OBJECTIVE:
To assist clinicians in the management of bleeding in patients receiving a newer direct oral anticoagulant (DOAC).

BACKGROUND:
Four DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are approved for clinical use in Canada based on findings from large randomized trials. Like all other anticoagulants, bleeding is the major complication of therapy. A specific antidote for dabigatran is now available in Canada, while specific antidotes for the other drugs are expected to be available soon. Studies of successful reversal strategies using non-specific products in patients with bleeding have not been reported. Appropriate management in all cases of bleeding requires a systematic approach to assessing the competing risks and consequences of bleeding and thrombosis.

MANAGEMENT OF BLEEDING EPISODES

Minor Bleeding e.g. extremity bruising, hemorrhoid bleeding, subconjunctival bleed
- Continue anticoagulant
- Confirm the patient is receiving the appropriate drug and dose based on indication, age, weight, and creatinine clearance.
- Consider checking hemoglobin, platelet count and renal function to see if they are stable.

Moderate Bleeding e.g. hemodynamically stable GI bleed, major epistaxis, hematuria
- Hold anticoagulant therapy
- Assess the patient to determine the cause of bleeding
- Apply local hemostatic measures (e.g. compression, packing) if applicable
- Obtain CBC, PT/INR, PTT, creatinine
- Determine the likely presence of drug and expected elimination rate using time of last dose, drug half-life and creatinine clearance (CrCl). Estimated half-life for DOACs are:
  - dabigatran: 7-17 h if CrCl ≥50 mL/min; 17-20 h if CrCl 30-49 mL/min
  - rivaroxaban: 7-11 h if CrCl ≥50 mL/min; 7-11 h if CrCl 30-49 mL/min
  - apixaban: 8-12 h if CrCl ≥50 mL/min; 8-12 h if CrCl 30-49 mL/min
  - edoxaban: 10-14 h if CrCl ≥50 mL/min
- If available, consider determining plasma concentration of DOAC using a validated assay (See Table 1).
- Transfusion therapy should be given as per standard supportive measures:
  - RBC transfusion if symptomatic anemia
  - Platelet transfusion if platelets less than 50 x 10⁹/L or if patient is taking antiplatelet therapy
  - Consultation for further investigations and definitive management, if indicated (e.g. endoscopy)
**Severe/Life-threatening bleeding** e.g. intracranial hemorrhage, severe GI bleed

**Initial management**

- Hold anticoagulant therapy
- Initiate resuscitation in a monitored setting
- Assess the patient to determine the cause of bleeding
- Apply local hemostatic measures (e.g. compression, packing, splinting) if applicable
- Consult an expert urgently (hematologist, internist, ER physician, pharmacist) for advice
- Refer for procedural/surgical intervention if appropriate
- Obtain CBC, PT/INR, PTT, creatinine STAT
- Determine the likely presence of drug and expected elimination rate using time of last dose, drug half-life and creatinine clearance.
- If available, determine plasma concentration of DOAC using a validated assay (See Table 1).
- Transfusion therapy should be given as per standard supportive measures:
  - RBC transfusion if symptomatic anemia. Maintain hemoglobin > 70 g/L during active bleeding.
  - Platelet transfusion if platelet count less than 50x10^9/L or if patient is taking antiplatelet therapy. Consider higher platelet count threshold of 100 x 10^9/L in patients with bleeding into a critical site (e.g. intracranial hemorrhage).
  - Plasma and/or cryoprecipitate transfusion only if concomitant coagulopathy (e.g. massive transfusion, disseminated intravascular coagulation, liver disease).

*Reversal for severe/life-threatening bleeding (see Table 2)*

**Recommended coagulation test assays and thresholds for clinically relevant plasma DOAC concentrations are estimates based on available evidence that require further study/validation.**

**Dabigatran**

- If dabigatran is likely still active (as per time of last dose and creatinine clearance) give idarucizumab (Praxbind®). Complete reversal is expected within minutes. Note, if dabigatran levels are rapidly available and < 30-50 ng/mL: no reversal required.
- If idarucizumab (Praxbind®) is not available, consider alternative therapies such as prothrombin complex concentrate (PCC) Octaplex® or Beriplex®, or FEIBA®.
- Inform patients/families regarding small thrombotic risk of idarucizumab, PCC and FEIBA® (e.g. stroke MI, DVT, PE), but consequences of uncontrolled bleeding likely exceed this risk
- Adjunctive therapy to consider: hemodialysis (~65% removal after 4 hrs) if feasible or tranexamic acid.

