Reversal of direct oral anticoagulants (DOACs)

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NO DISCLOSURES
Objectives

. Discuss DOAC-reversal strategies for severe bleeding and for perioperative management

. Role of laboratory testing

. Overview of reversal agents

. Case-based examples for application to practice
. Direct thrombin inhibitor
  - Dabigatran (Pradaxa®)

. Factor Xa inhibitors
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)
  - Edoxaban (Savaysa®)
<table>
<thead>
<tr>
<th></th>
<th>Direct thrombin inhibitor dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak onset</td>
<td>22 min-4.5 h</td>
<td>1-3 h</td>
<td>1-2 h</td>
<td>Unknown</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-14 h</td>
<td>5-9 h</td>
<td>8-15 h</td>
<td>10-14 h</td>
</tr>
<tr>
<td></td>
<td>&gt;24 h if CrCl is &lt;30 mL/min</td>
<td>9-13 h if patient is elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-gP</td>
<td>CYP3A4, CYP3A5, CYP2J2, P-gP</td>
<td>CYP3A4,P-gP</td>
<td>P-gP</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>80</td>
<td>33</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>

CrCL, creatinine clearance.
Coagulation cascade
Case

A 54-year-old woman is evaluated in the emergency department after she consumed half of bottle of dabigatran 6 hours ago in a suicide attempt. Medical history is notable for atrial fibrillation and depression. Medications are dabigatran, paroxetine, and metoprolol.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 80/60 mm Hg, pulse rate is 125/min, and respiration rate is 12/min. She has bleeding of the oral mucosa and gross blood per rectum. The reminder of the examination is normal.

Laboratory studies: Activated partial thromboplastin time 87 seconds
Hemoglobin 12.2 g/dL (112g/L)
Platelet count 185,000/µL (185x10⁹/L)
Thrombin time >65 seconds

In addition to an antifibrinolytic agent and intravenous normal saline, which of the following is the most appropriate treatment?

A. Andexanet alfa
B. Cryoprecipitate
C. Fresh frozen plasma
D. Idarucizumab
Risk Stratification

- Hemodynamic stability
- Identify source, severity, risk factors, history of bleeding
- Full medication history
- Time elapsed since last DOAC dose
- Ascertain presence of life-threatening anemia and renal function
General Approach

• Minor bleeding (epistaxis, ecchymoses, menorrhagia)
  - Local hemostatic measures
  - D/C or reduce dose
• Moderate bleeding (subacute GI bleeding, severe forms of above)
  - D/C
  - Consider adjuncts and reversal agents
    • Tranexamic acid for menorrhagia
    • Investigate the site of bleeding

Shih, Hematology 2016
Severe bleeding (life-threatening)
- All previous measures plus adjuncts, nonspecific reversal agents – targeted agents if available

Shih, Hematology 2016
Determining clinically significant drug levels

- Direct thrombin inhibitor (dabigatran)
  - Thrombin time (TT). Normal TT excludes clinically relevant levels
  - Subtherapeutic levels may prolong the TT due to its sensitivity
  - aPTT. Not as sensitive as TT
  - Prolonged aPTT indicates presence of drug, but a normal aPTT does not exclude clinically relevant drug levels
Determining clinically significant drug levels

• FXa inhibitors (rivaroxaban, apixaban, edoxaban)
  - Anti-Xa activity
    • Specific calibrated assays available
    • Most are for LMWH
    • Normal anti-Xa of any variety rules out clinically significant drug levels
Supportive Care

- Blood component transfusion
  - No studies
  - FFP transfusion inappropriate

- Antifibrinolytics (tranexamic acid, aminocaproic acid) - reduce fibrinolysis
  - No studies
  - Active in other groups with pathologic bleeding
  - Unclear if results in ↑ risk of thrombosis
Supportive Care

- Desmopressin
  - No studies
  - Risk of hyponatremia and potential prothrombotic risk
Idarucizumab - antidote to dabigatran
- MoAb, binds free dabigatran and thrombin-bound dabigatran
- FDA-approved for dabigatran reversal
  (emergency surgery, urgent procedures, life-threatening or uncontrolled bleeding.)
Targeted reversal agents

- Andexanet alfa – antidote to FXa inhibitors
  - Recombinant inactive form of FXa. Binds all FXa inhibitors, including enoxaparin
  - Rejected by FDA 2016; resubmitted August 2017
Targeted reversal agents

- Ciraparantag – reversal agent for all DOACs and heparins
  - small synthetic molecule that binds to FXa inhibitors, DTIs, and heparins.
  - currently in studies with healthy volunteers
Table 4. Summary of selected studies of DOAC-specific reversal agents

