NOACS/DOACS*: MANAGEMENT OF BLEEDING

Thrombosis Canada
Thrombose Canada

*NOACs/DOACs = Non-vitamin K antagonist Oral AntiCoagulants, also known as Direct Oral AntiCoagulants

Objective:

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

Background:

Four DOACs (dabigatran, apixaban, edoxaban, and rivaroxaban) are approved for clinical use in Canada based on findings from large randomized trials. Like all anticoagulants, bleeding is the major complication of DOAC therapy. Although the mainstay of bleeding management is supportive, a specific anticoagulant reversal agent is available for dabigatran (idarucizumab [Praxbind®]), and specific reversal agents for factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) may be available soon in Canada. There are a few observational studies evaluating the use of non-specific prohemostatic products (e.g. 4-factor prothrombin complex concentrate [PCC; Beriplex®, Octaplex®], activated PCC [aPCC; FEIBA®]) in bleeding patients receiving DOACs. 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, hemorrhoidal bleeding, subconjunctival bleed, self-limited epistaxis:

- Continue anticoagulant and monitor
- Confirm the patient is receiving the appropriate drug and dose based on indication, age, weight, and creatinine clearance
- Consider checking CBC and creatinine, to ensure they are stable
- Review concomitant medications which may contribute to bleeding (e.g. ASA, NSAIDs)

Clinically Relevant Nonmajor Bleeding

Non-Life-Threatening Bleeding (e.g. hemodynamically stable gastrointestinal bleed, epistaxis, hematuria, or menstrual bleeding; requiring medical attention and/or intervention):

Initial management

- Hold anticoagulant therapy
- Apply local hemostatic measures (e.g. compression, packing, splinting) when possible
- Obtain CBC, PT/INR, PTT, and creatinine
- Determine the likely presence of the DOAC and the expected elimination rate using time of last dose, drug half-life, and creatinine clearance (CrCl). Estimated half-life for DOACs are:
    - apixaban: 8-12 h if CrCl ≥50 mL/min; 8-12 h if CrCl 30-49 mL/min
    - dabigatran: 7-17 h if CrCl ≥50 mL/min; 17-20 h if CrCl 30-49 mL/min
    - edoxaban: 10-14 h if CrCl ≥50 mL/min
    - rivaroxaban: 7-11 h if CrCl >50 mL/min; 7-11 h if CrCl 30-49 mL/min

- If available with timely results, consider measuring plasma DOAC concentration using a specific validated assay (**Table 1**)
- Supportive transfusion therapy should be considered:
    - RBC transfusion if symptomatic anemia. Maintain hemoglobin greater than 70 g/L during active bleeding (consider higher target if ischemic heart disease is present)
    - Platelet transfusion if platelet count less than 50 x 10^9/L
    - Consultation for further investigation and definitive management (e.g. endoscopy, interventional radiology, surgery)

Major Bleeding

Severe/Life Threatening Bleeding (e.g. symptomatic bleeding in a critical area or organ, such as intracranial hemorrhage, severe gastrointestinal bleed with actual or impending hemodynamic instability, retroperitoneal bleed, intramuscular bleed with compartment syndrome, intraspinal bleed, pericardial bleed, or intramuscular bleed with compartment syndrome.

Initial management

- Hold anticoagulant therapy
- Initiate resuscitation in a monitored setting
- Apply local hemostatic measures (e.g. compression, packing, splinting) when possible
- Consult an expert urgently (hematologist, internist, ER physician, pharmacist) for advice
- Obtain CBC, PT/INR, PTT, and creatinine STAT
- Determine the likely presence of the DOAC and the expected elimination rate using time of last dose, drug half-life and CrCl
- If available with timely results, consider measuring plasma concentration of DOAC using a specific validated assay (**Table 1**)
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- Supportive transfusion therapy should be considered:
    - RBC transfusion if symptomatic anemia. Maintain hemoglobin greater than 70 g/L during active bleeding (consider higher target if ischemic heart disease is present)
    - Platelet transfusion if platelet count less than 50 x 10^9/L. Consider higher platelet count threshold of 100 x 10^9/L in patients with bleeding into a critical site (e.g. intracranial hemorrhage)
    - Plasma, cryoprecipitate, or fibrinogen concentrate only if concomitant coagulopathy (e.g. massive transfusion, disseminated intravascular coagulation, liver disease)
- Consultation for further investigation and definitive management (e.g. endoscopy, interventional radiology, surgery)
- Consider reversal and/or pro-hemostatic agents (see next section)

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 CrCl), give idarucizumab (Praxbind®). Complete reversal is expected within minutes. Note, if dabigatran levels are rapidly available and less than 30-50 ng/mL, no reversal is required.
- If idarucizumab (Praxbind®) is not available, consider alternative therapies such as prothrombin complex concentrate (PCC) Octaplex® or Beriplex®, or FEIBA®. Reversal may or may not occur.
- Inform patients/families regarding small thrombotic risk of idarucizumab, PCC, and FEIBA® (e.g. stroke, myocardial infarction, and venous thromboembolism), but that consequences of uncontrolled bleeding likely exceed this risk.
- Adjunctive therapy to consider: hemodialysis (~65% removal after 4 hours) if feasible or tranexamic acid.

