigatran etexilate: 3 - 7 %, pH sensitive</td>
<td>80 - 100 %: 10mg 66%: 15 - 20mg under fasting conditions</td>
<td>± 50%</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>35%</td>
<td>&gt;90%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation</td>
<td>CYP-dependent and independent mechanism</td>
<td>CYP-dependent mechanism</td>
</tr>
<tr>
<td><strong>Active metabolites</strong></td>
<td>Yes - glucuronide conjugates</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% renal</td>
<td>33% unchanged via the kidney</td>
<td>25% renal</td>
</tr>
<tr>
<td></td>
<td>20% bile (glucuronide conjugation)</td>
<td>66% metabolized in the liver into inactive metabolites then eliminated via the kidney or the colon in an approximate 50% ratio</td>
<td>75% through the kidney while the residue is excreted by the hepatobiliary route in the feces</td>
</tr>
<tr>
<td><strong>Effects of food</strong></td>
<td>Tmax delayed; Cmax &amp; AUC unchanged</td>
<td>Tmax delayed; Cmax &amp; AUC increased (76% and 30 - 40%, respectively)</td>
<td>Tmax delayed; Cmax &amp; AUC unchanged</td>
</tr>
<tr>
<td><strong>CYP substrate</strong></td>
<td>No</td>
<td>CYP3A4, CYP2J2</td>
<td>CYP3A4/5, 1A2, 2C8, 2C9; 2C19</td>
</tr>
<tr>
<td><strong>P-gp substrate</strong></td>
<td>dabigatran etexilate: Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Drug interactions: dabigatran

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa® (dabigatran étexilate)</th>
<th>Xarelto® (rivaroxaban)</th>
<th>Eliquis® (apixaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP</td>
<td>✗</td>
<td>✓ 3A4, 2J2</td>
<td>✓ 3A4/5, 1A2, 2J2</td>
</tr>
<tr>
<td>P-gp</td>
<td>✓ P-gp</td>
<td>✓ P-gp</td>
<td>✓ P-gp</td>
</tr>
</tbody>
</table>

### Dose Adjustment
- **P VTE post TKR/THR:** max 150mg/d (2 comp 75mg)
- **P stroke and systemic embolism in AF:** max 220mg/d (1 comp 110mg 2x)
  - Maximum increase: verapamil given 1 h before DE
  - Virtually no effect when DE given 2 h before verapamil.

### Strong P-gp inhibitor
- **Cl**
  - Ketoconazole
  - Itraconazole
  - Dronédarone
  - Cyclosporine
  - Tacrolimus

### Moderate P-gp inhibitor
- **Caution!**
  - Amiodarone
  - Verapamil
  - Quinidine
  - Clarithromycin

## + PD interactions
- AAS
- Clopidogrel
- NSAID
- SSRI and SNERI
- UFH
- LMWH
- CI
- VKA
- Anti-Xa
- Treatments that may influence hemostasis

Prevention of major bleeding in patients receiving DOACs

• It is likely that preventive strategies can significantly reduce the incidence rate of DOAC-related major bleeding.

• The following strategies will be discussed:
  - Improvement of appropriateness of prescription
  - Improvement of drug adherence (to avoid thrombosis recurrence)
  - How to deal with a missed dose?
  - Identification of modifiable bleeding risk factors
  - Improvement of individual benefit-risk by tailoring dose
  - Adherence to switching procedures
  - Adherence to bridging procedures
  - Adherence to anesthesia recommendations
Improvement of appropriateness of prescription

- The off-label use of DOACs (outside of appropriate indications or at inappropriate doses) can induce supra-therapeutic anticoagulation, and this may be associated with an increased risk of severe or even fatal bleeding.

- Therefore, it is important to adhere to the appropriate indications and drug dosing.

- Drug dosing and drug regimen
- Indication
- *Choice of the anticoagulant depending on the bleeding history or the renal function? No consensus*
Drug dosing and drug regimen

- Multiple dose regimens can lead to prescribing and administration errors.

- Several cases of severe bleedings (often leading to death) in older patients taking dabigatran.

- Renal failure: most recurrent risk factor.

- Renal function should be reassessed prior initiation and during treatment with Pradaxa® if clinically indicated (fluctuating renal function, dehydration, diuretic use, hypovolemia).

Pfeilschifter W Cerebrovasc Dis. 2013
Renal function

• Use of Cockcroft-Gault equation in clinical trials for NVAF

• Use of MDRD leads to surestimation of renal function at lower levels.

