Reversal and Treatment Strategies for DOAC-Related Bleeding

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Do determine the time of last dose of anticoagulant administration[1] • Do reverse life-threatening or uncontrolled bleeding with andexanet alfa in patients taking apixaban or rivaroxaban, if available[1,2] • Do reverse life-threatening or uncontrolled bleeding with idarucizumab in patients taking dabigatran, if available[1,3] • Do formulate an anticoagulation restart plan[1]	• Do not give FFP for DOAC reversal[1] • Do not delay administration of reversal agents for life-threatening bleeding while waiting for lab results[1]	• Consider reversing life-threatening or uncontrolled bleeding with PCC or aPCC if specific reversal agent unavailable[1] • Consider activated charcoal for known recent ingestion (within 2-4 hours)[1] • Consider hemodialysis for dabigatran removal if drug administered recently and idarucizumab not available[4] • Consider pre-reversal laboratory measurement of DOACs based on assay availability[1]	• Be cautious as there are no comparison trials for reversal strategies • Be cautious about potential thromboembolic risk with reversal[2-4] • Be cautious about reversal agent re-dosing due to limited safety and efficacy data

Assumption: In the setting of bleeding with hemodynamic compromise, standard supportive care and resuscitative measures should always be applied

Laboratory Assessment for "Clinically Significant" DOAC Levels

"Clinically significant" refers to DOAC levels that may contribute to bleeding. The minimum DOAC level that may contribute to bleeding is unknown. The International Society on Thrombosis and Haemostasis suggests consideration of DOAC reversal in patients with serious bleeding and a plasma DOAC concentration > 50 ng/mL[10].

Drug	Assays suitable for quantitation of DOAC levels	Screening assays *Not suitable for quantification, may be useful for screening "clinically significant" DOAC levels*
Dabigatran	dTT, ECA, LC-MS/MS	TT, Urine DOASENSE®
Apixaban	Apixaban anti-Xa, LC-MS/MS	Heparin or LMWH anti-Xa Urine DOASENSE®
Edoxaban	Edoxaban anti-Xa, LC-MS/MS	
Rivaroxaban	Rivaroxaban anti-Xa, LC-MS/MS	

Example: A normal thrombin time or negative Urine DOASENSE® indicates the absence of "clinically significant" dabigatran levels. A heparin or LMWH anti-Xa assay below the lower limit of quantitation or negative Urine DOASENSE® indicates the absence of "clinically significant" apixaban, edoxaban, or rivaroxaban levels. Note: DOASENSE® is currently not available in the United States.

Definitions and Abbreviations:

Critical Organ Sites: central nervous system (intracranial, intraocular, or spinal), airway (including posterior epistaxis), hemothorax, intra-abdominal (non-gastrointestinal), retroperitoneal, intramuscular, intra-articular
aPCC: activated prothrombin complex concentrate
dTT: dilute thrombin time
ECA: ecarin chromogenic assay
FFP: fresh frozen plasma
LC-MS/MS: liquid chromatography tandem mass spectrometry
LMWH: low molecular weight heparin
PCC: prothrombin complex concentrate
TT: thrombin time

Background and Scope

Despite improved safety with direct oral anticoagulants (DOACs) compared to vitamin K antagonists, 2.1% to 3.6% of patients taking DOAC therapy in Phase III clinical trials had major bleeding.[5,6] Guidance has been offered by the Anticoagulation Forum[7], American College of Cardiology[8], American College of Chest Physicians[1], American Society of Hematology[9], and the American College of Emergency Physicians[11] for management of patients with major hemorrhages while on anticoagulant therapy. This Rapid Resource provides summarized evidence-based guidance for DOAC reversal and bleeding management.

Reversal Strategy by DOAC Agent

Dabigatran

• **Idarucizumab**
5 grams IV x 1

• Consider activated charcoal for known recent ingestions within 2-4 hours

• *If idarucizumab not available:*
aPCC or PCC 50 units/kg IV x 1 (max 4,000 units)

• Hemodialysis
(if hemodynamically stable and idarucizumab not available)

Factor Xa Inhibitor

Andexanet alfa dosed per below:

Drug	Last Dose	Time from last dose: *<8 hrs or unknown*	Time from last dose: *≥8 hrs*
Rivaroxaban	≤10 mg >10 mg or unknown	Low Dose High Dose	Low Dose
Apixaban	≤5 mg >5 mg or unknown	Low Dose High Dose	Low Dose
Edoxaban[a]	Any Dose	High Dose	Limited data

Consider activated charcoal for known recent ingestions within 2-4 hours

If andexanet alfa not available:
4F-PCC 25-50 units/kg (ICH) *or* 2000 units IV x 1

Low Dose—400 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 minutes.

High Dose—800 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 minutes.

[a] Andexanet alfa is only approved by the U.S. Food and Drug Administration for apixaban and rivaroxaban induced bleeding. Off-label use of andexanet alfa for reversal of edoxaban may be considered.

Considerations

Andexanet alfa: Clinical judgement advised when selecting dose regimens based on time cut-offs in patients presenting with acute or chronic renal dysfunction and life-threatening bleeding, receiving non-renally dose adjusted baseline DOAC regimens

References: **1.** Tomaselli GF, Mahaffey KW, Cuker A, et al.Am Coll Cardiol. 2020 Aug 4;76(5):594-622. PMID: 32680646. **2.** Connolly SJ, Crowther M, Eikelboom JW, et al. N Engl J Med. 2019 Apr 4;380(14):1326-1335.PMID: 30730782. **3.** Pollack CV Jr, Reilly PA, Eikelboom J, et al.N Engl J Med. 2015 Aug 6;373(6):511-20. PMID: 26095746. **4.** Patanwala AE, Acquisto NM, Erstad BL. Ann Pharmacother. 2011 Jul;45(7-8):990-9. PMID: 21730276. **5.** Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. Blood. 2014 Oct 9;124(15):2450-8. PMID: 25150296. **6.** Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, et al. Lancet. 2014 Mar 15;383(9921):955-62. PMID: 24315724. **7.** Cuker A, Burnett A, Triller D, Crowther M, et al. Am J Hematol. 2019 Jun;94(6):697-709. PMID: 30916798. **8.** Holbrook A, Schulman S, Witt DM, et al. Chest. 2012 Feb;141(2 Suppl):e152S-e184S. PMID: 22315259. **9.** Piran S, Schulman S. Blood. 2019 Jan 31;133(5):425-435. PMID: 30559261. **10.** Levy JH, Ageno W, Chan NC, et al. J Thromb Haemost. 2016 Mar;14(3):623-7. PMID: 26911798. **11.** Baugh CW, Levine M, Cornutt D, et al. Ann Emerg Med. 2020 Oct;76(4):470-485. PMID: 31732375.

ACE Rapid Resources are not clinical practice guidelines; they are Anticoagulation Forum, Inc.'s best recommendations based on current knowledge, and no warranty or guaranty is expressed or implied. The content provided is for informational purposes for medical professionals only and is not intended to be used or relied upon by them as specific medical advice, diagnosis, or treatment, the determination of which remains the responsibility of the medical professionals for their patients.

Faculty: Scott Kaatz, DO, MSc; Megan Barra, PharmD, BCPS, BCCCP; Adam Cuker, MD, MS; Ronni Nemeth, PharmD, CACP, DPLA; Kelly Rudd, PharmD, BCPS, CACP, FCCP

This content was developed independently by the Anticoagulation Forum. Support for this project provided by Alexion Pharmaceuticals, Inc.

@2020 Anticoagulation Forum, Inc. All Rights Reserved

Last updated 1/2021