UNDERSTANDING THE VALUE OF DOAC MEASUREMENT TO OPTIMISE TREATMENT

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Dr. Anne-Laure Sennesael (UCLouvain)
HOW DO YOU FEEL ABOUT DOAC MEASUREMENT?

- I think it is completely useless.
- I think it could be of interest, but I don’t know how to perform and interpret DOAC measurement.
- I feel comfortable with DOAC laboratory assays.
86-year-old woman (weight 55 kg)

ADMISSION TO THE EMERGENCY DEPARTMENT WITH PERSISTENT EPISTAXIS
HB 8g/dL, CREATININE CLEARANCE 21 ML/MIN

Medical history
Atrial fibrillation
Peripheral arterial disease
Bioprosthetic heart valve
Heart failure
Hypertension
Urinary catheter

Medication history
Aspirin 80 mg OD
Bumetanide 5 mg 0.5 tablet OD
Bisoprolol 2.5 mg OD
Spironolactone 25 mg OD
Perindopril 4 mg OD
Tamsulosin 0.4 mg OD
Rivaroxaban 20 mg 0.5 tablet OD*
Calcium carb. 1.25 g OD
Lorazepam 1 mg OD

ROUTINE COAGULATION ASSAYS
aPTT 42.4 sec (Nl: 26-38)
PT 35.1 sec (Nl: 11-14)
INR 3.4
TT 17 sec (Nl: 14-21)

SPECIFIC ASSAY
323 ng/ml 4h after the last rivaroxaban intake

* The patient had been halving her rivaroxaban tablet intake for 2 months because of recurrent nosebleeds.
THE VALUE OF DOAC MEASUREMENT
DOAC have a predictable dose response. They are given in a fixed-dose regimen.

BUT inter-individual variability in DOAC levels has been described...

DOAC trough concentrations observed in phase 3 trials

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran*</th>
<th>Apixaban**</th>
<th>Rivaroxaban**</th>
<th>Edoxaban*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke prevention in NVAF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg BID</td>
<td>5 mg BID</td>
<td>20 mg OD</td>
<td>60 mg OD</td>
<td></td>
</tr>
<tr>
<td>61-143 ng/ml</td>
<td>41-230 ng/ml</td>
<td>12-137 ng/ml</td>
<td>19-62 ng/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment and secondary prevention of VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg BID</td>
<td>5 mg BID</td>
<td>20 mg OD</td>
<td>60 mg OD</td>
<td></td>
</tr>
<tr>
<td>61-143 ng/ml</td>
<td>22-177 ng/ml</td>
<td>6-87 ng/ml</td>
<td>10-39 ng/ml</td>
<td></td>
</tr>
</tbody>
</table>

BID: twice-daily, NVAF: non-valvular atrial fibrillation, OD: once-daily, VTE: venous thromboembolism
* 25-75<sup>th</sup> percentiles, ** 5-95<sup>th</sup> percentiles
THE VALUE OF DOAC MEASUREMENT

68 older patients (≥ 75 years)

**Pradaxa® (dabigatran etexilate) for atrial fibrillation**

Plasma concentrations at steady-state

- **PEAK**: 9 to 720 ng/ml
- **TROUGH**: 2 to 594 ng/ml

**RIVAROXABAN**

- (n = 94)
- 20 mg OD
- 15 mg OD

**APIXABAN**

- (n = 149)
- 5 mg BID
- 2.5 mg BID

Risk factors

- **OLDER AGE**
- **LOW WEIGHT**
- **RENAL FAILURE**

Chaussade et al, J Nutr Health Aging. 2018; Gulilat et al, Can J Cardiol. 2017
Correlation with clinical outcomes – 2ary analyses of phase 3 studies

Dabigatran concentrations of **210 ng/ml** at trough **DOUBLED** the risk of major bleeding compared with median trough levels of **88 ng/ml**.

THE VALUE OF DOAC MEASUREMENT

Correlation with clinical outcomes – real-life studies

565 NVAF patients in 4 anticoagulation clinics

- 208 apixaban, 185 dabigatran, 172 rivaroxaban

DOAC levels within 15-25 days after the start of treatment

1-year follow-up

✓ Thrombotic events occurred in 10 patients with LOWER trough anticoagulant levels.

