MEASUREMENT OF DIRECT ACTING ANTICOAGULANTS: CLINICAL AND LABORATORY ISSUES

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A Case-based Workshop: Clinical and Laboratory Aspects of Hemophilia and Thrombosis
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DISCLOSURES

Relevant Financial Relationship(s)
• Nothing to disclose

Off Label Usage:
• Nothing to Disclose
LEARNING OBJECTIVE

Define circumstances in which monitoring of DOACs may be useful

Demonstrate limitations of currently available assays

Illustrate the effects of novel anticoagulants on commonly ordered coagulation assays

WHEN (AND WHY) TO MONITOR DOACS

- Detection of drug accumulation:
  - Acute renal/liver failure
  - Overdose
- Special patient characteristics
  - Obesity
  - Absorption
  - Concomitant administration of other drugs
- Assess anticoagulant activity in bleeding/thrombosis
  - Planning timing urgent surgery
  - Prior to thrombolytics in acute stroke
  - Guiding reversal agents
  - Failure of anticoagulation

Other
- Influence on functional testing
LABORATORY ASSAYS

• Gold standard:
  • Ultraperformance liquid chromatography mass spectrometry

• Routine assays: Available in all/most laboratories
  • Prothrombin time
  • Activated partial thromboplastin time
  • Thrombin time

• Specialized tests: Not generally available
  • Diluted thrombin time
  • Ecarin clotting time
  • Anti Xa assays

WHAT IS OUR REFERENCE?

• Therapeutic range
  • Blood plasma or serum concentration usually expected to achieve desired therapeutic effects.
  • Commonly guides adjustments of the drug.

• “On therapy range”
  • Quantifying exposure
  • Comparing with therapeutic levels of clinical trials
WHAT DO WE NEED TO CONSIDER TO MAKE CLINICAL DECISIONS?

Laboratory/Institution
- Which tests we have available at our institution
- Influence of reagents in the results/interpretation
- Turn around time

Patient
- Timing last dose
- Concomitant medications
- Liver and renal function

VARIABILITY WITH DIFFERENT REAGENTS
WHEN WAS THE LAST DOSE?

CASE 1:

Assessing anticoagulant activity

75 y/o female

Atrial fibrillation on dabigatran 150 mg BID

Infected prosthetic knee

Creatinine clearance of 45

She can't remember the timing of the last dose

When is it safe to have surgery?
### PERIPROCEDURAL MANAGEMENT OF DOACS: PAUSE

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Procedure risk</th>
<th>Preoperative</th>
<th>Post operative</th>
<th>Excluded CrCl &lt;25/30ml/min</th>
<th>Procedure day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day -5 Day -4 Day -3 Day -2 Day -1</td>
<td>Day +1 Day +2 Day +3 Day +4</td>
<td>&lt;1% thromboembolism</td>
<td>Day +1 Day +2 Day +3 Day +4</td>
</tr>
<tr>
<td>Apixaban</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribaroxaban</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran CrCl&gt;60</td>
<td>High</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dabigatran CrCl&lt;60</td>
<td>High</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


### MONITORING DOACS

- **Quantitative:**
  - Xa specific titrated for the drug
    - Rivaroxaban
    - Apixaban
    - Edoxaban
    - Ecarin clotting time, dTT calibrated for the drug
    - Dabigatran

  Not widely available
  Not available 24/7

- **Qualitative:**
  - No linear relationship between drug levels and laboratory values
  - Sensitivity of the reagent influences the results
PROCEDURE CUTOFF AND LABORATORY TESTING

**Apixaban 5 mg BID**
- Peak
- Trough
- Calibrated Chromogenic anti-Xa

**Dabigatran 150 mg BID**
- Peak
- Trough
- dTT ECA

Detection <30ng/mL
- Sensitivity: 90-98%
- Specificity: 78-98%

Detecting "SAFE FOR TREATMENT" THRESHOLD

- False positives
- False negatives

Detection <30ng/mL
- Sensitivity: 90-98%
- Specificity: 78-98%

KNOW YOUR TESTS!

Ebner, JAMA 2018;7:e009807
CALIBRATED vs. UNCALIBRATED ANTI XA:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Coagulation Assay</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>HPI</td>
<td>93.0 (84.5–97.1)</td>
<td>78.2 (68.2–85.9)</td>
</tr>
<tr>
<td></td>
<td>BDTH</td>
<td>90.7 (82.0–95.6)</td>
<td>96.9 (93.2–99.9)</td>
</tr>
<tr>
<td></td>
<td>ECT</td>
<td>97.7 (91.1–99.6)</td>
<td>94.3 (86.5–97.9)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Calibrated AXA</td>
<td>98.2 (93.1–99.7)</td>
<td>97.1 (82.9–99.8)</td>
</tr>
<tr>
<td></td>
<td>Uncalibrated AXA &lt;ULN</td>
<td>98.2 (93.0–99.7)</td>
<td>64.7 (46.4–79.7)</td>
</tr>
<tr>
<td></td>
<td>Uncalibrated AXA &lt;2ULN</td>
<td>97.3 (91.7–99.3)</td>
<td>82.3 (64.8–92.6)</td>
</tr>
<tr>
<td></td>
<td>Uncalibrated AXA &lt;0.3 U/mL</td>
<td>92.0 (84.9–96.0)</td>
<td>94.1 (78.8–99.0)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Calibrated AXA</td>
<td>73.8 (65.1–81.0)</td>
<td>96.8 (81.5–99.8)</td>
</tr>
<tr>
<td></td>
<td>Uncalibrated AXA &lt;ULN</td>
<td>93.7 (87.5–97.0)</td>
<td>90.3 (73.1–97.5)</td>
</tr>
<tr>
<td></td>
<td>Uncalibrated AXA &lt;2ULN</td>
<td>91.0 (72.8–87.2)</td>
<td>96.8 (81.5–99.8)</td>
</tr>
<tr>
<td></td>
<td>Uncalibrated AXA &lt;0.3 U/mL</td>
<td>68.3 (59.3–76.1)</td>
<td>100 (96.3–100)</td>
</tr>
</tbody>
</table>