Hellden A et al. BMJ Open 2013
MacCallum and coll., BMJ Open. 2013
Renal function

• Thus, many elderly patients with AF would either incorrectly become eligible for them or would receive a too high a dose.

• Regulatory authorities and drug companies should therefore alert physicians of the need to use the Cockcroft-Gault formula to calculate eligibility for and dosing of the DOACs in elderly patients with AF and not rely on the MDRD-derived eGFR
Indication

- Off-label use is frequent (between 8 and 43.5%).

- Ex: treatment of venous thromboembolism, >80 years, patients with liver or kidney disease, patients with previous bleeding for dabigatran

- There is no consensus on the definition of the NVAF, which could partly explain an off-label-use in some patients.

Administration mode: feeding tubes

Pradaxa® (dabigatran etexilate)

\[ F = 3-7\% \]

The opening of capsules \( \uparrow \) \( F \) (bioavailability) of 75% with \( \uparrow \) of bleeding risk

Xarelto® (rivaroxaban)

\[ F=80-100\% \ (2,5-10mg), 66\% \ (15-20mg) \]

\( \rightarrow \) with applesauce
\( \rightarrow \) in suspension (water)

✓ Administration by nasogastric tube and gastrostomy

Gastrostomy and Jejunostomy

US Xarelto® Prescribing Information
How to deal with a missed dose?

**Pradaxa®** (dabigatran etexilate)

If < 6h → take the forgotten capsule immediately
If > 6h → do not take the forgotten capsule and go on with the treatment

In AF, never take a double dose at the same time of the day!

**Xarelto®** (rivaroxaban)

AF and P2 VTE
If < 12h → take the forgotten capsule immediately
If > 12h → do not take the forgotten capsule and go on with the treatment

Never take a double dose at the same time of the day!

**Eliquis®** (apixaban)

Trt VTE
Take the forgotten capsule immediately and go on with the treatment

Take the forgotten capsule immediately. Possibility to take simultaneously 2 capsules of 15mg to ensure 30mg/d.
Identification of modifiable bleeding risk factors

- Will help ascertain and manage the risk of major bleeding.
- HAS-BLED score:
  - $\geq 3 \rightarrow$ high risk for hemorrhage $\rightarrow$ correction of modifiable risk factors
  - debate: Usefulness to predict any clinically relevant bleeding
- Age-appropriate colon cancer screening is advisable before initiation of DOAC.
- Dabigatran etexilate:
  - renal protective strategies
  - patient must be alerted that concurrent medications (e.g. NSAIDs) or clinical co-morbidity (e.g. dehydration) may cause a deterioration in renal function and hence increase and prolong dabigatran anticoagulant effect.

Burgess S J Thromb Haemost 2013
Apostolakis S JACC 2012
Identification of modifiable bleeding risk factors

- New contraindication for all NOACs since September 2013

- Lesion or condition, if considered to be a significant risk for major bleeding.

- This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
Improvement of individual benefit-risk by tailoring dose: Why?

- >90th percentile of DOAC at Ctrough → risk of bleeding (AF dabigatran 150mg bid → 200ng/ml)
- Correlation between bleeding outcomes and dabigatran plasma concentrations.
- Individual benefit-risk might be improved by tailoring dabigatran dose

Reilly PA and coll, JACC 2013
EMA SPC 2013
Point measurement: Why?

- Phase IV studies have clearly shown that there is significant interindividual variability in drug concentration when the same dosage is used in a group of patients such that while the majority of patients will obtain an adequate plasma level, a measurable proportion will either achieve an insufficient, or a supra-therapeutic drug level, when given a fixed dose.

- One should not abolish the opportunity to further improve the efficacy and safety of DOACs in practice.

- By not monitoring, there is a risk of losing track of the patient during long-term (often life-long) treatment. 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%.

Freyburger et al., 2011
Mani et al., 2013
Samama et al., 2013a.
Ten Cate H. Thromb Haemost 2012
Liesenfeld KH, J Thromb Haemost. 2011
Point measurement: When?

• Before urgent surgery or procedure (with last administration in the last 24h or more if CLCR < 50ml/min)
• Before fibrinolytic therapy of acute ischaemic stroke.
• In case of bridging therapy
• Patients not eligible for inclusion in the clinical trials (patients at extremes of body weight (<50-60kg and >110-120kg), and/or with kidney ((rivaroxaban: 30 ml/min (trial) → 15ml/min (indication), apixaban (25ml/min (trial)→15ml/min (indication) ) or liver impairment).