✓ Bleeding events were more frequent among patients with HIGHER peak anticoagulant levels.

Testa et al, J Thromb Haemost 2018; Testa et al, J Thromb Haemost 2019
Optimal plasma concentrations vary with clinical characteristics (age and renal function).

Alternative approach to interpret DOAC measurement: comparison to the «ON-THERAPY» range described in large clinical trials

Eikelboom et al, JAMA cardiology, 2017
DOAC have a predictable dose response. They do not require CLOSE therapeutic monitoring.

BUT measurement of the anticoagulant intensity remains useful in common clinical situations...

Urgent Need to Measure Effects of Direct Oral Anticoagulants
Jeffrey I. Weitz and John W. Eikelboom

*Circulation, 2016;134:186-188*

doi: 10.1161/CIRCULATIONAHA.116.022307

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539
DOAC have a predictable dose response. They do not require **CLOSE** therapeutic monitoring.

**BUT measurement of the anticoagulant intensity remains useful in common clinical situations...**

**BLEEDING**
- DOAC contribution?
- Specific reversal agents?

**STROKE**
- Therapeutic failure?
- Thrombolysis?

**INVASIVE PROCEDURE**
- Significant DOAC levels?
- Specific reversal agents?

**MODIFIED PK**
- Drug accumulation?
- Therapeutic failure?

*Risk factors:* Extreme body weight, renal impairment, drug interactions
THE VALUE OF DOAC MEASUREMENT

BLEEDING

“Measurement of anticoagulant activity is a key step in the evaluation.”

2017 ACC EXPERT CONSENSUS

“Both routine coagulation tests and assays that specifically measure plasma levels of NOACs are important pillars in the assessment of NOAC related bleeding.”

2018 EHRA PRACTICAL GUIDE

452 DOAC patients admitted for severe bleeding

<table>
<thead>
<tr>
<th>Plasma concentration of DOACs</th>
<th>Dabigatran (n = 207)</th>
<th>Rivaroxaban (n = 472)</th>
<th>Apixaban (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>123 (59)</td>
<td>285 (60)</td>
<td>34 (64)</td>
</tr>
<tr>
<td>Median (range), ng/ml</td>
<td>162 (3–3,500)</td>
<td>124 (0–1,245)</td>
<td>111 (18–537)</td>
</tr>
</tbody>
</table>

ACUTE MANAGEMENT

SUBSEQUENT REEVALUATION OF ANTICOAGULATION THERAPY!

Steffel et al, Eur Heart J. 2018; Tomaselli et al, J Am Coll Cardiol. 2017; Albaladejo et al, Anesthesiology, 2017
ADMINISTRATION OF SPECIFIC REVERSAL AGENTS

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Anticoagulant(s)</th>
<th>Indication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>Dabigatran</td>
<td>Life-threatening or uncontrolled bleeding/Emergency surgery/urgent procedures</td>
<td>EMA 11/2015 2687€/5g</td>
</tr>
<tr>
<td>Andexanet alpha</td>
<td>Rivaroxaban, apixaban</td>
<td>Life-threatening or uncontrolled bleeding</td>
<td>CHMP 03/2019</td>
</tr>
</tbody>
</table>

WHEN?

- Urgent surgery with a high bleeding risk: > 30 ng/ml
- Serious bleeding: > 50 ng/ml

MONITORING OF SPECIFIC REVERSAL AGENTS

The recommended dose of idarucizumab (5g) might not be sufficient for sustained reversal.

