DOACS*:
MANAGEMENT OF BLEEDING

* DIRECT ORAL ANTICOAGULANTS

OBJECTIVE:

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

BACKGROUND:

Four direct oral anticoagulants (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®]). There are currently nonspecific reversal agents available for factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) available in Canada. The use of non-specific pro-hemostatic products (e.g. 4-factor prothrombin complex concentrate [PCC; Beriplex®, Octaplex®], activated PCC [aPCC; FEIBA®]) has been evaluated in small cohorts of DOAC-treated patients with major bleeding . 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 (examples: 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 measuring hemoglobin, platelet count, creatinine, and liver function tests
- Review concomitant medications which may contribute to bleeding (e.g. antiplatelet therapies, NSAIDs)

Clinically Relevant Nonmajor Bleeding

Non-Life-Threatening Bleeding is that which requires medical attention and/or non-urgent intervention (examples: hemodynamically stable chronic gastrointestinal bleed, epistaxis, hematuria, or menstrual bleeding):

Initial management

- Hold anticoagulant therapy
- Apply local hemostatic measures if appropriate (e.g. compression, packing, suturing)
- Obtain hemoglobin, platelet count, coagulation tests (PT/INR, aPTT), creatinine, and liver function tests. Note that routine coagulation tests are not sensitive or specific for the presence of DOACs but can be used qualitatively. Otherwise, unexplained abnormalities in routine coagulation tests in patients receiving DOACs suggests that clinically significant DOAC levels are likely present.
- Determine the likely presence of the DOAC and the expected elimination rate with the following information:
    1. Timing of last dose

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

Major Bleeding

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

Initial management

- Hold anticoagulant therapy
- Initiate resuscitation in a monitored setting
- Apply local hemostatic measures (e.g. compression, packing, suturing) when applicable
- Consult an expert urgently for advice regarding management of coagulopathy (e.g. hematologist, internist, ER physician, pharmacist) and consult for definitive hemostatic therapy as applicable (e.g. gastroenterology, interventional radiology, surgery)
- STAT laboratory testing: hemoglobin, platelet count, coagulation tests (PT/INR, aPTT), creatinine, liver function tests, group and screen. Note that routine coagulation tests are not sensitive or specific for the presence of DOACs but can be used qualitatively. Otherwise, unexplained abnormalities in routine coagulation tests in patients receiving DOACs suggests that clinically significant DOAC levels are present.
- Determine the likely presence of the DOAC and the expected elimination rate with the following information:
    1. Timing of last dose
    2. Drug half-life and creatinine clearance. See estimated half-life for DOACs, #2 under Initial Management, above.
- If available with timely results, and the results would change management, consider measuring plasma concentration of DOAC using a specific validated assay (**Table 1**)
- Supportive transfusion therapy should be considered:
    - RBC transfusion for symptomatic anemia. Maintain hemoglobin greater than 70 g/L during active bleeding (consider higher target if ischemic heart disease is present)

    - Platelet transfusion for 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 critical sites (e.g. spinal cord) with expert consultation
    - Administer plasma, cryoprecipitate, or fibrinogen concentrate only if indicated for concomitant coagulopathy (e.g. massive transfusion, disseminated intravascular coagulation, liver disease)
- Consider reversal or pro-hemostatic agents (see next section)
- Consider (clinical setting) appropriate blood pressure management to facilitate on-going hemostasis (e.g. permissive hypotension in trauma)

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 present (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 less than 30-50 ng/mL, no reversal is required.
- If idarucizumab (Praxbind®) is not available, consider alternative non-specific hemostatic therapies such as activated prothrombin complex concentrate (aPCC; FEIBA®) or prothrombin complex concentrate (PCC) Octaplex® or Beriplex®. PCCs are not selective reversal agents, and their effect is debatable.
- Inform patients/families regarding potential thrombotic risk in this setting due to interruption of anticoagulation, activation of coagulation to stop bleeding and administration of idarucizumab, PCC, or FEIBA® (e.g. stroke, myocardial infarction, and venous thromboembolism), but highlight that consequences of uncontrolled bleeding likely exceed this risk.
- Adjunctive therapy to consider hemodialysis (~65% removal after 4 hours) if feasible or tranexamic acid (limited data in this setting).

