DOACs: Management of Bleeding

Thrombosis Canada
Thrombose Canada

* 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; apixaban, edoxaban, rivaroxaban, and dabigatran) 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. DOACs have short half-lives (generally about 10 to 12 hours in the absence of renal or hepatic dysfunction) and significant drug clearance occurs within 24 hours of ingestion. Referral for surgical/procedural intervention to stop bleeding should be considered as appropriate for patients with serious bleeding. A specific reversal agent is available for patients treated with dabigatran who have acute serious bleeding or require emergency surgery (idarucizumab [Praxbind®]). Andexanet alfa (Ondexxya®) is indicated for adult patients treated with FXa inhibitors rivaroxaban or apixaban when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The 4-factor prothrombin complex concentrates (4F-PCC; e.g. [4F-PCC; Beriplex®, Octaplex®] or activated PCC products [aPCC; FEIBA®]) may aid hemostasis by supplying coagulation factors to overcome anticoagulant effect but they do not reverse anticoagulant effect, nor do they reduce the level of active drug. Appropriate management in all cases of bleeding requires a systematic approach to assessment and management including an understanding of 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 DOAC and monitor
- Confirm the patient is receiving the appropriate drug and dose based on indication, age, weight,creatinine clearance, co-medications
- 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 that requires medical attention and/or non-urgent intervention (examples: hemodynamically stable chronic gastrointestinal bleed, epistaxis, hematuria, or menstrual bleeding):

- Hold DOAC therapy
- Apply local hemostatic measures if appropriate (e.g. compression, packing, suturing)
- Laboratory testing: e.g. hemoglobin, platelet count, coagulation tests (PT/INR, aPTT), creatinine,liver function tests, group and screen (as appropriate).
    - As per Table 1 below, note that PT/INR and aPTT can "rule in" but are not sensitive enough to "rule out" clinically significant DOAC effect. Otherwise unexplained abnormalities in routine coagulation tests in patients receiving DOACs suggest that clinically significant DOAC levels are likely present.
    - An exception is the thrombin time (TT) which is very sensitive for detecting low levels of dabigatran. A normal TT rules out the presence of dabigatran.
- Determine whether clinically significant levels of DOAC are likely to be present and the expected rate of drug clearance with the following information:
    - Timing of last dose
    - Drug half-life, and creatinine clearance (CrCl). Estimated half-lives for DOACs are:

DOAC	CrCl ≥50 mL/min	CrCl 30-49 mL/min
Apixaban	8 to 12 hours	8 to 12 hours
Dabigatran	7 to 17 hours	17 to 20 hours
Edoxaban	10 to 14 hours	
Rivaroxaban	7 to 11 hours	7 to 11 hours

- **If available with timely results AND the results would change management**, consider measuring plasma DOAC concentration using a specific validated assay which provides a quantitative DOAC level (**Table 1**)
- If indicated, administer transfusion therapies as per guidelines
- Consultation for investigation and definitive management of bleeding source as appropriate (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).

- Hold DOAC 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 procedural intervention 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 (as appropriate). As per Table 1 below, note that PT/INR and aPTT can "rule in" but are not sensitive enough to "rule out" clinically significant anticoagulant effect. Otherwise unexplained abnormalities in routine coagulation tests in patients receiving DOACs suggest that clinically significant DOAC levels are likely present.
    - An exception is the thrombin time (TT) which is very sensitive to even low levels of dabigatran. A normal TT rules out the presence of dabigatran.

- Determine whether clinically significant levels of DOAC are likely to be present and the expected rate of drug clearance with the following information:
    - Timing of last dose
    - Drug half-life and creatinine clearance.

DOAC	CrCl ≥50 mL/min	CrCl 30-49 mL/min
Apixaban	8 to 12 hours	8 to 12 hours
Dabigatran	7 to 17 hours	17 to 20 hours
Edoxaban	10 to 14 hours	
Rivaroxaban	7 to 11 hours	7 to 11 hours

- If available with timely results, AND the results would change management, consider measuring plasma concentration of DOAC using a specific validated assay which provides a quantitative level of DOAC (**Table 1**).
- If indicated, administer transfusion therapies as per guidelines
- Consider specific reversal or hemostatic agents (see next section)

Anticoagulant reversal agents and non-specific hemostatic therapies for DOAC-related severe/life-threatening bleeding (see Table 2)

Reversal or hemostatic therapies are indicated for bleeding when both of the following are present:

√ Severe bleeding

AND

√ Clinically significant DOAC levels are likely to be present

Suspected based on clinical assessment (timing of last dose, renal function, routine coagulation tests)

OR

Measured using specific DOAC assay (levels over 30 to 50 ng/mL)*

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

Dabigatran

- Specific reversal with idarucizumab (Praxbind®)
    - The dose of idarucizumab is 5 g IV (2 x 2.5 g vials)
    - Complete reversal of anticoagulant effect is expected within minutes after administration.
- If idarucizumab (Praxbind®) is not available, consider alternative non-specific hemostatic therapies such as activated prothrombin complex concentrate (aPCC; FEIBA®) or 4-factor prothrombin complex concentrate (4F-PCC; Octaplex® or Beriplex®).

- 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.
- Hemodialysis can be considered as an adjunctive measure (~65% removal of dabigatran after 4 hours) if feasible).