- Case-reports of a rebound effect for patients with high baseline drug levels
- Redistribution of unbound dabigatran from the extravascular to the intravascular compartment

THE VALUE OF DOAC MEASUREMENT

MONITORING OF SPECIFIC REVERSAL AGENTS

77-year-old man
Dabigatran 110mg BID for atrial fibrillation

- Admission with acute renal failure
  CREATININE CLEARANCE 14 ML/MIN

Rectal bleeding + Multiples hematomas
↓ Hb 4g/dl

[dabi] = 1630 ng/ml

+ 30’: STOP bleeding
+ 50’: [dabi] < 30ng/ml
+ 8h: ↑ [dabi]

Simon et al, J Thromb Haemost. 2017
77-year-old man

**Dabigatran 110mg BID for atrial fibrillation**

- Admission with acute renal failure

**CREATININE CLEARANCE 14 ML/MIN**

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Administration of a second 5 g dose of Praxbind may be considered in the following situations:

- recurrence of clinically relevant bleeding together with prolonged clotting times, or
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or
- patients require a second emergency surgery/urgent procedure and have prolonged clotting times.

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*Simon et al, J Thromb Haemost. 2017*
**INTERPRETATION OF DOAC MEASUREMENT IN URGENT SITUATIONS**

- **Surgery with high risk of bleeding**: 
  - < 30 ng/ml

- **Drug reversal in case of serious bleeding**: 
  - > 50 ng/ml

- **Risk of bleeding**: 
  - > 200 ng/ml at trough

- **Thombolysis**: 
  - No consensus
  - < 50 ng/ml, < 100 ng/ml

Douxfils et al, J Thromb Haemost 2018
HOW TO MEASURE DOAC?
### HOW TO MEASURE DOAC

<table>
<thead>
<tr>
<th></th>
<th>APIXABAN</th>
<th>DABIGATRAN</th>
<th>EDOXABAN</th>
<th>RIVAROXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td>Eliquis®</td>
<td>Praxaxa®</td>
<td>Lixiana®</td>
<td>Xarelto®</td>
</tr>
<tr>
<td><strong>$T_{\text{MAX}}$</strong></td>
<td>3-4 h</td>
<td>0.5-2 h</td>
<td>1-2 h</td>
<td>2-4 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>8-15 h (healthy individuals)</td>
<td>12-14 h (healthy individuals)</td>
<td>10-14 h (healthy individuals)</td>
<td>5-9 h (healthy individuals)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11-13 h (elderly)</td>
</tr>
</tbody>
</table>

! Dabigatran: Half-life = 28h in case of severe renal impairment

**Interpretation according to the delay between the last drug intake and blood sampling**

![Graph showing concentration over time with key parameters](attachment:image.png)

Heidbuchel et al. Europace 2015
The IDEAL DOAC assay...

- Readily available
  24h/day and 7 days/week

- Easily performed
  Short turnaround time

- Reliable for measurement of
  “low” and “high “ concentrations

**Gold standard**: liquid chromatography with tandem mass spectrometry (LC-MS/MS)
WHICH OF THE FOLLOWING IS TRUE?

- **Red**: An elevated INR is a sign of excessive anticoagulation in a rivaroxaban patient.

- **Yellow**: Routine coagulation assays are not interpretable in DOAC patients.

- **Blue**: Antidote administration is useless in a dabigatran patient with a normal TT.

**Routine Coagulation Assays**
ROUTINE COAGULATION ASSAYS

INRINSIC PATHWAY

EXTRINSIC PATHWAY

INITIATION

AMPLIFICATION

COMMON PATHWAY

Daniels et al. BMJ 2015;351:h2391
aPTT (activated Partial Thromboplastin Time)

- Factor XIIa
- Factor XII
- Factor IX
- Factor VIII
- Phospholipids
- Calcium
- Kaolin (activation of FXII)
- Platelet-poor plasma
- Clotting time

Examples of aPTT prolongation:
- Unfractionated heparin
- FXII, FXI, FIX, FVIII deficiency
- Vitamin K deficiency
**PT Prothrombin Time**

Examples of PT prolongation:
- Vitamin K deficiency
- Hepatic impairment
- FVII deficiency

**EXTRINSIC PATHWAY**
- Tissue factor
- Phospholipids
- Calcium

**COMMON PATHWAY**
- Factor Va
- Factor VIIIa
- Factor VIII
- Factor X
- Factor IIa (thrombin)
- Fibrin

**PPP** Clotting time

Daniels et al. BMJ 2015;351:h2391
**TT Thrombin Time**

Examples of TT prolongation:
- Fibrinogen deficiency
- Hepatic impairment
- Heparin

**EXTRANISC PATHWAY**

- Vitamin K antagonist
- Oral Xa inhibitors
- Dabigatran

**COMMON PATHWAY**

- Fibrin
Impact of DOAC on routine coagulation assays

Concentration-dependent prolongation of aPTT and PT

Dabigatran
aPTT more sensitive than PT
TT highly sensitive

Rivaroxaban, edoxaban
PT more sensitive than aPTT

Apixaban
PT/ aPTT not sensitive enough

REAGENT-DEPENDENCE!