Detection <30ng/mL

Rivaroxaban

Calibrated

Sensitivity: 98.2
Specificity: 97.1

Uncalibrated:
Sensitivity: 98-92
Specificity: 64-94

QUICK TESTING: TAKE HOME POINTS

- Normal TT for Dabigatran and normal PT for Rivaroxaban suggest no clinically significant drug levels
- No quick qualitative test for Apixaban and Edoxaban
- Quantitative tests need to be calibrated for each specific drug
CASE 2: Special patient characteristics

28 y/o male
Unprovoked DVT 6 months ago
Treated with warfarin
Weight of 182 Kg
Can he be on a DOAC for secondary prophylaxis?

DOACS AND EXTREMES OF WEIGHT

- Extremes of weight were underrepresented in clinical trials:
  - <20% weighed > 90 to 100 kg
  - <15% weighed <50Kg

- Dabigatran plasma trough concentrations (reference 50-100Kg)
  - 21% higher for weight <50Kg
  - 21% lower for weight > 100 Kg

- Apixaban peak concentration (reference 65-85Kg)
  - 31% lower for weight >120 kg and BMI > 30 kg/m2

ISTH GUIDANCE ON TREATMENT OF OBESE PATIENTS

- **DOACs should not be used** in patients with a BMI of >40 Kgm$^2$ and weigh of >120 Kg (264lbs)

- If they are used:
  - Check a drug-specific peak and trough level
    - Anti-FXa for apixaban, edoxaban, and rivaroxaban
    - Ecarin time or dilute thrombin time with appropriate calibrators for dabigatran
    - Mass spectrometry drug level for any of the DOACs

- If the level falls within the expected range, continuation of the DOAC seems reasonable.

- If the drug-specific level is found to be below the expected range suggest changing to a VKA rather than adjusting the dose of the DOAC.

EXTREMES OF BODY WEIGHT: TAKE HOME POINTS

- Obesity may lead to **decreased** level of DOACs for fixed standard doses

- Limited efficacy data and no adjustment guidelines

- If drug-specific peak and trough are in the expected range it could be reasonable to use DOACs

- If outside the expected range, use alternatives (VKA)
Case 3: Concomitant administration of other drugs

45 y/o female with truncus arteriosus
On apixaban 2.5 mg BID for atrial fibrillation. No h/o embolic events
Admitted with a large aortic pseudoaneurysm requiring repair.
Decompensated heart failure and Liver failure.
Off apixaban for 5 days. Apixaban level: 60
When can she go to surgery? She is currently on IV heparin

HOW MUCH OF THE ANTI-XA IS HEPARIN AND HOW MUCH IS DOAC?

- Bridging is NOT advised but...

- Anti-Xa:
  - Monitoring LMWH and UFH
  - Test rivaroxaban, apixaban and edoxaban

- Note: Dabigatran is not monitored by anti Xa but high doses of LMWH and heparin will alter dTT

Faust, Am J Health-Syst Pharm. 2016; 73:2037-41
ANTI-XA IS AFFECTED BY BOTH: heparin and DOACs

Anti Xa calibrated for Rivaroxaban

Mass spectrometry

HEPARINS AND DOACS: TAKE HOME POINTS

- Clinical circumstances requiring overlap of these anticoagulants are rare
- Starting heparin at the time of the next dose of the DOAC is acceptable (unless there is liver or renal failure)
- Use aPTT if you need to monitor unfractionated heparin and you suspect persistent DOAC levels
- High doses of LMWH may interfere with dTT testing for Dabigatran
CASE 4: Influence on functional testing

20 y/o female on 20mg/day Rivaroxaban for DVT 1 months ago.

Mother and sister have history of thrombosis but were never tested.

Does she have a thrombophilia?
WHICH TESTS ARE **NOT** AFFECTED

- Antigenic methods (ELISA, LIA)
  - AT, protein S free ag, protein C antigen
  - Beta 2 GP, anticardiolipin antibodies
- Genetic testing
  - Prothrombin gene mutation
  - Factor V Leiden
- Chromogenic assays:
  - Protein C


WHICH TESTS **ARE** AFFECTED

- Coagulation factor levels: Underestimation
- Clot based protein C activity: Overestimation
- Clot based protein S activity: Overestimation
- AT activity: Overestimation (anti Xa based, anti IIa based)
- APCR: Overestimation (false negative) depending on test
- Lupus anticoagulant: False positives OR indeterminate results
- Fibrinogen (Clauss): affected by Dabigatran. Underestimation

ALTERNATIVES FOR A PATIENT ON DOACS

• Discontinuation of therapy (If safe for the patient)
  • Minimum of 48 hs
  • Renal function, concomitant drugs
• Antidote/reversal agent to neutralize DOAC:
  • Idarucizumab: inhibits dabigatran without altering tests
  • Andexanet: prohibitive cost, anti Xa effect of the drug
• Under investigation/validation
  • Activated charcoal (DOAC-stop, DOAC-Remove)
  • Filters

THROMBOPHILIA TESTING & DOACS:
TAKE HOME POINTS

Coagulation based tests will be influenced by DOACs (depending on DOAC and test)

Some tests will have interference even at trough levels

Genetic and immunologic testing are not affected

Discontinuation may be the only alternative (or switching to LMWH)