Apixaban/Edoxaban/Rivaroxaban

- If apixaban/edoxaban/rivaroxaban is likely still active (as per time of last dose and CrCl), give PCC. Reversal may or may not occur. If drug levels are available and less than 30-50 ng/mL, no reversal is required.
- Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke, myocardial infarction, and venous thromboembolism), but that consequences of uncontrolled bleeding likely exceed this risk.
- Consider adjunctive therapy with tranexamic acid.
- Andexanet alfa, a specific antidote, was studied in a single-arm study. A randomized controlled trial of this antidote is underway. It is not yet approved by Health Canada.

TABLE 1: INTERPRETATION OF COAGULATION TESTS FOR DOACS

Test	Apixaban (Eliquis®)	Dabigatran (Pradaxa®)	Edoxaban (Lixiana®)	Rivaroxaban (Xarelto®)*
PT/INR	**Normal value does NOT exclude anticoagulant effect.** If increased, may indicate anticoagulant effect[2]			
aPTT	**Normal value does NOT exclude anticoagulant effect** If increased, may indicate anticoagulant effect[2]			
Dilute TT (dTT, Hemoclot®) or ECT (Ecarin clotting time)	Not relevant	• <30 ng/mL = likely no significant anticoagulant effect[1] • >30 ng/mL = likely significant anticoagulant effect[1]	Not relevant	Not relevant
Thrombin time	Not relevant	• **Normal indicates no dabigatran present** • If increased, indicates some anticoagulant effect	Not relevant	Not relevant
Calibrated anti-Xa	• <30 ng/mL = likely no significant anticoagulant effect[1]	Not relevant	• <30 ng/mL = likely no significant anticoagulant effect[1]	• <30 ng/mL = likely no significant anticoagulant effect[1]

	● >30 ng/mL = likely significant anticoagulant effect[1]		● >30 ng/mL = likely significant anticoagulant effect[1]	● >30 ng/mL = likely significant anticoagulant effect[1]

[1]There 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.
[2]Rule 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: ADULT DOSING OF PROTHROMBOTIC THERAPIES AND PRODUCTS

Product	Bleeding on	Dosing	Notes
Idarucizumab (Praxbind®)	dabigatran	● Administered as two 50-mL bolus infusions containing 2.5 g each of idarucizumab (total 5 g) no more than 15 minutes apart	● Complete reversal is expected within minutes and lasts for 24 hrs or more in most patients. ● Ongoing bleeding is due to anatomical cause
PCC (Octaplex®)	apixaban dabigatran* edoxaban rivaroxaban	● 50 units/kg, max 3000 units (typical initial dose of 2000 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	● 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®)	apixaban dabigatran* edoxaban rivaroxaban	● 50 units/kg, max 3000 units (typical initial dose of 2000 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	● 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*	● 50 units/kg, max 2000 units	● 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, edoxaban and rivaroxaban but PCC preferred
Frozen plasma	Coagulopathy (e.g. dilutional from massive transfusion, hepatic failure, DIC)	● 10-15 mL/kg (3-4 units for adults)	● Should not be used to reverse abnormal lab parameters from DOACs ● Caution in patient at risk for volume overload (e.g. CHF)
Cryoprecipitate	Coagulopathy (e.g. dilutional from massive transfusion, hepatic failure, DIC)	● 10 units	● Should not be used to reverse abnormal lab parameters from DOACs ● Only consider if fibrinogen level is less than 1.0 g/L
Fibrinogen concentrate	Coagulopathy (e.g. dilutional from massive transfusion, hepatic failure, DIC)	● 4 grams	● Should not be used to reverse abnormal lab parameters from DOACs ● Only consider if fibrinogen level is less than 1.0 g/L
Tranexamic Acid (Cyclokapron®)	rivaroxaban apixaban edoxaban dabigatran	● 1 gram IV bolus then 1 gram over 8 hours	● May exacerbate prothrombotic effect if given with other prothrombotic products or in high doses

*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 randomized study has assessed the clinical efficacy and safety of these agents in patients with active bleeding. The possible role of these agents is mostly based on in vitro studies, animal models, and studies in human volunteers evaluating coagulation markers. Small observational studies have evaluated the use of PCC and aPCC in DOAC-treated bleeding patients.
- PCC (Octaplex®, Beriplex®) and activated PCC (FEIBA®) are coagulation factor concentrates, not DOAC antidotes. They do not affect the inhibitory effect of DOACs on coagulation factors IIa (thrombin) and Xa, and they do not impact on DOAC drug levels. These agents may reduce DOAC-associated bleeding by providing large amounts of exogenous 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. Therefore, it can be a useful adjunct in the treatment of DOAC-associated bleeding.
- 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 anticoagulant drug and dose based on clinical characteristics such as indication, age, weight, and creatinine clearance.
- Assess concomitant 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: Perioperative Management
- Rivaroxaban (Xarelto®)

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