Impact of DOAC on routine coagulation assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>DOAC</th>
<th>Interpretation</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>Dabigatran</td>
<td>Exclusion of above on-therapy levels if normal</td>
<td>Qualitative assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rapid turnaround time</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>24/7, all laboratories</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reagent dependence</td>
</tr>
<tr>
<td>TT</td>
<td>Dabigatran</td>
<td>Exclusion of clinically relevant levels if normal</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>Rivaroxaban</td>
<td>Exclusion of above on-therapy levels if normal</td>
<td></td>
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<tr>
<td></td>
<td>Edoxaban</td>
<td></td>
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</tbody>
</table>

SCREENING TESTS

<table>
<thead>
<tr>
<th>Assay</th>
<th>DOAC</th>
<th>Interpretation</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
INR = \[
\frac{\text{Patient PT}}{\text{Mean normal PT}}\]

\text{INR} \quad \text{International Normalized Ratio}
\text{ISI} \quad \text{International Sensitivity Index}
\text{PT} \quad \text{Prothrombine Time (sec.)}

- \text{INR = another way of expressing prothrombin time}
- To compare results from different laboratories
- ISI determination according to reagent response to VKA

\text{INR should not be used for DOAC measurement !}
The **IDEAL DOAC assay**...

- **Readily available**
  - 24h/day and 7 days/week

- **Easily performed**
  - Short turnaround time

- **Reliable for measurement of**
  - “low” and “high” concentrations

**Gold standard**: liquid chromatography with tandem mass spectrometry (LC-MS/MS)
WHAT IS YOUR EXPERIENCE REGARDING SPECIFIC ASSAYS?

- They are not available in my hospital/site of practice.

- They are implemented in my hospital.

- I do not know if they are available or not in my hospital.
CHROMOGENIC ANTI-XA ASSAY

In vitro inhibition of an exogenous excess of Fxa by the drug

Calibration curves to convert activity into concentration

Van Pelt et al, Thromb Res. 2018
SPECIFIC ASSAYS

DILUTE THROMBIN TIME

HemoClot® Thrombin Inhibitors
Principe de mesure

R1: pool of plasma normal (100 μl)
R2: α-Thrombine Humaine + CaCl₂ (100 μl)

37 °C

Measure the time of coagulation

DABIGATRAN

ECARIN CHROMOGENIC ASSAY

Ecarin (snake venom)

Prothrombin (excess)

Meizothrombin

Chromogenic substrate

Dabigatran (patient’s sample)

Inversely proportional
pNA (405 nm)
Correlation between LC-MS/MS and specific assays

Douxfils et al, Thromb Haemost, 2013
### SPECIFIC ASSAYS

<table>
<thead>
<tr>
<th>Specific assays</th>
<th>Quantitative assessment</th>
<th>Calibrators and controls</th>
<th>Not in all laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>dTT ECA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromogenic Anti-Xa</td>
<td>Rivaroxaban</td>
<td>Estimation of plasma levels*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Edoxaban</td>
<td></td>
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</tbody>
</table>

*Adapted procedure (< 50 ng/ml) and sensitivity to heparin for some tests

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**Commercial assays are available for all DOAC, using any coagulometer.**

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<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Test</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>Dabigatran</td>
<td>Diluted thrombin time</td>
<td>Hyphen-BioMed, Neuville-Sur-Oise, France</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ecarin chromogenic assay</td>
<td>Diagnostica Stago, Asnieres, France</td>
</tr>
<tr>
<td>Factor Xa</td>
<td>Rivaroxaban</td>
<td>Calibrated anti-factor Xa</td>
<td>Hyphen-BioMed, Instrument Laboratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diagnostica Stago, Technoclon</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>Calibrated anti-factor Xa</td>
<td>Hyphen-BioMed, Diagnostica Stago</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Technoclon</td>
</tr>
<tr>
<td></td>
<td>Edoxaban</td>
<td>Calibrated anti-factor Xa</td>
<td>Diagnostica Stago (not yet commercially available)</td>
</tr>
</tbody>
</table>
The **IDEAL DOAC assay**...

