

NOACS/DOACS*: MANAGEMENT OF BLEEDING



Thrombosis Canada
Thrombose Canada

OBJECTIVE:

To assist clinicians in the management of bleeding in patients receiving a 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. 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) are expected to be available soon. There are few observational studies evaluating the use of using non-specific prohemostatic products (e.g. 4-factor prothrombin complex concentrate [PCC; Beriplex®, Octaplex®], activated PCC [aPCC; FEIBA®]) in DOAC-treated patients with 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

Non-Major Bleeding e.g. extremity bruising, hemorrhoid 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 hemoglobin, platelet count and renal function to see if they are stable
- Review concomitant medications which may contribute to bleeding (e.g. ASA, NSAIDs)

Major Bleeding

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

- Hold anticoagulant therapy
- 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:
 - apixaban: 8-12 h if CrCl \geq 50 mL/min; 8-12 h if CrCl 30-49 mL/min
 - dabigatran: 7-17 h if CrCl \geq 50 mL/min; 17-20 h if CrCl 30-49 mL/min
 - edoxaban: 10-14 h if CrCl \geq 50 mL/min
 - rivaroxaban: 7-11 h if CrCl $>$ 50 mL/min; 7-11 h if CrCl 30-49 mL/min
- If available, consider measuring 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 $50 \times 10^9/L$
- Consultation for further investigations and definitive management, if indicated (e.g. endoscopy)

Severe/Life Threatening Bleeding (e.g. intracranial hemorrhage, or severe gastrointestinal bleed with actual or impending hemodynamic instability, retroperitoneal bleed, 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) if applicable
- Consult an expert urgently (hematologist, internist, ER physician, pharmacist) for advice
- Refer for procedural/surgical intervention as 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 $50 \times 10^9/L$. 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 DOAC concentrations are estimates based on available evidence that require further study/validation.

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 is required.
- Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke, myocardial infarction, venous thromboembolism), but consequences of uncontrolled bleeding likely exceed this risk.
- Consider adjunctive therapy with 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 is required.
- Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke, myocardial infarction, venous thromboembolism), but consequences of uncontrolled bleeding likely exceed this risk.
- Consider adjunctive therapy with tranexamic acid.

- Specific antidote in development and not yet available.

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, myocardial infarction and venous thromboembolism), but consequences of uncontrolled bleeding likely exceed this risk.
- Adjunctive therapy to consider: hemodialysis (~65% removal after 4 hrs) if feasible or tranexamic acid.

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 is required.
- Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke, myocardial infarction, venous thromboembolism), 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

Test	Apixaban (Eliquis®)	Dabigatran (Pradaxa®)	Edoxaban (Lixiana®)	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 	<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 does NOT exclude anticoagulant effect • If increased, may indicate anticoagulant effect² 	<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"> • 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"> • Not relevant 	<ul style="list-style-type: none"> • Not relevant
Thrombin time	<ul style="list-style-type: none"> • Not relevant 	<ul style="list-style-type: none"> • Normal indicates no dabigatran present 	<ul style="list-style-type: none"> • Not relevant 	<ul style="list-style-type: none"> • Not relevant

		<ul style="list-style-type: none"> If increased, indicates some anticoagulant effect 		
Calibrated anti-Xa	<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"> <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
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 and lasts for 24 hrs or more in most patients. Ongoing bleeding is due to anatomical cause
PCC (Octaplex®)	apixaban dabigatran* edoxaban rivaroxaban	<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®)	apixaban dabigatran* edoxaban rivaroxaban	<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, edoxaban 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 DOACs 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 edoxaban 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 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[®]), 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: Perioperative Management
- Rivaroxaban (Xarelto[®])

REFERENCES:

Alikhan R, et al. The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran. *Emerg Med J* 2014;31(2):163-168.

Cuker A, et al. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am Coll Cardiol 2014;64:1128-1139.

Levy JH, Ageno W, Chan NH, Crowther M, Verhamme P, Weitz, JI, Subcommittee on Control of Anticoagulation. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost 2016; 14:623-627.

Pollack CV, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373(6):511-520.

Siegal DM, et al. How I treat target-specific oral anticoagulant-associated bleeding. Blood 2014;123(8):1152-1158.

Date of version: 2019Mar29

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.