Current Reversal & Treatment Strategies for DOAC-Related Bleeding

A new *Rapid Resource* from the AC Forum

Tuesday | January 19, 2021 | 6:00pm-7:00pm EST

Presenters:

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

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Presenters

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- Clinical Pharmacy Specialist, Neurocritical Care, Massachusetts General Hospital, Department of Pharmacy

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- Associate Professor of Medicine and Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania

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- Clinical Professor of Medicine, Wayne State University School of Medicine
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- Manager, Anticoagulation Clinics, Confluence Health
- Co-chair of Confluence Health Anticoagulation Steering Committee

Kelly Rudd, PharmD, BCPS, CACP, FCCP

- Director, Network Pharmacy Operations, Bassett Healthcare Network
- Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons

Disclosures & Notification of Support

Acknowledgement of Financial Commercial Support:

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The below speaker disclosure has the listed relevant financial relationships with commercial interests:

Adam Cuker, MD, MS

- Alexion Pharmaceuticals | Novartis Pharmaceuticals | Novo Nordisk | Pfizer Pharmaceuticals Inc | Spark Therapeutics | Sanofi | Synergy

Scott Kaatz, DO, MSc

- Bristol-Myers Squibb (BMS) |Osmosis | Janssen Pharmaceuticals | Pfizer Pharmaceuticals Inc | Novartis | Portola/Alexion Pharmaceuticals

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Rapid Resource

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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®
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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
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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:

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Edoxaban[a]	Any Dose	High Dose	Limited data

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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

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- The rate of MAJOR bleeding in AF/VTE DOAC trials is about 2.0 per 100 patient years [3]
  - Distribution:
    - AF: 48% GI vs. 13% ICH
    - VTE: 31% GI vs. 11% ICH

1. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. Blood. 2014 Oct 9;124(15):2450-8. PMID: 25150296.
2. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, et al. Lancet. 2014 Mar 15;383(9921):955-62. PMID: 24315724
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Background and Scope

- 30-day mortality in DOAC-associated hemorrhages in VKA vs. DOAC trials
  - Major bleeds: 8.9 – 20.4% [1, 2, 3, 4]
  - ICH: 36 – 48%

- Withholding anticoagulant reversal in DOAC-associated ICH:

1.5-fold ↑ risk of death and poor outcomes [5]

1. Held C, Hylek EM, Alexander JH, et al. Eur Heart J 2015; 36(20): 1264-1272
2. Piccini JP, Garg J, Patel MR, et al. Eur Heart J 2014; 35(28): 1873-1880
3. Majeed A, Hwang HG, Connolly SJ, et al. Circulation 2013; 128(21): 2325-2332
4. Wilson D, Seiffge DJ, Traenka C, et al. Neurology 2017; 88(18): 1693-1700
5. Apostolaki-Hansson T, Ullberg T, Pihlsgard M, et al. Front Neurol 2020; 11: 760

Anticoagulant Therapy and Bleeding

- Many clinical practice guidelines & expert panels exist to guide the management of patients with anticoagulant-associated bleeds:

American College of Emergency Physicians – 2020
American Society of Hematology - 2019
Anticoagulation Forum – 2019
European Stroke Organization – 2019
American College of Chest Physicians – 2018
American College of Cardiology – 2017 and 2019
American Heart Association – 2017
Heart Rhythm Society – 2017
British Society of Hematology – 2016
Neurocritical Care Society – 2015

Bleeding Management: Non-Pharmacologic

- In the setting of bleeding with hemodynamic compromise, standard supportive care and resuscitative measures should always be applied:
  - Hold anticoagulation
  - Mechanical intervention for local hemostasis
  - Topical agents
  - Replace losses (fluid/blood transfusions, calcium, supplemental oxygen)
  - Optimize management of comorbid situations

Dager W, et al. Am J Health-Syst Pharm. 2013;70(10 suppl 1):S21-S31.
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• 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[5-8] • 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*
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Critical Organ Sites: central nervous system (intracranial, intraocular, or spinal), airway (including posterior epistaxis), hemothorax, intra-abdominal (non-gastrointestinal), retroperitoneal, intramuscular, intra-articular
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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
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Edoxaban[a]	Any Dose	High Dose	Limited data

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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.

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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

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Rapid Resource

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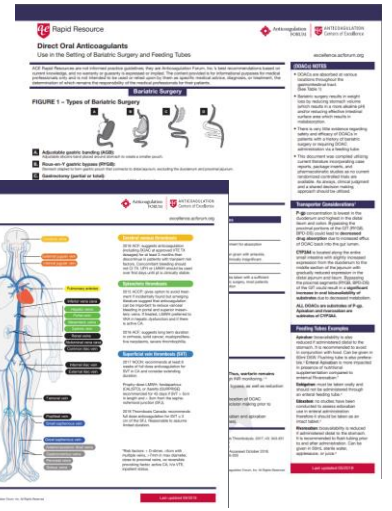

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ALEXION

The content was developed independently by the Anticoagulation Forum and the funder had no input in the content of the Rapid Resource or webinar