- **Readily available**
  - 24h/day and 7 days/week

- **Easily performed**
  - Short turnaround time

- **Reliable for measurement of**
  - “low” and “high “ concentrations

**Turnaround times around 30 min have been reported in a daily practice context.**

**Gold standard**: liquid chromatography with tandem mass spectrometry (LC-MS/MS)

Examples from the literature
58-year-old woman (BMI>30)
**Dabigatran 150mg BID for atrial fibrillation**

- Onset of left upper limb hyposthenia

**Medical history**
- Atrial fibrillation
- Heart failure
- Hypertension
- Type 2 diabetes
- Obesity

**DABIGATRAN MEASUREMENT**
- Dilute Thrombin Time
- Delay: 2h after the last intake
- Within 1h of admittance

dTT below the limit of quantification (< 30 ng/ml)

Intravenous thrombolysis was performed within 4h of the onset of symptoms.

Absence of dabigatran anticoagulant activity at admission despite regular drug administration. The patient was switched to VKA therapy.

Tala et al. EJCRIM 2018
**72-year-old man (BMI>30)**

**Dabigatran 110mg BID for atrial fibrillation**

- Car crash with severe brain injury and # of the left arm

**Medical history**
- Atrial fibrillation
- Right nephrectomy
- Myocardial infarction
- Hypertension
- Type 2 diabetes

- **Brain CT scan showing intracranial haemorrhage**
- Sudden worsening of patient’s neurological status

**DABIGATRAN MEASUREMENT**

\[ dTT = 188.6 \text{ ng/ml} \]

- Administration of idarucizumab at the recommended dose (2x2.5g).
  Dabigatran level lower than the limit of quantification 10 min after administration.

- Reduction in intracranial haemorrhage on day 5 (prophylactic dose of LMWH started)
  Complete resolution 18 days after discharge (dabigatran restarted)

Tala et al. EJCRIM 2018
CLINICAL CASES
CLINICAL CASE 1

86-year-old woman, weighing 55 kg
ADMISSION TO THE EMERGENCY DEPARTMENT WITH PERSISTENT EPISTAXIS

Medical history
Atrial fibrillation
Peripheral arterial disease
Bioprosthetic heart valve replacement (4 years ago)
Heart failure
Hypertension
Urinary catheter

Biological parameters
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>8 g/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>126/µl</td>
</tr>
<tr>
<td>aPTT</td>
<td>42.4 sec (NI: 26-38)</td>
</tr>
<tr>
<td>PT</td>
<td>35.1 sec (NI: 11-14)</td>
</tr>
<tr>
<td>INR</td>
<td>3.4</td>
</tr>
<tr>
<td>TT</td>
<td>17 sec (NI: 14-21)</td>
</tr>
<tr>
<td>crCL</td>
<td>21 ml/min</td>
</tr>
</tbody>
</table>

According to Cockroft-Gault

Comprehensive medication history
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>80 mg OD</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>5 mg 0.5 tablet OD</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2.5 mg OD</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25 mg OD</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4 mg OD</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>0.4 mg OD</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg 0.5 tablet OD*</td>
</tr>
<tr>
<td>Calcium carb.</td>
<td>1.25 g OD</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1 mg OD</td>
</tr>
</tbody>
</table>

* The patient had been halving her rivaroxaban tablet intake for 2 months because of recurrent nosebleeds.

