The Anticoagulated Patient – A Hematologist’s Perspective

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Conflicts of Interest

• Advisory Board, Boehringer Ingelheim, Daiichi Sankyo
• Educational Material, Interactive Forums Inc.
Objectives

• Briefly review the characteristics NOACs
• Describe NOAC effects on routine coagulation tests
• Evaluate evidence for reversal of anticoagulant effect
• Discuss periprocedural anticoagulant management
Fixa

FVIIIa

TF

FVIIa

Extrinsic Tenase Complex

Intrinsic Tenase Complex

FIXa

FVIIIa

FXa

Rivaroxaban

Apixaban

Edoxaban

Dabigatran

Contact

Prothrombin

Thrombin

Prothrombinase Complex

FXIIa

FXIa
Advantages of NOACs compared to warfarin

• Rapid onset of action
• Short half-lives
• Predictable pharmacokinetics
• Fewer drug interactions
• Lack of need for routine monitoring
Disadvantages compared to warfarin

• Monitoring compliance
• Drug accumulation with renal impairment
• No specific antidotes to reverse anticoagulant effect
## NOAC characteristics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time to peak concentration (hrs)</th>
<th>Half-life (hrs)</th>
<th>Population</th>
<th>Renal excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1 – 3</td>
<td>7 – 9</td>
<td>Healthy adults, single dose</td>
<td>80 – 85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 – 17</td>
<td>Healthy adults, multiple doses</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2 – 4</td>
<td>7 – 17</td>
<td>Healthy adults, single dose</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 – 13</td>
<td>Healthy elderly, single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 – 9</td>
<td>Healthy adults, multiple doses</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>1 – 3</td>
<td>8 – 14</td>
<td>Healthy adults, single dose</td>
<td>25%</td>
</tr>
</tbody>
</table>

Coagulation Testing
The problem of coagulation testing for NOACs

• Conventional coagulation assays not accurate or reliable
• Modified/alternative assays are more reliable but not routinely available
• Interpretation of tests influenced by:
  • Performance of test with drug
  • Dosing interval
  • Pharmacokinetics
  • Renal function
• Lack of clinical data regarding testing in bleeding patients
Excluding clinically significant drug levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Below on-therapy drug levels</th>
<th>Within on-therapy drug levels</th>
<th>Above on-therapy drug levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>TT</td>
<td>Dilute TT, ECT</td>
<td>APTT, dilute TT, ECT</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-Xa, PT</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
</tbody>
</table>

Reversal
NOAC reversal strategies

- Coagulation factor replacement
  - PCC (factors II, IX, X ± VII)
- Prohemostatic agents
  - APCC (activated factors II, VII, IX, X)
  - rFVIIa
- Specific reversal agents in development
  - Idarucizumab (dabigatran)
  - Andexanet alfa (oral factor Xa inhibitors)
  - Aripazine

Lack of efficacy and safety data in NOAC-treated patients with bleeding complications
Studies of patients with TSOAC-associated bleeding

Studies of TSOAC-treated healthy volunteers
Laboratory endpoints might not predict clinically relevant outcomes
Healthy volunteers may differ from patients on anticoagulation

Animal studies
Animals may differ from humans
Artificial injury models may differ from clinical bleeding

In vitro studies
In vitro might not simulate in vivo biology
Laboratory endpoints might not predict clinically relevant outcomes

Risk stratification

Minor bleeding
- Local hemostatic measures
- Consider anticoagulant withdrawal (balance thrombotic and bleeding risks)

Moderate bleeding
- General measures
  - Anticoagulant withdrawal
  - Mechanical compression
  - Monitor hemodynamic status
  - Volume replacement
  - Definitive interventions
- Blood product transfusion
  - RBC transfusion for anemia
  - Plasma for coagulopathy (e.g., DIC, dilutional)
  - Consider platelets for patients on antiplatelet agents

Severe/life-threatening bleeding
- General measures and blood product transfusion as per moderate bleeding
  - Intensive care setting
  - Hemodynamic support
  - Consider:
    - 4-factor PCC (50 U/kg)*
    - Activated PCC (80 U/kg)**
- Adjunctive therapies
  - Oral charcoal for dabigatran ingestion within 2 hours
  - Hemodialysis for dabigatran removal
  - Desmopressin
  - Antifibrinolytic agents

Initial assessment
- Hemodynamic stability
- Source of bleeding
- Time elapsed since last dose
- Renal function

