Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Anticoagulation and Thrombophilia Clinic, Minneapolis Heart Institute®, Abbott Northwestern Hospital.
Tel: 612-863-6800 | Reviewed August 2016, June 2018, July 2019

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Bleeding Category				
	Mild Bleeding (all criteria below)	**Moderate Bleeding** (all criteria below)	**Major Bleeding** (one or more of the below)	**Life-Threatening Bleeding** (one or more of the below)
Hemoglobin decrease and/or transfusion needs	• No significant decrease in hemoglobin • No blood transfusion necessary	• Bleeding associated with ○ decrease in hemoglobin of less than 2 g/dL or ○ transfusion of < 2 units of blood	• Bleeding associated with ○ decrease in hemoglobin of at least 2 g/dL or ○ transfusion of at least 2 units of blood	• Bleeding associated with ○ decrease in hemoglobin of at least 5 g/dL or ○ transfusion of at least 4 units of blood
Symptoms	• Asymptomatic contained, local bleeding	• Symptomatic bleeding excluding critical organs (e.g., intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal, intra-articular, or pericardial)	• Symptomatic bleeding in a critical area or organ (e.g. intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal, intra-articular, or pericardial)	• Potentially fatal hemorrhage • Symptomatic intracranial bleed • Hypotension requiring use of intravenous inotropic agents • Surgical intervention necessary

General Measures				
	Mild Bleeding	**Moderate**	**Major**	**Life-Threatening**
Anticoagulant management	▪ Hold one or more anticoagulant doses based on bleeding severity and renal function ▪ Consider other anticoagulant if ≥ 2 doses of drug need to be interrupted and/or it can no longer be used. Consider bridging agent if CHADS2 score > 4. ▪ Check and monitor for ○ possible medication interactions ○ renal function to verify correct dosing (see 'Direct Oral Anticoagulants (DOACs) Guide') ○ hepatic function to verify correct dosing of rivaroxaban and apixaban (see 'Direct Oral Anticoagulants (DOACs) Guide') ○ restart anticoagulation when bleeding is controlled and no contraindications.	▪ Hold anticoagulant ▪ Consider activated charcoal (1-2 gm/kg) ○ If < 2 hours since last dose of dabigatran or rivaroxaban ○ If < 6 hours since last dose of apixaban ○ For edoxaban, there are currently no data or ongoing studies to evaluate if activated charcoal can be used in cases of overdose/toxicity. ▪ • Check and monitor for ○ possible medication interactions ○ renal function to verify correct dosing (see 'Direct Oral Anticoagulants (DOACs) Guide') ○ hepatic function to verify correct dosing (see 'Direct Oral Anticoagulants (DOACs) Guide')		
Lab	None recommended	Monitor CBC		
Interventions	Local bleeding control	Local bleeding control		

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Factor Xa Inhibitors (apixaban/Eliquis®, betrixaban/Bevyxxa®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
General approach	See general measures above	• See general measures above	• See general measures above • Maintain adequate diuresis	• See general measures above • Maintain adequate diuresis
Bleeding source recommendations		• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: compression and surveillance imaging	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult. • Local hemorrhage including hematoma: compression and surveillance imaging • Intracranial or intraspinal bleed: neurology and neurosurgery consults. Intraocular: ophthalmology consult • Intramuscular or intra-articular: orthopedic consult. • Pericardial: cardiac surgery and cardiology consults • Retroperitoneal: general surgery consult	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult. • Local hemorrhage including hematoma: Compression and surveillance imaging • Intracranial or intraspinal bleed: neurology and neurosurgery consults. • Intraocular: ophthalmology consult • Intramuscular or intra-articular: orthopedic consult. • Pericardial: cardiac surgery and cardiology consults. • Retroperitoneal: general surgery consult
Transfusion		• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Recommend blood transfusion

Labs		• Not recommended	• Check heparin levels (aka anti-Xa)
			  ○ if not available, check PT (in seconds) to estimate medication clearance (see Lab Considerations)
				• Check heparin levels (aka anti-Xa)
				  ○ if not available, check PT (in seconds) to estimate medication clearance (see Lab Considerations)