Management at the ED
- Interruption of rivaroxaban treatment
- Local hemostatic measure: anterior nasal packing left in place 72 hours before removal
- No blood transfusion needed
CLINICAL CASE 1

Table 1: DOAC pharmacokinetic properties and dosage regimen in NVAF

<table>
<thead>
<tr>
<th>Brand name</th>
<th>APIXABAN</th>
<th>DABIGATRAN</th>
<th>EDOXABAN</th>
<th>RIVAROXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor IIa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Dosing in NVAF*</td>
<td>5 mg twice a day</td>
<td>150 mg twice a day</td>
<td>60 mg once a day</td>
<td>20 mg once a day</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>2.5 mg twice a day if CrCl 15-29 ml/min or ≥2 risk factors: ≥ 80 years, ≤ 60 kg or serum creatinine ≥ 1.5 mg/dl</td>
<td>110 mg twice a day if &gt; 80 years or verapamil</td>
<td>To consider if 75-80 years or CrCl 30-50 ml/min</td>
<td>15 mg once a day if CrCl 15-49 ml/min</td>
</tr>
<tr>
<td>Concomitant use not recommended</td>
<td>Ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors, rifampicin, St John’s wort, phenytoin, carbamazepine</td>
<td>Ketoconazole, itraconazole, HIV protease inhibitors, dronedarone, ciclesonide, tacrolimus, rifampicin, St John’s wort, phenytoin, carbamazepine</td>
<td>HIV protease inhibitors, St John’s wort</td>
<td>Ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors, rifampicin, St John’s wort, phenytoin, carbamazepine</td>
</tr>
</tbody>
</table>

- **DOSE**
  20 mg OD instead of 15 mg OD

- **CHOICE**
  DOAC not a 1st choice in severe renal failure (+ low body weight)

- **MODALITIES**
  ½ tablets

- **INTERACTIONS**
  Concomitant intake of aspirin
CLINICAL CASE 1

DOAC CONTRIBUTION TO BLEEDING?

Risk factors for accumulation

OLDER AGE + LOW BODY WEIGHT + RENAL FAILURE

Routine coagulation assays

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>42.4 sec</td>
<td>↑</td>
<td>Rivaroxaban prolongs aPTT in a concentration-dependent manner.</td>
</tr>
<tr>
<td>PT</td>
<td>35.1 sec</td>
<td>↑↑</td>
<td>Rivaroxaban prolongs PT in a concentration-dependent manner.</td>
</tr>
<tr>
<td>INR</td>
<td>3.4</td>
<td></td>
<td>INR can not be used for rivaroxaban measurement.</td>
</tr>
<tr>
<td>TT</td>
<td>17 sec</td>
<td>-</td>
<td>No effect of rivaroxaban on TT.</td>
</tr>
</tbody>
</table>

Specific assays

- **323 ng/ml** 4h after the last rivaroxaban intake
- **76 ng/ml** 22h after the last rivaroxaban intake
- **67 ng/ml** 48h after the last rivaroxaban intake

<table>
<thead>
<tr>
<th>Peak</th>
<th>Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>184 to 343 ng/ml</td>
<td>12 to 137 ng/ml</td>
</tr>
</tbody>
</table>

5th -95th percentile

Slow drug elimination
Indication of anticoagulation?

CHA2DS2-VASC score=6

- High thrombotic risk
- Oral Anticoagulation indicated

Which oral anticoagulant?

- Lack of clinical data regarding the use of DOAC in patients < 50kg
- Severe renal impairment
- Rivaroxaban accumulation and slow drug elimination
- Lack of patient adherence

A VKA OFTEN REMAINS MORE SUITABLE.
### CLINICAL CASE 2

#### 71-year-old man, weighing 136 kg
**HOSPITALIZATION FOR COPD EXACERBATIONS**

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Biological parameters</th>
<th>Comprehensive medication history</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (2016) – double stent</td>
<td>Hemoglobin 13.9 g/dL</td>
<td>Phenobarbital 100mg OD</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Platelets 264/µl</td>
<td>Phenytoïn 100mg 2 tablets OD</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>aPTT 29.5 sec (NL: 26-38)</td>
<td>Aspirin 100mg OD</td>
</tr>
<tr>
<td>Hypertension</td>
<td>PT 77 % (NL: 75-100)</td>
<td>Apixaban 5mg BID</td>
</tr>
<tr>
<td>COPD Gold 2</td>
<td>INR 1.2</td>
<td>Amiodarone 200mg OD</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Creatinin 0.86 mg/dl</td>
<td>Bisoprolol 2.5mg OD</td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td>Atorvastatin 80mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bumetanide 1mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spironolactone 25mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losartan 100mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pantoprazole 20mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitagliptin 100mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metformin 850mg TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gliclazide 60mg 0.5 tablet OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Budesonide/formoterol 1 puff BID</td>
</tr>
</tbody>
</table>