**Apixaban**

- If apixaban is likely still active (as per time of last dose and creatinine clearance) give PCC. Reversal may or may not occur. If apixaban levels are available and < 30-50 ng/mL: no reversal required.
- Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke MI, DVT, PE), but consequences of uncontrolled bleeding likely exceed this risk
- Adjunctive therapy to consider: tranexamic acid
- Specific antidote in development and not yet available
**Rivaroxaban**
- If rivaroxaban is likely still active (as per time of last dose and creatinine clearance) give PCC. Reversal may or may not occur. If rivaroxaban levels are available and < 30-50 ng/mL: no reversal required
- Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke MI, DVT, PE), but consequences of uncontrolled bleeding likely exceed this risk
- Adjunctive therapy to consider: tranexamic acid
- Specific antidote in development and not yet available

**Edoxaban**
- If edoxaban is likely still active (as per time of last dose and creatinine clearance) give PCC. Reversal may or may not occur. If edoxaban levels are available and < 30-50 ng/mL: no reversal required
- Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke MI, DVT, PE), but consequences of uncontrolled bleeding likely exceed this risk
- Adjunctive therapy to consider: tranexamic acid
- Specific antidote in development and not yet available

**Table 1: Interpretation of coagulation tests for DOACs**

<table>
<thead>
<tr>
<th>Test</th>
<th>Dabigatran (Pradaxa&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>Apixaban (Eliquis&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>Rivaroxaban (Xarelto&lt;sup&gt;®&lt;/sup&gt;)&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Edoxaban (Lixiana&lt;sup&gt;®&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT/INR</td>
<td>Normal value does NOT exclude anticoagulant effect&lt;br&gt; If increased, may indicate anticoagulant effect&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>aPTT</td>
<td>Normal value may not exclude anticoagulant effect&lt;br&gt; If increased, indicates anticoagulant effect&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Normal value does NOT exclude anticoagulant effect.&lt;br&gt; If increased, may indicate anticoagulant effect&lt;sup&gt;2&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Dilute TT (dTT, Hemoclot&lt;sup&gt;®&lt;/sup&gt;) or ECT (Ecarin clotting time)</td>
<td>&lt;30 ng/mL = likely no significant anticoagulant effect&lt;sup&gt;1&lt;/sup&gt;&lt;br&gt; &gt;30 ng/mL = likely significant anticoagulant effect&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Not relevant</td>
<td>Not relevant</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Normal indicates no dabigatran present&lt;br&gt; If increased, indicates some anticoagulant effect</td>
<td>Not relevant</td>
<td>Not relevant</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Calibrated anti-Xa</td>
<td>Not relevant</td>
<td>&lt;30 ng/mL = likely no significant anticoagulant effect&lt;sup&gt;1&lt;/sup&gt;&lt;br&gt; &gt;30 ng/mL = likely significant anticoagulant effect&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;30 ng/mL = likely no significant anticoagulant effect&lt;sup&gt;1&lt;/sup&gt;&lt;br&gt; &gt;30 ng/mL = likely significant anticoagulant effect&lt;sup&gt;1&lt;/sup&gt;</td>
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</tr>
</tbody>
</table>
1There are no data to establish a hemostatic threshold below which drug levels are unlikely to affect hemostasis. These estimates are extrapolated from observations in clinical trials and are in agreement with other guidelines.

2Rule out other causes of increased PT/INR/PTT e.g. DIC, coagulopathy of liver disease, vitamin K deficiency, warfarin, a coagulation factor inhibitor, or a factor deficiency.