Hemodialysis		• Not beneficial	• Not beneficial	• Not beneficial
Recombinant Coagulation Factor Xa, inactivated-zhzo (AndexXa®)		• Not recommended	• If continuous active bleeding and abnormal heparin level (aka anti-Xa) or PT and patient taking: ○ apixaban or rivaroxaban: Consider recombinant coagulation factor Xa, inactivated-zhzo (AndexXa®) • Betrixaban, edoxaban: not indicated	• Patient taking apixaban or rivaroxaban: recommend recombinant coagulation factor Xa, inactivated-zhzo (AndexXa®) • Betrixaban, edoxaban: not indicated

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Factor Xa Inhibitors (apixaban/Eliquis®, betrixaban/Bevyxxa®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
PCC or aPCC, rFVIIa		• Not recommended	• If continuous active bleeding and abnormal heparin level (aka anti-Xa) or PT and patient taking: ○ apixaban or rivaroxaban: consider recombinant coagulation factor Xa, inactivated-zhzo (AndexXa®) ○ betrixaban or edoxaban: consider PCC (Kcentra®). ▪ See PCC dosing table ▪ If PCC not available, aPCC or rFVIIa	• Patient taking apixaban or rivaroxaban if AndexXa not available: recommend PCC (Kcentra®). • Patient taking betrixaban or edoxaban: recommend PCC (Kcentra®). ○ If Kcentra not available, consider aPCC or rFVIIaas soon as possible (see Alternatives dosing table).
Coverage with another anticoagulant		• Consider another anticoagulant if ≥ 2 doses of the drug need to be interrupted and/or can no longer be used. Consider bridging agent if $CHADS_2$ score > 4.	• Cover with another anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.	• Cover with another anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.
Resume anticoagulation		• Restart anticoagulation when bleeding is controlled and no further risk of bleeding.	• Decision about restarting anticoagulation should be based on risks and benefits.	• Decision about restarting anticoagulation should be based on risks and benefits.

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Thrombin (factor IIa) Inhibitor (dabigatran/Pradaxa®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
General approach	See general measures above	• See general measures above	• See general measures above • Maintain adequate diuresis	• See general measures above • Maintain adequate diuresis
Bleeding source recommendations		• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: compression and surveillance imaging	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: compression and surveillance imaging • Intracranial or intraspinal bleed: neurology and neurosurgery consults. Intraocular: ophthalmology consult • Intramuscular or intra-articular: orthopedic consult • Pericardial: cardiac surgery and cardiology consults • Retroperitoneal: general surgery consult	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: Compression and surveillance imaging Intracranial or intraspinal bleed: • neurology and neurosurgery consults. • Intraocular: ophthalmology consult Intramuscular or intra-articular: orthopedic consult • Pericardial: cardiac surgery and cardiology consults • Retroperitoneal: general surgery consult
Transfusion		• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Recommend blood transfusion
Labs		• Not recommended	• Check dabigatran level • If dabigatran level not available, check thrombin time (TT) • if TT not available, check aPTT (see Lab Considerations)	• Check dabigatran level • If dabigatran level not available, check thrombin time (TT) • if TT not available, check aPTT (see Lab Considerations)
Hemodialysis		• Not recommended	• Consider hemodialysis ○ especially if abnormal renal function, continuous active bleeding and abnormal dabigatran level, TT or aPTT	• Recommend hemodialysis as soon as possible
idarucizumab (Praxbind®)		• Not recommended	• If continuous active bleeding and abnormal dabigatran level, TT or aPTT (see Lab Considerations), consider idarucizumab (Praxbind®)	• Recommend idarucizumab (Praxbind®) as soon as possible. If not available, recommend PCC (Kcentra®)

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Thrombin (factor IIa) Inhibitor (dabigatran/Pradaxa®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
PCC or aPCC, rFVIIa		• Not recommended	• Consider PCC (Kcentra®) ONLY if idarucizumab is not available and active bleeding with an abnormal dabigatran level, TT or aPTT (see Lab Considerations) • If PCC not available, recommend aPCC or rFVIIa (see PCC dosing table).	• Recommend PCC (Kcentra®) as soon as possible ONLY if idarucizumab (Praxbind®) is not available. • If PCC not available, recommend aPCC or rFVIIa (see PCC dosing table).
Coverage with another anticoagulant	**See general measures above**	• Consider other anticoagulant if ≥ 2 doses of dabigatran need to be interrupted and/ or it can no longer be used. Consider bridging agent if $CHADS_2$ score > 4.	• Cover with other anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.	• Cover with other anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.
Resume anticoagulation		• Restart anticoagulation when bleeding is controlled and no further risk of bleeding.	• Decision about restarting anticoagulation should be based on risks and benefits.	• Decision about restarting anticoagulation should be based on risks and benefits.