**Anticoagulant treatment**
- Apixaban since 2016. No adverse effect reported.
- The patient has never received another anticoagulant treatment.
CLINICAL CASE 2

Routine coagulation assays

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>29.5 sec</td>
<td>aPTT is not a reliable measurement for apixaban (not sensitive enough)</td>
</tr>
<tr>
<td>PT</td>
<td>77%</td>
<td>PT is not a reliable measurement for apixaban (not sensitive enough)</td>
</tr>
<tr>
<td>INR</td>
<td>1.2</td>
<td>INR can not be used for apixaban measurement.</td>
</tr>
</tbody>
</table>

Specific assays

- **Peak** 91 to 321 ng/ml
- **Trough** 41 to 230 ng/ml  

5th -95th percentile

Trough level near the lower limit of the « on-therapy » range

Higher risk of thromboembolic event in patients with:
- CHA2DS2-VASC score>3 and
- apixaban trough level < 145 ng/ml
CLINICAL CASE 2

Why did the clinical pharmacist ask for a specific assay?

- Lack of clinical data regarding the use of DOAC in patients > 120kg.

We suggest that DOACs should not be used in patients with a BMI of > 40 kg m⁻² or a weight of > 120 kg, because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposure.

Guidance from the SSC of the ISTH

Ischemic Stroke in an Obese Patient Receiving Dabigatran

48-year-old man, 153kg

Plasma levels after 3 days of observed administration

CLINICAL CASE 2

Why did the clinical pharmacist ask for a specific assay?

- Concomitant intake of strong Pgp/CYP3A4 inducers

<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>P-GP</th>
<th>Evidence</th>
<th>CYP 3A4</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>↑ (Giessmann et al., 2004)</td>
<td>Humans</td>
<td>↑ (Puranik et al., 2013)</td>
<td>Humans</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>No effect (Wang-Tilz et al., 2006)</td>
<td>Animals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>↑ (Moerman et al., 2011)</td>
<td>Animals</td>
<td>No effect (Nicolas et al., 1999)</td>
<td>In vitro</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>NR</td>
<td></td>
<td>↑ (Andreasen et al., 2007)</td>
<td>Humans</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↑ (Jing et al., 2010)</td>
<td>Animals</td>
<td>↑ (Ohno et al., 2009)</td>
<td>In vitro</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↑ (Alvariza et al., 2014)</td>
<td>Animals</td>
<td>↑ (Lim et al., 2004)</td>
<td>Humans</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>No effect (Wang-Tilz et al., 2006)</td>
<td>Animals</td>
<td>↑ (Nallani et al., 2003)</td>
<td>In vitro</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>↑ (Eyal et al., 2006), ↑ (Tang et al., 2004)</td>
<td>In vitro</td>
<td>↑ (Cerveny et al., 2007), ↑ (Wen et al., 2001)</td>
<td>In vitro</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

↑ = Inducer.
↓ = Inhibitor.
NR = not reported.