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Clinical trial identifier</th>
<th>Study name</th>
<th>Study phase</th>
<th>Study description</th>
<th>No. of patients</th>
<th>Results summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crispranmab</td>
<td>NCT02220606</td>
<td>1</td>
<td>Open-label, single-dose, non-randomized pharmacokinetic study in healthy male patients</td>
<td>6</td>
<td>Completed; results pending publication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT01822956</td>
<td>1</td>
<td>Double-blind RCT of efficacy/safety of escalating doses after single dose of edoxaban 60 mg</td>
<td>60</td>
<td>Administration of 100-300 mg reversed anticoagulation within 10-30 min and was sustained for 24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT02207707</td>
<td>2</td>
<td>Single-blind RCT of safety/efficacy of escalating doses after study-start edoxaban and effects after re-anticoagulation and second reversal</td>
<td>60</td>
<td>Recruiting as of second quarter of 2016</td>
<td></td>
</tr>
<tr>
<td>Idarucizumab</td>
<td>NCT01689930</td>
<td>1</td>
<td>Double-blind RCT in healthy patients for (A) an escalating dose assessment; (B) Effect of efficacy/safety</td>
<td>110</td>
<td>(A) Rapid peak plasma exposure and elimination; no adverse effects.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT01865720</td>
<td>1</td>
<td>Double-blind RCT to study pharmacokinetics/pharmacodynamics</td>
<td>12</td>
<td>(B) Efficacy in reversal of coagulation test abnormalities (TT, aPTT, aPT, ECT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT02104447 REVERSE-AD</td>
<td>3</td>
<td>Cohort study of efficacy/safety in patients with (A) severe bleeding on dabigatran who (B) required urgent procedure on dabigatran</td>
<td>200</td>
<td>Interim analysis (n = 80); aPTT normalized in ≥88% and ECT normalized in ≥85% of patients; (A) median time for cessation of bleeding was 11.4 h; (B) normal interoperative hemostasis was achieved in 92% of patients; Dose-dependent reduction in factor Xa activity lasting until 2 h</td>
<td></td>
</tr>
<tr>
<td>Andexanet alfa</td>
<td>NCT01789492</td>
<td>2</td>
<td>Double-blind RCT to study pharmacokinetics/pharmacodynamics</td>
<td>144</td>
<td>Anti-Xa activity reduced by 64%; thrombin generation restored in 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT02207726 ANNEXA-A</td>
<td>3</td>
<td>Double-blind RCT of efficacy/safety in reversing apixaban</td>
<td>48</td>
<td>Anti-Xa activity reduced by 92%; thrombin generation restored in 98%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT02207726 ANNEXA-R</td>
<td>3</td>
<td>Double-blind RCT of efficacy/safety in reversing rivaroxaban</td>
<td>59</td>
<td>Anti-Xa activity reduced by 64%; thrombin generation restored in 95%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCT03209327 ANNEXA-4</td>
<td>5B to 4</td>
<td>Cohort study of efficacy/safety in achieving hemostasis in those with major bleeding on factor Xa INhibitors</td>
<td>270</td>
<td>Interim analysis (n = 67); anti-Xa activity reduced by 99% with marlexaban and 83% with apixaban; 79% had good/excellent hemostasis 12 h after infusion; 18% had thrombotic events</td>
<td></td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial.
Nonspecific reversal strategies

- Hemodialysis for dabigatran (low plasma protein binding and small molecular size). Consider if idarucizumab unavailable.

- Prothrombin complex concentrates (PCCs) – contain factors II, IX, and X (4-factor PCCs contain normal amounts of factor VII).
  - Lack of supporting evidence – considered experimental.
Nonspecific reversal strategies

- Activated prothrombin complex concentrates (aPCCs)
- Recombinant FVIIa
  - No supporting evidence for use
- Activated charcoal within 2-3 hours of administration for dabigatran, within 6 hours for apixaban (unclear if effective with other DOACs).
Case

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A 63-year old man is scheduled for recommended repeat colonoscopy in follow-up of adenomatous polyps detected on screening 3 years ago. Medical history is significant for an unprovoked pulmonary embolism 5 years ago. He was initially treated with warfarin but switched to rivaroxaban 1 year ago because of fluctuating INR values with warfarin. He is otherwise healthy and has had not bleeding.

Laboratory studies show a normal complete blood count and a serum creatinine level of 0.8 mg/dL (70.7 umol/L).

Which of the following is the most appropriate management of this patient’s anticoagulation for undergoing colonoscopy?

A. Continue rivaroxaban without interruption
B. Stop rivaroxaban 1 day before colonoscopy without bridging
C. Stop rivaroxaban 1 day before colonoscopy and bridge with low-molecular-weight heparin
D. Stop rivaroxaban 5 days before colonoscopy without bridging
E. Stop rivaroxaban 5 days before colonoscopy and bridge with low-molecular-weight heparin
Conclusion

• Moderate/severe/life-threatening bleeding – temporary D/C drug + supportive care

• Specific antidotes promising – only idarucizumab for dabigatran is currently available

• Adjuncts and non-specific reversal agents can be considered in severe bleeding, but evidence is lacking