**TABLE 2: DOSING OF PROTHROMBOTIC THERAPIES AND PRODUCTS**

<table>
<thead>
<tr>
<th>Product</th>
<th>Bleeding on</th>
<th>Dosing</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab (Praxbind®)</td>
<td>dabigatran</td>
<td>• administered as two 50-mL bolus infusions containing 2.5 g each of idarucizumab (total 5 g) no more than 15 minutes apart</td>
<td>• Complete reversal is expected within minutes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ongoing bleeding is due to anatomical cause.</td>
</tr>
<tr>
<td>PCC (Octaplex®)</td>
<td>rivaroxaban</td>
<td>• 50 units/kg, max 3000 units</td>
<td>• Contraindicated in heparin-induced thrombocytopenia.</td>
</tr>
<tr>
<td></td>
<td>apixaban</td>
<td>• Mix diluent and PCC following manufacturer instructions</td>
<td>• For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal</td>
</tr>
<tr>
<td></td>
<td>edoxaban</td>
<td>• infuse at 1 mL/min followed by maximum 3 mL/min (180 mL/hr) per institution/Blood Bank instructions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dabigatran*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCC (Beriplex®)</td>
<td>rivaroxaban</td>
<td>• 50 units/kg, max 3000 units</td>
<td>• Contraindicated in heparin-induced thrombocytopenia.</td>
</tr>
<tr>
<td></td>
<td>apixaban</td>
<td>• Mix diluent and PCC following manufacturer instructions</td>
<td>• For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal</td>
</tr>
<tr>
<td></td>
<td>edoxaban</td>
<td>• infuse at 1 mL/min followed by maximum 8 mL/min (480 mL/hr) per institution/Blood Bank instructions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dabigatran*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated PCC (FEIBA®)</td>
<td>dabigatran*</td>
<td>• 50 units/kg, max 2000 units</td>
<td>• Limited availability through Canadian Blood Services.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Can also use for apixaban and rivaroxaban but PCC preferred.</td>
</tr>
<tr>
<td>Frozen plasma</td>
<td>Coagulopathy</td>
<td>• 10-15 mL/kg (3-4 units for adults)</td>
<td>• Should not be used to reverse abnormal lab parameters from DOACs.</td>
</tr>
<tr>
<td></td>
<td>(e.g. dilutional from massive transfusion, hepatic failure, DIC)</td>
<td></td>
<td>• Caution in patient at risk for volume overload (eg. CHF)</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Coagulopathy</td>
<td>• 10 units IV</td>
<td>• Only consider if fibrinogen level is &lt; 1.0 g/L</td>
</tr>
<tr>
<td></td>
<td>(e.g. dilutional from massive transfusion, hepatic failure, DIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranexamic Acid (Cyclokapron®)</td>
<td>rivaroxaban apixaban edoxaban dabigatran</td>
<td>• 1g IV bolus then 1 g over 8 hrs</td>
<td>• May exacerbate prothrombotic effect if given with other prothrombotic products</td>
</tr>
</tbody>
</table>

*If idarucizumab unavailable.

Abbreviations: CHF, congestive heart failure; DIC, disseminated intravascular coagulation.

**Notes regarding pro-hemostatic therapies (PCC, FEIBA®, recombinant factor VIIa) for DOAC-associated severe/life-threatening bleeding:**

- Supportive clinical data for pro-hemostatic agents (PCC, FEIBA®, rVIIa) are very limited. No study has assessed the clinical efficacy and safety of these agents in patients with active bleeding. The possible role of these agents is based on in vitro studies, animal models and studies in human volunteers evaluating coagulation markers.
- PCC (Octaplex®, Beriplex®), activated PCC (FEIBA®) are coagulation factor concentrates, not DOAC antidotes and do not affect the inhibitory effect of DOACs on pre-existing coagulation factors IIa (thrombin) and Xa. These agents may reduce DOAC-associated bleeding by providing large amounts of factors II and X. They may be associated with a small increased prothrombotic risk.
- The use of antifibrinolytic agents such as tranexamic acid (Cyclokapron®) and aminocaproic acid (Amicar®) has no direct supporting evidence of benefit in patients with DOAC-associated bleeding. However, early use of tranexamic acid has shown to be of benefit in trauma patients with significant bleeding and has a good safety profile.
- Recombinant factor VIIa (rFVIIa; NovoSeven®, Niastase®) is generally not recommended because of a lack of benefit in animal studies and increased prothrombotic risk.

**WHEN BLEEDING HAS RESOLVED**
- Restart anticoagulant when hemostasis is achieved. Prolonged anticoagulant interruption exposes patients to an increased risk of thrombosis.
- Reassess appropriateness of drug and dose of anticoagulant based on clinical characteristics such as indication, age, weight and creatinine clearance.
- Assess co-medications which may contribute to bleeding (e.g. ASA, NSAIDs).

**SPECIAL CONSIDERATIONS:**

**Pediatrics**
There are no studies evaluating the management of bleeding in children receiving DOACs.

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**
- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Edoxaban (Lixiana®)
- NOACs/DOACs: Comparison and Frequently Asked Questions
- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs): Peri-Operative Management
- Rivaroxaban (Xarelto®)

**REFERENCES:**

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Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.