Reduced Anticoagulant Effect of Dabigatran in a Patient Receiving Concomitant Phenytoin

45-year-old man
Undetectable dabigatran levels

Stollberger et al, Epilepsy Research, 2016;
RE EV ALU TA TION OF AN TICOAGULANT THERAPY

**Indication of anticoagulation?**

CHA2DS2-VASC score=4

- Oral Anticoagulation indicated

**Which oral anticoagulant?**

- Lack of clinical data regarding the use of DOAC in patients > 120kg
- Drug interactions with antiepileptics expected with all DOAC

**A VKA OFTEN REMAINS MORE SUITABLE.**
# CLINICAL CASE 3

### 76-year-old man, weighing 58 kg
HOSPITALIZATION FOR DETERIORATION OF GENERAL STATUS

### Medical history
- NSTEMI (2011)
- Atrial fibrillation
- Heart failure
- Hypertension
- COPD

### Biological parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>13.8 g/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>303/µl</td>
</tr>
<tr>
<td>aPTT</td>
<td>37.5 sec (NI: 26-38)</td>
</tr>
<tr>
<td>PT</td>
<td>55% (NI: 75-100)</td>
</tr>
<tr>
<td>INR</td>
<td>1.5</td>
</tr>
<tr>
<td>Creatinin</td>
<td>1.24 mg/dl</td>
</tr>
<tr>
<td>crCL*</td>
<td>41 ml/min</td>
</tr>
</tbody>
</table>

* Creatinine clearance estimated according to the Cockroft-Gault equation

### Comprehensive medication history

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>5mg BID</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>200mg OD</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40mg 0.5 tablet OD</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.125mg OD</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2.5mg OD</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40mg OD</td>
</tr>
<tr>
<td>Ramipril</td>
<td>10mg 0.5 tablet OD</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40mg OD</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10mg 0.5 tablet BID</td>
</tr>
</tbody>
</table>

### Anticoagulant treatment
- Apixaban for 10 days
- No other OAC previously
**INDICATION**  
Non-valvular atrial fibrillation

**DOSE**  
<60kg but < 80 years old and creat < 1.5 mg/dl => OK

**CHOICE**  
No contra-indication (low body weight)

**INTERACTIONS**  
Amiodarone + simvastatin
CLINICAL CASE 3

**Routine coagulation assays**

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<thead>
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<th>Test</th>
<th>Value</th>
<th>Interpretation</th>
</tr>
</thead>
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<td>55%</td>
<td>Apixaban prolongs PT in a concentration-dependent manner (not very sensitive).</td>
</tr>
<tr>
<td>INR</td>
<td>1.5</td>
<td>INR cannot be used for apixaban measurement.</td>
</tr>
</tbody>
</table>

**Specific assays**

<table>
<thead>
<tr>
<th>Value</th>
<th>Unit</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>391</td>
<td>ng/ml</td>
<td>at peak</td>
</tr>
<tr>
<td>203</td>
<td>ng/ml</td>
<td>at trough</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PEAK</th>
<th>TROUGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>91 to 321 ng/ml</td>
<td>41 to 230 ng/ml</td>
</tr>
</tbody>
</table>

5th -95th percentile

Apixaban peak level is above the « on-therapy » range.
Why did the clinical pharmacist ask for a specific assay?

HIGH RISK OF APIXABAN ACCUMULATION

- OLDER AGE + LOW BODY WEIGHT + RENAL FAILURE
- The apixaban dosing is questionable (even if appropriate according to SmPC)

Criteria for dose reduction:

- WEIGHT < 60 kg
- AGE > 80 years
- CREAT > 1.5 mg/dl

BUT 76 years old...
BUT 1.28 mg/dl...

= Tricky zone of apixaban in elderly patients

- Concomitant intake of a moderate Pgp/CYP3A4 inhibitor (amiodarone)
CLINICAL CASE 3

Why did the clinical pharmacist ask for a specific assay?

The straw that broke the camel's back...
REEVALUATION OF ANTICOAGULANT THERAPY

**Indication of anticoagulation?**

CHA2DS2-VASC score=4

- Oral Anticoagulation indicated

**Which oral anticoagulant?**

- Drug accumulation despite an appropriate apixaban dosing
- **Switch to another DOAC** (Xarelto 15mg OD)

For a given subject, the measured plasma concentration of either one of the two DOACs did not predict that of the other DOAC. [Gouin-Thibault et al, J Thomb Haemost, 2017]

3 weeks later: rivaroxaban level above on-therapy range at peak
Amiodarone was stopped for suspected pulmonary fibrosis
Following rivaroxaban measurements were within the on-therapy range.
THANK YOU