Faxon DP and coll. Thromb Haemost. 2011
Samama MM and coll. Drug Development Research 2013
Turpie Thromb Haemost 2012
Point measurement: When?

- In patients with multiple risk factors for DOACs accumulation (i.e. patients older than 75 years, drug-drug interactions as with frequently used medication like amiodarone and verapamil)
- In patients with renal impairment (in case of progressive decrease of renal function but also in acute decrease during dehydration, antibiotics administration, ...)
- Patients with a high bleeding risk.
- Control of laboratory tests in patients receiving a reversal treatment.
- Control of patient compliance.
- Suspected overdose.

Faxon DP and coll. Thromb Haemost. 2011
Samama MM and coll. Drug Development Research 2013
Turpie Thromb Haemost 2012
Point measurement: How?

- Influence on a wide range of coagulation assays.

- Assays should be easily available, easily done and should give a result within 30-60 min.

- Interpretation: anticoagulant, dose, time between the last dose and sampling ($C_{\text{max}} \sim 2-4$ hours and $C_{\text{through}}$ before the next ingestion)
Point measurement: How?

Variable sensitivity of the reagents

Dabigatran  Rivaroxaban  Apixaban

Point measurement: How?

Dabigatran: same schedule with the following modifications
Screening test → APTT (qualitative)
Confirm test → Dilute thrombin time or ecarin chromogenic assay (quantitative)
Apixaban: PT not sensitive → only anti-Xa assays
Point measurement: How? (similar schedule for rivaroxaban)

Adherence to switching procedures

Dabigatran etexilate

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Start times recommenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>From VKAs to dabigatran</td>
<td>Discontinue VKA and start dabigatran when INR &lt;2</td>
</tr>
</tbody>
</table>
| From dabigatran to VKAs\(^a\) | Start times for VKAs are based on renal function:  
  - If CrCL ≥50 ml/min, start VKA 3 days before stopping dabigatran  
  - If CrCL ≥30 to <50 ml/min, start VKA 2 days before stopping dabigatran  
  - If CrCL 15–30 ml/min, start VKA 1 day before stopping dabigatran\(^b\) |
| From dabigatran to parenteral | Start parenteral anticoagulant 12 h after last dose of dabigatran |
| From parenteral to dabigatran | Start dabigatran at the same time or up to 2 hours before the next parenteral drug dose. For continuous infusions of parenteral drugs, start dabigatran at the time of discontinuation of the continuous infusion. |

\(^a\) Because dabigatran may contribute to an elevated INR, the INR will better reflect the effect of the VKA after dabigatran has been stopped for at least 2 days; \(^b\) Applies to patients treated in the US and for patients in whom the CrCL drops below 30 ml/min. CrCL, Creatinine clearance; h, hours; INR, International normalised ratio; VKA, vitamin K antagonists.

Menno V. Huisman et al., Thromb Haemost, 2012;107:838-47
Adherence to bridging procedures: timing of discontinuation

Dabigatran etexilate

<table>
<thead>
<tr>
<th>Renal function (creatinine clearance in mL/min)</th>
<th>Half-life (hours)</th>
<th>Timing of discontinuation of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>13 (11-22)</td>
<td>1 - 1.5 days</td>
</tr>
<tr>
<td>&gt;50 to ≥80</td>
<td>15 (12-34)</td>
<td>2 - 3 days</td>
</tr>
<tr>
<td>&gt;30 to ≤50</td>
<td>18 (13-23)</td>
<td>1 - 2 days</td>
</tr>
<tr>
<td>≤30*</td>
<td>27 (22-35)</td>
<td>1.5 - 2 days</td>
</tr>
</tbody>
</table>

For patients at high risk of bleeding, aPTT or Hemoclot should be performed the day before surgery. A normal result, as defined by the local laboratory, indicates no clinically significant dabigatran effect.

Post-Procedure
- Consider rapid onset of action (1.5 hours) when restarting dabigatran
- Consider prophylaxis against venous thromboembolism until hemostasis is established to the point where full dose treatment can be resumed

*In some countries, dabigatran is contraindicated in patients with creatinine clearance <30 mL/min

Figure 2. Proposed algorithm for periprocedural management of dabigatran.

