



OBJECTIVE:

To assist clinicians in the management of bleeding in patients receiving direct oral anticoagulants (NOACs).

BACKGROUND:

Two oral Factor Xa inhibitors (apixaban and rivaroxaban) and an oral thrombin inhibitor (dabigatran) 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. Specific antidotes for these 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. anterior epistaxis, 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

- Interrupt 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 NOACs are:
 - dabigatran: 7-17 h if CrCl \geq 50 mL/min; 17-20 h if CrCl 30-49 mL/min
 - rivaroxaban: 7-11 h if CrCl \geq 50 mL/min; 7-11 h if CrCl 30-49 mL/min
 - apixaban: 8-12 h if CrCl \geq 50 mL/min; 8-12 h if CrCl 30-49 mL/min
- If available, determine plasma concentration of NOAC 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 $50 \times 10^9/L$ 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

- Interrupt 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 NOAC 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 $50 \times 10^9/L$ or if patient is taking antiplatelet therapy. Consider higher platelet count threshold of $100 \times 10^9/L$ 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 NOAC concentrations are estimates based on available evidence that require further study/validation.

Dabigatran

- If dabigatran level < 30-50 ng/mL: no reversal required
- If dabigatran level \geq 30-50 ng/mL **OR** dilute thrombin time (dTT, Hemoclot[®]) unavailable and clinically significant dabigatran levels suspected, give idarucizumab (Praxbind[®]). Complete reversal is expected within minutes.
- 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 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 level < 30-50 ng/mL: no reversal required

- If apixaban level \geq 30-50 ng/mL, **OR** apixaban-calibrated anti-Xa assay not available and clinically significant apixaban levels suspected, give PCC. Reversal may or may not occur.
- 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 level $<$ 30-50 ng/mL: no reversal required
- If rivaroxaban level \geq 30-50 ng/mL, **OR** rivaroxaban-calibrated anti-Xa assay not available and clinically significant rivaroxaban levels suspected, give PCC. Reversal may or may not occur.
- 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 NOACS

Test	dabigatran (Pradaxa®)	apixaban (Eliquis®)	rivaroxaban (Xarelto®)*
PT/INR	<ul style="list-style-type: none"> • Normal value does NOT exclude anticoagulant effect • If increased, may indicate anticoagulant effect² 	<ul style="list-style-type: none"> • Normal value does NOT exclude anticoagulant effect. • If increased, may indicate anticoagulant effect² 	<ul style="list-style-type: none"> • Normal value does NOT exclude anticoagulant effect • If increased, may indicate anticoagulant effect²
aPTT	<ul style="list-style-type: none"> • Normal value may not exclude anticoagulant effect • If increased, indicates anticoagulant effect² 	<ul style="list-style-type: none"> • Normal value does NOT exclude anticoagulant effect • If increased, may indicate anticoagulant effect² 	<ul style="list-style-type: none"> • Normal value does NOT exclude anticoagulant effect • If increased, may indicate anticoagulant effect²
Dilute TT (dTT, Hemoclot®) or ECT (Ecarin clotting time)	<ul style="list-style-type: none"> • $<$30 ng/mL = likely no significant anticoagulant effect¹ • $>$30 ng/mL = likely significant anticoagulant effect¹ 	<ul style="list-style-type: none"> • Not relevant 	<ul style="list-style-type: none"> • Not relevant
Thrombin time	<ul style="list-style-type: none"> • Normal indicates no dabigatran present • If increased, indicates some anticoagulant effect 	<ul style="list-style-type: none"> • Not relevant 	<ul style="list-style-type: none"> • Not relevant
Calibrated anti-Xa	<ul style="list-style-type: none"> • Not relevant 	<ul style="list-style-type: none"> • $<$30 ng/mL = likely no significant anticoagulant effect¹ • $>$30 ng/mL = likely significant anticoagulant effect¹ 	<ul style="list-style-type: none"> • $<$30 ng/mL = likely no significant anticoagulant effect¹ • $>$30 ng/mL = likely significant anticoagulant effect¹

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

Product	Bleeding on	Dosing	Notes
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Idarucizumab (Praxbind®)	dabigatran	<ul style="list-style-type: none"> administered as two 50-mL bolus infusions containing 2.5 g each of idarucizumab (total 5 g) no more than 15 minutes apart 	<ul style="list-style-type: none"> Complete reversal is expected within minutes. Ongoing bleeding is due to anatomical cause
PCC (Octaplex®)	rivaroxaban apixaban dabigatran*	<ul style="list-style-type: none"> 50 units/kg, max 3000 units Mix diluent and PCC following manufacturer instructions infuse at 1 mL/min followed by maximum 3 mL/min (180 mL/hr) per institution/Blood Bank instructions 	<ul style="list-style-type: none"> Contraindicated in heparin-induced thrombocytopenia For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal
PCC (Beriplex®)	rivaroxaban apixaban dabigatran*	<ul style="list-style-type: none"> 50 units/kg, max 3000 units Mix diluent and PCC following manufacturer instructions infuse at 1 mL/min followed by maximum 8 mL/min (480 mL/hr) per institution/Blood Bank instructions 	<ul style="list-style-type: none"> Contraindicated in heparin-induced thrombocytopenia For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal
Activated PCC (FEIBA®)	dabigatran*	<ul style="list-style-type: none"> 50 units/kg, max 2000 units 	<ul style="list-style-type: none"> Limited availability through Canadian Blood Services For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal Can also use for apixaban and rivaroxaban but PCC preferred
Frozen plasma	Coagulopathy (e.g. dilutional from massive transfusion, hepatic failure, DIC)	<ul style="list-style-type: none"> 10-15 mL/kg (3-4 units for adults) 	<ul style="list-style-type: none"> Should not be used to reverse abnormal lab parameters from NOACs Caution in patient at risk for volume overload (eg. CHF)
Cryoprecipitate	Coagulopathy (eg. dilutional from massive transfusion, hepatic failure, DIC)	<ul style="list-style-type: none"> 10 units IV 	<ul style="list-style-type: none"> Only consider if fibrinogen level is < 1.0 g/L
Tranexamic Acid (Cyclokapron®)	rivaroxaban apixaban dabigatran	<ul style="list-style-type: none"> 1g IV bolus then 1 g over 8 hrs 	<ul style="list-style-type: none"> May exacerbate prothrombotic effect if given with other prothrombotic products

*If idarucizumab unavailable.

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

Notes regarding pro-hemostatic therapies (PCC, FEIBA®, recombinant factor VIIa) for NOAC-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 NOAC antidotes and do not affect the inhibitory effect of NOACs on pre-existing coagulation factors IIa (thrombin) and Xa. These agents may reduce NOAC-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 NOAC-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 NOACs.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- New/Novel Oral Anticoagulants (NOACs): Comparison and Frequently Asked Questions
- New/Novel Oral Anticoagulants (NOACs): Coagulation Tests
- New/Novel Oral Anticoagulants (NOACs): Peri-Operative Management
- Rivaroxaban (Xarelto®)

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Date of version: 2016Jan12

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.