DOAC Bleeding Management (v1.4)

Determine Bleed Severity

- Determining bleed severity is a key step in making treatment decisions.
- Bleeds can be classified into major and non-major based on several clinical factors.
- **If one or more of the following factors apply, the bleed should be considered major.**

For additional information , visit www.anticoagulationtoolkit.org

Bleeding in critical site (examples below)	Hemodynamic instability (examples below)	Overt bleeding with either:
• Central nervous system bleeds (intracranial, spinal, intraocular) • Pericardial tamponade • Airway, including posterior epistaxis • Hemothorax • Intra-abdominal • Retroperitoneal • Intra-articular • Intra-muscular	• Elevated heart rate • Decrease in SBP >40 mm Hg • Mean arterial pressure (intra-arterial)<65 mm Hg • SBP <90 mm Hg • Orthostatic blood pressure changes • Urine output <0.5 mL/kg/hr	• Hemoglobin drop of ≥2 g/dL or • Administration of ≥2 U of packed RBCs

Assess for Clinically Relevant Drug Levels

- If last dose taken at least 24 hr ago in patients with normal renal function, drug levels probably not clinically relevant.[1]
- If patient taking dabigatran, a TT can be used to rule out clinically relevant drug levels. Specialized tests can quantify drug levels.
- If apixaban, edoxaban, rivaroxaban, or betrixaban, anti-Xa is the preferred test and can be used to rule out relevant drug levels or quantify levels.
- Don't wait for results before administering reversal agents in life-threatening bleeds[1]

	Specialized Test	Drug Level Interpretation	General Test	Drug Level Interpretation
Dabigatran	dTT, ECT, ECA	Normal: not clinically relevant Results correlate with drug level	TT	Normal: not clinically relevant Prolonged: may/may not be clinically relevant
			aPTT	Normal: likely indicates lower drug level but can't exclude drug presence Prolonged: clinically relevant
Apixaban Betrixaban Edoxaban Rivaroxaban	Anti-Xa	Absent activity: not clinically relevant Results correlate with drug level (if calibrated for specific DOAC)	PT	Normal: does not exclude clinically relevant levels Prolonged: clinically relevant levels

Anti-Xa= anti-factor Xa; aPTT= activated partial thromboplastin time; dTT= dilute thrombin time; ECA= ecarin chromogenic assay; ECT= ecarin clotting time; PT= prothrombin time; TT= thrombin time

Manage Bleeding

All bleeds	Major Bleeds		Minor Bleeds	
	Critical site or life threatening	NOT critical site or life threatening	More serious minor bleeds†	Less serious minor bleeds

• Provide local therapy/ manual compression
• Assess for and manage comorbidities contributing to the bleed*
	• Stop DOAC
	• Provide supportive care
	  • Secure airway and large-bore IV access
	  • Aggressive volume resuscitation (NS or LR)
	  • Correct hypothermia and acidosis
	  • Early involvement of other services (eg. surgery)
	  • RBC transfusions to achieve Hgb ≥7 g/dL (≥8 g/dL if pt has CAD)
	  • Platelet transfusion to achieve counts >50 x 10^9/L
	  • Cryoprecipitate transfusion to maintain fibrinogen >100 mg/dL
	• Stop any antiplatelets
	• Consider surgical/procedural management
	• **Administer reversal agent**
		• Stop DOAC
		• Provide supportive care
		  • Secure airway and large-bore IV access
		  • Aggressive volume resuscitation (NS or LR)
		  • Correct hypothermia and acidosis
		  • Early involvement of other services (eg. surgery)
		  • RBC transfusions to achieve Hgb ≥7 g/dL (≥8 g/dL if pt has CAD)
		  • Platelet transfusion to achieve counts >50 x 10^9/L
		  • Cryoprecipitate transfusion to maintain fibrinogen >100 mg/dL
		• Stop any antiplatelets
		• Consider surgical/procedural management
		• **Administer reversal agent if above not effective**
			• Stop DOAC
			• Provide supportive care
			• Stop any antiplatelets
			• Consider surgical/procedural management
				• Consider continuing DOAC if appropriate indication
				• Assess risk/ benefits of stopping any antiplatelets
				• Verify that DOAC dosing is correct and patient taking as directed

*eg. renal dysfunction, liver disease, thrombocytopenia; † Patient requires hospitalization, transfusion, or procedural intervention

DOAC Reversal

Dabigatran	Apixaban, Betrixaban, Edoxaban, Rivaroxaban
• Administer 5 g idarucizumab IV (two separate 2.5 g/50 mL vials) • If bleeding persists and there is laboratory evidence of persistent dabigatran effect after 12-24 hours, a second dose may be reasonable. • If idarucizumab not available, administer aPCC at 50 units/kg IV (refer to package insert for max units) • Activated charcoal (50 g) can be considered if ingested within 2-4 hours • Hemodialysis could be considered if drug level is high, especially in patients with poor renal function. • Fresh-frozen plasma is not recommended for DOAC reversal	• Apix/Riva: Admin ANDEXXA per package insert • Betrix/Edox: Admin off-label ANDEXXA* (800 mg at 30 mg/min then 8 mg/min for up to 120 min)[4] • Admin 4F-PCC 2,000 units (fixed dose) (if ANDEXXA not avail/used) • If 4F-PCC is not available, consider aPCC 50 units/kg IV (refer to prescribing information for max units) • Consider Activated charcoal (50 g) if ingested <2-4 hrs • Fresh-frozen plasma is not recommended

PCC= prothrombin complex concentrate; aPCC= activated prothrombin complex concentrate; *Off-label ANDEXXA OR 4F-PCC suggested for Betrix/Edox[4]

Restart DOAC

- Most patients benefit from restarting anticoagulation after bleeds, but make sure there is still a valid indication.
  - eg. CHA_2DS_2-VASc is ≥ 1 (in AF), length of treatment hasn't been reached (for VTE treatment or post-op prophylaxis).
- Base plan on the balance between bleeding and thromboembolic risks and discussions with other appropriate practitioners (eg. surgeons), the patient, and caregivers.
- Timing of restart: Delay restart if bleeding occurred in a critical site or if patient has a high risk for re-bleeding. Patients with GI bleed should typically wait at least 7-14 days. Patients with intracranial hemorrhage (and no mechanical valve) should wait at least 4 weeks.[2] In patients with moderate to high risk of recurrent VTE without high risk of recurrent bleeding, ASH suggests resuming anticoagulation within 90 days rather than discontinuation.[3]
- Make sure dose is correct based on age, renal function, weight, and indication and address any reversible risk factors such as interacting medications or unnecessary antiplatelet therapy.

References

- Unless otherwise referenced, document adapted from: 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. Am Coll Cardiol 2020;76:594-622. https://doi.org/10.1016/j.jacc.2020.04.053

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[2]Hemphill, et al. 2015 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Stroke. 2015;46:000-000. DOI: 10.1161/STR.0000000000000069

[3]Witt WM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. DOI 10.1182/ bloodadvances.2018024893

[4]Cuker A, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol.2019;94:697–709. doi.org/10.1002/ajh.25475

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