Perioperative Anticoagulant Management
Balance of risk and benefit

1. Is anticoagulant interruption needed?
   • Most patients who undergo endoscopy

2. Is bridging anticoagulation needed during NOAC interruption?
   • No (short half-lives)

3. Is bridging anticoagulation needed during warfarin interruption?
   • Driven by patients’ estimated risk for thromboembolism

Minimizing bleeding is important because of associated morbidity. Delays in resumption expose patients to an increased risk of thromboembolism.
## Balance of risk and benefit: thrombosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
</table>
| **Atrial fibrillation**          | Stroke/TIA <3 mo  
CHADS 5-6  
Rheumatic heart | CHADS 3-4                                      | CHADS 0-2 (no previous stroke)                  |
| **Mechanical heart valve**       | Caged-ball/tilting disc  
Mitral valve  
Stroke/TIA <6 mo | Bileaflet AVR + risk factors | Bileaflet AVR without risk factors              |
| **Venous thrombosis**            | VTE <3 mo  
Severe thrombophilia | VTE 3-12 mo or cancer | VTE >12mo                                       |

# Balance of risk and benefit: thrombosis

<table>
<thead>
<tr>
<th></th>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Stroke/TIA &lt;3 mo CHADS 5-6 CHADS 3-4</td>
<td>CHADS 0-2 (no previous stroke)</td>
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</tr>
<tr>
<td>Mechanical heart valve</td>
<td>Caged ball/tilting disc Mitral valve</td>
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<tr>
<td>Venous thrombosis</td>
<td>Severe thrombophilia</td>
<td>Venous thrombosis</td>
<td>Venous thrombosis</td>
</tr>
</tbody>
</table>

Suggest bridging (2C)  
Consider individual cases  
Suggest NO bridging (2C)

Calculating CHADS2 Score

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$ 75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>2</td>
</tr>
</tbody>
</table>
Resuming anticoagulation

• When is it safe?
  • Procedural bleeding risk
  • Post-operative hemostasis
  • Class of anticoagulant used
  • With removal of large (> 1 cm) polyps bleeding can occur 2-3 days after polypectomy
  • Polyp-related bleeding may be reduced with endoscopic application of clips over polyp stalk
## Perioperative management of warfarin

<table>
<thead>
<tr>
<th>No bridging</th>
<th></th>
<th>Bridging with therapeutic dose LMWH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop warfarin 5 days before surgery</td>
<td>1C</td>
<td>Last dose 24 hrs before surgery</td>
<td>2C</td>
</tr>
<tr>
<td>Restart warfarin 12-24 hrs after surgery</td>
<td>2C</td>
<td>• Low bleed risk: resume 12-24 hrs</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Moderate bleed risk: resume 24-48 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High bleed risk: resume 48-72 hrs*</td>
<td></td>
</tr>
</tbody>
</table>

# Standardized pre-operative interruption of dabigatran

<table>
<thead>
<tr>
<th>Renal function (CrCl)</th>
<th>Estimated half-life (hrs)</th>
<th>High bleed risk surgery/procedure</th>
<th>Low bleed risk surgery/procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 mL/min</td>
<td>15 (12-18)</td>
<td>48 hrs (skip 3-4 doses)</td>
<td>24 hrs (skip 1-2 doses)</td>
</tr>
<tr>
<td>30 to &lt;50 mL/min</td>
<td>18 (28-24)</td>
<td>96 hrs (skip 7-8 doses)</td>
<td>48 hrs (skip 3-4 doses)</td>
</tr>
<tr>
<td>&lt;30 mL/min</td>
<td>27 (&gt;24)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

## Post-operative management of dabigatran

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Suggested Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major (or high bleed risk) surgery</td>
<td>Resume 48-72 hrs post-op</td>
</tr>
<tr>
<td>Minor (or low bleed risk) surgery</td>
<td>Resume 24 hrs post-op</td>
</tr>
</tbody>
</table>

Spyropoulos A, Douketis J. *Blood* 2012;120:2954
Perioperative management of rivaroxaban and apixaban

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major (or high bleed risk) surgery</th>
<th>Minor (or low bleed risk) surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>48 hrs (skip 2 doses) Resume 48 – 72 hrs post-op</td>
<td>24 hrs (skip 1 dose) Resume 24 hrs post-op</td>
</tr>
<tr>
<td>Apixaban</td>
<td>48 hrs (skip 4 doses) Resume 48 – 72 hrs post-op</td>
<td>24 hrs (skip 2 doses) Resume 24 hrs post-op</td>
</tr>
</tbody>
</table>

Thank you for your attention.