Apixaban/Edoxaban/Rivaroxaban

- If apixaban/edoxaban/rivaroxaban is likely still present (as per time of last dose and creatinine clearance), give PCC. PCCs are not selective reversal agents, and their effect is debatable. If specific drug levels are rapidly available and less than 30-50 ng/mL, no treatment is required.
- Inform patients/families regarding potential thrombotic risk in this setting due to interruption of anticoagulation, activation of coagulation to stop bleeding, and administration of PCC (e.g. stroke, myocardial infarction, and venous thromboembolism), but highlight that consequences of uncontrolled bleeding likely exceed this risk.
- Consider adjunctive therapy with tranexamic acid for uncontrolled bleeding (limited data in this setting)
- Note: Andexanet alfa is a specific antidote for factor Xa inhibitors but is not currently available in 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] • >30 ng/mL = likely significant anticoagulant effect[1]	Not relevant	• <30 ng/mL = likely no significant anticoagulant effect[1] • >30 ng/mL = likely significant anticoagulant effect[1]	• <30 ng/mL = likely no 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 REVERSAL AGENTS, PROHEMOSTATIC THERAPIES, AND TRANSFUSION PRODUCTS

Product	Bleeding on	Dosing	Notes
Idarucizumab (Praxbind®)	dabigatran	• Total dose is 5 g administered as two 50-mL bolus infusions containing 2.5 g each of idarucizumab no more than 15 minutes apart	• Complete reversal is expected within minutes and lasts for 24 hrs or more in most patients.
PCC (Octaplex®)	apixaban dabigatran* edoxaban rivaroxaban	• 25 to 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	• Optimal dosing has not been established • Refer to institutional guidelines for dosing (if available) • **Contraindicated in heparin-induced thrombocytopenia**
PCC (Beriplex®)	apixaban dabigatran* edoxaban rivaroxaban	• 25 to 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	• Optimal dosing has not been established • Refer to institutional guidelines for dosing (if available) • **Contraindicated in heparin-induced thrombocytopenia**

Activated PCC (FEIBA®)	dabigatran*	• 50 units/kg, max 2000 units	• Optimal dosing has not been established • Limited availability through Canadian Blood Services • Can also be used for apixaban, edoxaban and rivaroxaban but PCC is preferred when available
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 IV 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 limited and based on the results of several small observational cohorts of DOAC-treated bleeding patients, in vitro studies, animal models, and studies in human volunteers evaluating coagulation markers.
- 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 affect 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 benefit in traumatic bleeding, postpartum bleeding, and cardiac surgery and it has a good safety profile. Therefore, it may be considered as an adjunct for the treatment of DOAC-associated bleeding although specific data in this setting are lacking.
- Recombinant factor VIIa (rFVIIa; NovoSeven®, Niastase®) is generally not recommended because of a lack of benefit in animal and in vitro studies and is associated with prothrombotic risk.

WHEN BLEEDING HAS RESOLVED

1. Assess patients for resumption of anticoagulation when hemostasis is achieved with consideration of patient values and preferences. Confirm ongoing indication for anticoagulation.
2. Estimate the risks of recurrent bleeding and thrombosis (and their clinical sequelae) with multidisciplinary input.
3. Assess baseline laboratory tests (hemoglobin, platelet count, creatinine, liver function tests) and current patient's weight.

4. Review concomitant medications and reassess the need for medications which may contribute to bleeding (e.g. antiplatelet therapies, NSAIDs).
5. Confirm the appropriateness of the type and dose of anticoagulant based on clinical characteristics such as indication, age, weight, and creatinine clearance.
6. Provide education and counselling regarding bleeding complications and when to seek medical attention.
7. Ensure routine follow-up and reassessment of #1 to #6 at regular intervals.

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®)
- DOACs: Comparison and Frequently Asked Questions
- DOACs: Coagulation Tests
- DOACs: Perioperative Management
- Edoxaban (Lixiana®)
- Rivaroxaban (Xarelto®)

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