Management of Bleeding Associated with the Novel Oral Anticoagulants

March 2014

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

General Measures		
	Mild Bleeding	**Moderate or Major or Life-Threatening Bleeding**
Anticoagulant drug	• 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 appendix) • hepatic function to verify correct dosing of rivaroxaban and apixaban (see appendix) • Restart anticoagulation when bleeding is contained 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 • Check and monitor for • possible medication interactions • renal function to verify correct dosing (see appendix) • hepatic function to verify correct dosing of rivaroxaban and apixaban (see appendix)
Lab	Not recommended	Monitor CBC
Interventions	Local bleeding control	Local bleeding control

Direct Thrombin 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 bleed 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 appendix)	Check dabigatran level →If dabigatran level not available, check thrombin time (TT) →if TT not available, check aPTT (see appendix)
Hemodialysis		Not recommended	• Consider hemodialysis - especially if abnormal renal function, continuous active bleeding and abnormal dabigatran level, TT or aPTT tests.	• Recommend hemodialysis as soon as possible.
PCC, APCC or rVIIa		Not recommended	If continuous active bleeding and abnormal dabigatran level, TT or aPTT (see appendix). • Consider PCC, - if not available, aPCC or rFVIIa	Recommend PCC as soon as possible - if not available, recommend aPCC or rFVIIa (see appendix).
Coverage with other anticoagulant and/or		Consider other anticoagulant if ≥ 2 doses of dabigatran need to be interrupted &/or it can no longer be used. Consider bridging agent if CHADS2 score is > 4	Cover with other anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if CHADS2 score > 4	Cover with other anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if CHADS2 score > 4
Resume anticoagulant		Restart anticoagulation when bleeding is contained 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

Direct Factor Xa Inhibitors (rivaroxaban/Xaralto©, apixaban/Eliquis©)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
General approach	See general measure 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 bleed 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	• Recommend blood transfusion
Labs		Not recommended	Check heparin levels (aka Anti-Xa) →if not available, check PT (in seconds) to estimate medication clearance (see appendix)	Check heparin levels (aka Anti-Xa) →if not available, check PT (in seconds) to estimate medication clearance (see appendix)
Hemodialysis		Not beneficial	Not beneficial	Not beneficial
PCC or, APCC rVIIa		Not recommended	If continuous active bleeding and abnormal heparin levels (aka Anti-Xa) or PT (see appendix for level monitoring and dosing) • Consider PCC, - if not available, aPCC or rFVIIa	Recommend PCC, - if not available, consider aPCC or rFVIIa as soon as possible (see appendix for dosing)
Coverage with other anticoagulant and/or		Consider other anticoagulant if ≥ 2 doses of the drug need to be interrupted and or it can no longer be used. Consider bridging agent if CHADS2 score is > 4	Cover with other anticoagulant (preferable low intensity unfractionated heparin) when deemed safe especially if CHADS2 score > 4	Cover with other anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if CHADS2 score > 4
Resume anticoagulant		Restart anticoagulation when bleeding is contained 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

APPENDIX

	Dabigatran (Pradaxa):	Rivaroxaban (Xarelto):	Apixaban (Eliquis):
Non-valvular atrial fibrillation	- 150 mg po BID (CrCl; >30 mL/min) - 75 mg po BID (CrCl: 15-30 mL/min) - Consider using 75 mg po BID if used with permeable glycoprotein transport system (P-gp) inhibitors such systemic ketoconazole and dronedarone in patients with impaired renal function (CrCl 30-50 mL/min). Avoid concomitant use if CrCl <30 mL/min.	- 20 mg po daily (CrCl >50 mL/min) - 15 mg po daily (CrCl 15-50 mL/min) - Avoid using if CrCl <15 mL/min	- 5 mg po BID - Consider 2.5 mg po BID if at least 2 of: 1- Age ≥ 80 2- Cr ≥ 1.5 mL/min 3- Weight ≤ 60 kg
VTE prophylaxis with total hip and knee replacement (THR/TKR)	Not currently indicated	- 10 mg po daily for 35 days (after THR) - 10 mg po daily for 12 days (after TKR) - Avoid using if CrCl <30 mL/min	- 2.5 mg po BID starting 12-24 hours after surgery 1- Knee: for 12 days 2- Hip: for 35 days
Treatment of acute VTE:	Not currently indicated	- 15 mg po BID for 3 weeks then 20 mg po daily - Avoid using if CrCl <30mL/min	Not currently indicated
VTE risk reduction	Not currently indicated	- 20 mg daily - Avoid using if CrCl <30mL/min	Not currently indicated
Drug interactions	- Avoid using with P-gp inducers such as rifampin. - Consider reducing dabigatran dose to 75mg twice daily if used with strong P-gp inhibitors like systemic ketoconazole and dronedarone.	- Avoid using with strong P-gp and CYP3A4 inhibitors such as systemic ketoconazole, itraconazole and ritonavir or with inducers such as phenytoin or rifampin.	- Reduce apixaban dose to 2.5 mg or avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp. - Avoid concomitant use with strong inducers of CYP3A4 and P-gp.

Dosing: *For detailed prescription information, please refer to the manufacturer's prescribing information for each medication!*

Factor Products			
	Four Factor Prothrombin Complex Concentrate (PCC), Kcentra:	**Active Prothrombin Complex Concentrate (APCC), Feiba:**	**Recombinant active factor VII (rVIIa):**
Dose	- 50 units/kg IV. - May repeat another dose in 12 hours if bleeding continues - Maximum dose 5000 units/day - Dosing might change based on the bleeding severity and thrombotic risk of the patient	- 50-80 units/kg IV - May repeat another dose in 12 hours if bleeding continues - Maximum dose: 200 units/kg/day - Dosing might change based on the bleeding severity and thrombotic risk of the patient	- 20 mcg/kg - May repeat dose every 2 hours until hemostasis is achieved or until the treatment is judged ineffective. Max dose of 90mcg/kg - Dosing might change based on the bleeding severity and thrombotic risk of the patient
Side Effects	- Side effects: DIC and systemic thromboembolism	- Side effects: DIC and systemic thromboembolism	- Side effects: DIC and systemic thromboembolism
Considerations	- Contraindicated in patients with known heparin-induced thrombocytopenia. Contains heparin		

Lab Assessments	
Direct Thrombin Inhibitor (dabigatran/Pradaxa©)	**Direct Factor Xa Inhibitors (rivaroxaban/Xaralto©, apixaban/Eliquis©)**
○ *Dabigatran level* - The preferred test if available (performed at Allina Health Central Lab at Abbott Northwestern) ○ *Thrombin time:* - 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. - A normal aPTT rules out clinically significant levels of dabigatran - An elevated aPTT cannot quantify the amount of dabigatran present	○ *Heparin level (aka Anti-Xa)* - The assay used to calculate heparin levels shows reasonable linear correlation with increasing levels of direct factor X inhibitors - A heparin (Anti-Xa) level of <0.1 U/mL suggests lack of significant factor X inhibitor activity ○ *PT/INR:* - The PT (reported in seconds) shows some correlation with the direct factor aX inhibitor level; however, correlation with the calculated INR is weaker. - PLEASE CONTACT THE LAB to request reporting of the PT in seconds. - A normal PT rules out clinically significant levels of the 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 X inhibitor. - Heparin levels (aka Anti-Xa) should be ordered instead.

Note: A specific assay for rivaroxaban and apixaban levels should be available in 6-12 months, pending reagent availability in the USA.

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-2012-11-468207Epub 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;119:3016-3023
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