Apixaban/Edoxaban/Rivaroxaban (oral factor Xa inhibitors)

- Specific reversal agents should be used if available.
- Andexanet alfa is a specific antidote for factor Xa inhibitors. Andexanet alfa is indicated for adult patients treated with FXa inhibitors rivaroxaban or apixaban when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
- 4F-PCC is not a specific reversal agent but may be given to aid hemostasis for patients presenting with severe or life-threatening bleeding who are likely to have clinically significant drug levels
- The optimal dosing strategy of 4F-PCC is uncertain, and regimens include:
    - (i) 2000 units fixed dose
    - (ii) 25 – 50 units/kg with a maximum for single dose of 3000 units.
- Consult local institutional protocols or hematology/thrombosis for advice as 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.

Notes regarding non-specific pro-hemostatic therapies (PCC, FEIBA®) for DOAC-associated severe/life-threatening bleeding:

- Supportive clinical data for pro-hemostatic agents (PCC, FEIBA®, rVIIa) are based on the results of observational cohorts of DOAC-treated bleeding patients, in vitro studies, animal models, and studies in human volunteers evaluating coagulation markers.
- 4F-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. The use of tranexamic acid is not recommended for genitourinary bleeding or gastrointestinal bleeding.
- 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 patient's weight.
4. Review concomitant medications and reassess the need for medications which may contribute to bleeding (e.g. antiplatelet therapies, NSAIDs, SSRIs, herbal supplements).
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.

Table 1: Interpretation of coagulation tests for DOACs*

Test	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
PT/INR	**Normal value does NOT exclude anticoagulant effect.** If increased, may indicate anticoagulant effect[1]			
aPTT	**Normal value does NOT exclude anticoagulant effect** If increased, may indicate anticoagulant effect[1]			
Dilute TT (dTT, Hemoclot®) or ECT (Ecarin clotting time)	Not relevant	<50 ng/mL = likely no clinically significant anticoagulant effect[2] >50 ng/mL = likely clinically significant anticoagulant effect[2]	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	<50 ng/mL = likely no clinically significant anticoagulant effect[2] >50 ng/mL = likely clinically significant anticoagulant effect[2]	Not relevant	<50 ng/mL = likely no clinically significant anticoagulant effect[2] >50 ng/mL = likely clinically significant anticoagulant effect[2]	<50 ng/mL = likely no clinically significant anticoagulant effect[2] >50 ng/mL = likely clinically significant anticoagulant effect[2]

[1] Suggests clinically significant anticoagulant effect in the absence of another cause of coagulopathy (e.g. DIC, coagulopathy of liver disease, vitamin K deficiency, warfarin, a coagulation factor inhibitor, factor deficiency)

[2]The term "clinically significant" anticoagulant effect refers to levels that may contribute to bleeding. The threshold for clinically significant anticoagulant effect is unknown. The level chosen (< 50 ng/mL) is extrapolated from observations in clinical trials and agrees with other guidelines (Levy JH, et al. J Thromb Haemost. 2016 Mar;14(3):623-7.)

**Best practices for the use and interpretation of coagulation tests in patient on DOACs is evolving and will be informed by ongoing research; the guidance herein reflects a summation of the available evidence.

Table 2: Adult Dosing of Reversal Agents and Coagulation Concentrates for DOAC-Related Bleeding

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.
Andexanet alfa (Ondexxya®)	apixaban rivaroxaban	• See Table 3, below	• Andexanet alfa is not approved for the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.
4-Factor PCC (Octaplex®)	apixaban dabigatran* edoxaban rivaroxaban	• Fixed dose of 2000 units *OR* 25 to 50 units/kg +/- cap of 3000 units per dose • 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 • Maximum single dose for warfarin reversal is 3000 units • Refer to institutional guidelines for dosing (if available) • **Contraindicated in heparin-induced thrombocytopenia**
4-Factor PCC (Beriplex®)	apixaban dabigatran* edoxaban rivaroxaban	• Fixed dose of 2000 units *OR* 25 to 50 units/kg +/- cap of 3000 units per dose • 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 • Maximum single dose for warfarin reversal is 3000 units • Refer to institutional guidelines for dosing (if available) • **Contraindicated in heparin-induced thrombocytopenia**
Activated PCC (FEIBA®)	dabigatran*	• 50 units/kg, max 2000 units suggested	• 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

*If idarucizumab unavailable.
Abbreviations: CHF, congestive heart failure; DIC, disseminated intravascular coagulation.

Table 3: Andexanet Alfa Dose Based on Rivaroxaban or Apixaban Dose and Timing of Last Dose of FXa Inhibitor Before Andexanet Alfa Initiation

FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low dose*	Low dose*
	> 10 mg or unknown	High dose*	
Apixaban	≤ 5 mg	Low dose*	
	> 5 mg or unknown	High dose*	

*Andexanet Alfa High- and Low-dose regimens:

Dose**	Initial IV Bolus	Follow-on IV Infusion***	Total number of 200 mg vials
Low dose	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes (480 mg)	5 (2 vials bolus + 3 vials infusion)
High dose	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes (960 mg)	9 (4 vials bolus + 5 vials infusion)

** The safety and efficacy of more than one dose have not been evaluated

*** Because the recommended infusion doses are lower than the andexanet alfa content of the vials there will be a small amount of solution remaining in the bag after completion of the infusion.

Special Considerations:

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

Other Relevant Thrombosis Canada Clinical Guides:

- Apixaban
- Dabigatran
- DOACs: Comparison and Frequently Asked Questions
- DOACs: Coagulation Tests
- DOACs: Peri-operative Management
- Edoxaban
- Rivaroxaban

References:

Recommendations for Use of Prothrombin Complex Concentrates in Canada, National Advisory Committee on Blood and Blood Products (https://nacblood.ca/en/resource/recommendations-use-prothrombin-complex-concentrates-canada)

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