First-line Reversal Agents for Direct Factor Xa Inhibitors			
	Dose	**Side Effects**	**Considerations**
Recombinant Coagulation Factor Xa, inactivated-zhzo (AndexXa®) **To reverse apixaban or rivaroxaban only.**	• If last dose of apixaban or rivaroxaban taken ≥ 8 hours prior, OR last apixaban dose ≤ 5 mg OR last rivaroxaban dose ≤ 10 mg taken < 8 hours prior (or unknown): ○ 400 mg AndexXa IV infused at 30 mg/min followed within 2 minutes by 4 mg/min IV for up to 120 minutes • If last apixaban dose > 5 mg (or unknown) OR last rivaroxaban dose > 10 mg (or unknown) taken < 8 hours prior (or unknown when): ○ 800 mg AndexXa IV infused at 30 mg/min followed within 2 minutes by 8 mg/min IV for up to 120 minutes	• Systemic thromboembolism • UTI • Pneumonia • Infusion-related reaction	• Indicated for reversal of anticoagulation in patients treated with apixaban or rivaroxaban only. • AndexXa was FDA-approved based on change in anti-Xa activity in healthy volunteers. • Improvement in hemostasis has not been established. • Safety and efficacy of more than one dose have not been established. • Re-elevation or incomplete reversal of anticoagulant activity can occur. • Arterial and venous thromboembolic events have occurred within 30 days post-reversal with AndexXa. • Resume anticoagulant therapy as soon as appropriate. • Not studied in patients going for urgent or emergent surgeries or procedures.
Kcentra© (PCC, Four-Factor Prothrombin Complex Concentrate)	• **Kcentra 50 units/kg IV** ○ May repeat dose in 12 hours if bleeding continues ○ Maximum dose 5000 units/day ○ Dosing may change based on bleeding severity and thrombotic risk of patient	• DIC • Systemic thromboembolism	• Contains heparin. • Contraindicated in patients with known heparin-induced thrombocytopenia (HIT).

Alternatives if Kcentra is Unavailable		
	Dose	**Side Effects**
Active Prothrombin Complex Concentrate (aPCC, Feiba©)	• **aPCC 50-80 units/kg IV** ○ May repeat dose in 12 hours if bleeding continues ○ Maximum dose: 200 units/kg/day ○ Dosing may change based on bleeding severity and thrombotic risk of patient ○ Does not contain heparin	• DIC • systemic thromboembolism
Recombinant active factor VII (rVIIa, NovoSeven©)	• **rVIIa 20 mcg/kg IV** ○ May repeat dose every 2 hours until hemostasis achieved or until treatment judged ineffective. ○ Maximum dose: 90 mcg/kg ○ Dosing may change based on bleeding severity and thrombotic risk of patient ○ Does not contain heparin	• DIC • systemic thromboembolism

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

First-line Reversal Agent for Dabigatran (Pradaxa)			
	Dose/Administration	**Side Effects**	**Considerations**
idarucizumab (Praxbind©)	• **idarucizumab 5 gm IV divided in two 2.5 gm doses** • Administer as two consecutive infusions by hanging vials or as consecutive bolus injections of both vials one after another via syringe • A pre-existing IV line may be used but must be flushed with saline prior to infusion. No other infusion should be administered via the same IV access. • There is limited data to support administration of an additional 5 gm dose in 24 hours • Dosing may change based on bleeding severity and thrombotic risk of patient	• Headache • Hypokalemia • Delirium • Constipation • Pyrexia • Pneumonia	• Idarucizumab is a specific reversal agent for dabigatran with no impact on the effect of other anticoagulants or antithrombotic therapies. • Dabigatran can be re-initiated 24 hours after administration of idarucizumab when clinically appropriate. • Serious adverse reactions have been reported in patients with hereditary fructose intolerance due to sorbitol excipient • Idarucizumab is also indicated for reversal of dabigatran-related anticoagulation prior to emergency surgery/urgent procedures