Importance of common guidances within a hospital

Adherence to bridging procedures: bridging or no bridging

Adherence to bridging procedures: timing of resumption

### Table 5. Postoperative resumption of new oral anticoagulants: a suggested management approach

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low bleeding risk surgery</th>
<th>High bleeding risk surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Resume on day after surgery (24 h postoperative), 150 mg twice daily</td>
<td>Resume 2-3 days after surgery (48-72 h postoperative), 150 mg twice daily*</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Resume on day after surgery (24 h postoperative), 20 mg once daily</td>
<td>Resume 2-3 days after surgery (48-72 h postoperative), 20 mg once daily†</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Resume on day after surgery (24 h postoperative), 5 mg twice daily</td>
<td>Resume 2-3 days after surgery (48-72 h postoperative), 5 mg twice daily†</td>
</tr>
</tbody>
</table>

*For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran (eg, 110-150 mg once daily) on the evening after surgery and on the following day (first postoperative day) after surgery.
†Consider a reduced dose (ie, rivaroxaban 10 mg once a day or apixaban 2.5 mg twice a day) in patients at high risk for thromboembolism.
Adherence to anesthesia recommendations

- Neuraxial anesthesia → risk of hematoma and long-term paralysis
  → requires close and frequent monitoring for potential neurologic impairment

- Anticoagulation should be restarted after 8 h minus the time to reach maximum activity (Tmax) (8h: time to establish a stable clot)

Rosencher. Anesthesia 2007
Adherence to anesthesia recommendations

<table>
<thead>
<tr>
<th>Table 3. Recommendations for Novel Anticoagulants for Venous Thromboembolic Prophylaxis in the Setting of Peridural/Regional Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 3. Recommendations for Novel Anticoagulants for Venous Thromboembolic Prophylaxis in the Setting of Peridural/Regional Anesthesia</strong></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
</tr>
<tr>
<td>Time between epidural anesthetic technique and next anticoagulant dose</td>
</tr>
<tr>
<td>Time before last anticoagulant dose and epidural catheter removal</td>
</tr>
<tr>
<td>Time between removal of epidural catheter and next anticoagulant dose</td>
</tr>
</tbody>
</table>

* Dabigatran in not recommended in patients undergoing anesthesia with postoperative indwelling catheters. NR = not recommended.

In the presence of neuraxial blockade:
- Extreme caution with the use of rivaroxaban/apixaban (Class IIb, level C)
- The manufacturer advises against the use of dabigatran (Class III, level C)

Gogarten and coll. Eur J Anesthesiol 2010 (ESA recommendations)
Levy and coll. Anesthesiology 2013
Absence of antidote

- Reinforces the importance of setting strategies to prevent massive bleeding.

- In large RCTs, number of fatal bleedings similar between DOACs and warfarin groups, unlike absence of antidote for DOACs.
EMA position Rivaroxaban

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states

The Member States shall ensure that the following conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

- The MAH shall provide an educational pack targeting all physicians who are expected to prescribe/use Xarelto prior to the launch of the new indication for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.
- The MAH shall provide an educational pack targeting all physicians who are expected to prescribe/use Xarelto prior to the launch of the new indication for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.
- The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Xarelto and providing guidance on how to manage that risk.
- The content and format of the educational material, together with a communication plan, should be agreed with the MAH prior to distribution of the educational pack and launch of the new indication.
- The physician educational pack should contain:
  - The Summary of Product Characteristics
  - Prescriber Guide
  - Patient Alert Cards
- The Prescriber Guide should contain the following key safety messages:
  - Details of populations potentially at higher risk of bleeding
  - Recommendations for dose reduction in at risk populations
  - Guidance regarding switching from or to rivaroxaban treatment
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Management of overdose situations
  - The use of coagulation tests and their interpretation
  - That all patients should be provided with a Patient alert card and be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance
    - The need for intake of the 15 mg and 20 mg tablets with food
    - Necessity to carry the Patient alert card with them at all times
    - The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.
- The Patient alert card should contain the following key safety messages:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Necessity to carry the Patient alert card with them at all times
  - The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.

Last updated 08/02/2012
Conclusions: Consensus

- DOACs are indisputably an important step in the field of anticoagulation

- However, an inappropriate use can possibly lead to a higher risk of bleeding.

- This highlights the importance of strengthening education of health care professionals and patients

- Modifiable bleeding risk factors should also be screened and reviewed before initiation of DOACs (Has-bled: no consensus).
Conclusions: No Consensus

- Individual benefit-risk might be improved by tailoring dose following coagulation monitoring in some clinical settings or patient subpopulations.
Acknowledgments