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Lab Considerations

Direct Factor Xa Inhibitors
(apixaban/Eliquis®, betrixaban/Bevyxxa®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)

Rivaroxaban and apixaban

Heparin level (aka anti-Xa)

- The assay used to calculate heparin levels shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
- A heparin (anti-Xa) level of <0.1 units/mL suggests lack of significant factor Xa inhibitor activity

PT/INR

- The PT (reported in seconds) shows some correlation with direct factor Xa inhibitor level; correlation with the calculated INR is weaker.
- A normal PT likely rules out clinically significant levels of direct factor Xa inhibitor.
- Due to variability of PT/INR reagents, this test is not recommended to try to rule out the presence of the direct factor Xa inhibitor. Heparin levels (aka anti-Xa) should be ordered instead.

Edoxaban and Betrixaban

Heparin level (aka anti-Xa)

- The assay used to calculate heparin levels shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
- A heparin (anti-Xa) level of <0.1 units/mL suggests lack of significant factor Xa inhibitor activity

PT/INR

- No good correlation with PT or aPTT

Direct Thrombin (factor IIa) Inhibitor
(dabigatran/Pradaxa®)

Dabigatran level

- The preferred test if available (performed at Allina Health Central Lab at Allina Commons)

Thrombin time (TT)

- Useful to rule out presence of dabigatran
- A normal thrombin time essentially rules out clinically significant levels of dabigatran

aPTT

- Can be used if dabigatran level and TT tests are not available.
- aPTT is less sensitive than TT and may be normal at trough drug level
- An elevated aPTT cannot quantify the amount of dabigatran present

PT/INR

- Less sensitive than TT and aPTT

NOTE: *Specific assays for apixaban, betrixaban, edoxaban, or rivaroxaban are not currently available.*

Disclaimer

"Guidelines are not meant to replace clinical judgment or professional standards of care. Clinical judgment must take into consideration all the facts in each individual and particular case, including individual patient circumstances and patient preferences. They serve to inform clinical judgment, not act as a substitute for it. These guidelines were developed by a Review Organization under Minn. Statutes §145.64 et. seq., and are subject to the limitations described as Minn. Statues §145.65."

References

1. J Thromb Thrombolysis. 2013 Aug 9. [Epub ahead of print]
2. Eur Heart J 2013;34:489
3. J Thromb Thrombolysis 2013;35:387
4. J Thromb Thrombolysis 2013;35:391
5. Blood. 2013 May 2;121(18):3554-62.doi: 10.1182/blood-2012-11-468207 Epub 2013 Mar 8
6. Am J Health Syst Pharm. 2013;70(10 Suppl 1):S12-21.
7. Int J Lab Hematol. 2013 Jun;35(3):262-8. doi: 10.1111/ijlh.12065
8. Am J Hematol. 2012;87 Suppl 1:S141-5
9. Clinical Chemistry 2012;59:807
10. Circulation 2012;126:343
11. Thromb Haemost 2012;10:1841
12. Blood. 2012:119:3016-23.
13. Circulation 2011;124:1573
14. ASH 2011. Abstract 2316
15. Thromb Haemost. 2010;103:1116–1127.
16. J Thromb. Haemost. 2009 Jul;7 Suppl 1:107–10
17. Transfusion. 2004 Apr;44(4):605-17
18. New Engl J Med 2013;369:1406-15
19. N Engl J Med 2013;369:2093-104
20. Thromb Res. 2014 Oct;134(4):909-13
21. Thromb Haemost. 2012 Feb;107(2):253-9
22. J Am Coll Cardiol 2014;64:1128-39 23. N Engl J Med 2015;373:511-20
23. Praxbind package insert. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. Oct 2015
24. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, Florido R, Hucker W, Mehran R, Messé SR, Pollack CV Jr., Rodriguez F, Sarode R, Siegel D, Wiggins BS. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017;70:Epub ahead of print.
25. AndexXa package insert. Portola Pharmaceuticals, Inc. South San Fransicso, CA. May 2018