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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Disclosures & Notification of 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
• 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.¹,²

• 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
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 \(\uparrow\) risk of death and poor outcomes \(^5\)

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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

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
# Reversal and Treatment Strategies for DOAC-Related Bleeding

## Background and Scope

Despite improved safety with direct oral anticoagulants (DOACs) compared to vitamin K antagonists, this has not equated to improved outcomes for DOAC reversal in Phase II clinical trials indicating bleeding. Guidance has been offered by the American College of Chest Physicians (ACCP) [1] and the American Heart Association (AHA) [2] which are well accepted and can be found online [3]. This Rapid Resource provides summaries of evidence-based guidance for DOAC reversal and bleeding management.

## Reversal Strategy by DOAC Agent

<table>
<thead>
<tr>
<th>Drug</th>
<th>Last Dose</th>
<th>Reversal Agent</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban, Apixaban, Edoxaban, and Eptacoplan</td>
<td>5-10 mg or 5-15 mg</td>
<td>HIT: Ecaritide</td>
<td>5 mg bolus and 5 mg continuous infusion for 2 hours</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5 mg or 5 mg or 10 mg or 20 mg</td>
<td>HIT: Ecaritide</td>
<td>5 mg bolus and 5 mg continuous infusion for 2 hours</td>
</tr>
<tr>
<td>Direct Factor Xa inhibitors</td>
<td>10 mg or 20 mg or 50 mg or 100 mg</td>
<td>HIT: Ecaritide</td>
<td>5 mg bolus and 5 mg continuous infusion for 2 hours</td>
</tr>
<tr>
<td>Direct Thrombin inhibitors</td>
<td>10 mg or 20 mg or 50 mg or 100 mg</td>
<td>HM: LMWH or UFH</td>
<td>5000 U bolus followed by continuous infusion of 2500 U or 5000 U for 24 hours</td>
</tr>
</tbody>
</table>

## Laboratory Assessment for "Clinically Significant" DOAC Levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Assay available for quantification of DOAC levels</th>
<th>Screening strategy</th>
<th>&quot;Clinically significant&quot; DOAC levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban, Apixaban, Edoxaban, and Eptacoplan</td>
<td>HIT: Ecaritide</td>
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<td>Direct Thrombin inhibitors</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Example: A normal prothrombin time (PT) and or normal partial thromboplastin time (PTT) indicates the absence of "clinically significant" DOAC levels. A prolonged PT or PTT and or a low aPTT or aPTTand or a low INR or a low INR and or a low CRP or a low CRP and or a low INR and or a low INR and or a low INR indicates the presence of "clinically significant" DOAC levels.

## Definitions and Interactions

- APTT: activated partial thromboplastin time
- INR: international normalized ratio
- CRP: C-reactive protein
- LMWH: low molecular weight heparin
- UFH: unfractionated heparin
- Ecaritide: recombinant factor C
- LMWH: low molecular weight heparin
- UFH: unfractionated heparin

References:

This material was developed independently by the Anticoagulation Forum. Support for this project provided by Phrixon Pharmaceuticals, Inc.
<table>
<thead>
<tr>
<th><strong>DO</strong></th>
<th><strong>DON’T</strong></th>
<th><strong>CONSIDER</strong></th>
<th><strong>CAUTION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do determine the time of last dose of anticoagulant administration¹</td>
<td>• Do not give FFP for DOAC reversal¹</td>
<td>• Consider reversing life-threatening or uncontrolled bleeding with PCC or aPCC if specific reversal agent unavailable¹</td>
<td>• Be cautious as there are no comparison trials for reversal strategies</td>
</tr>
<tr>
<td>• Do reverse life-threatening or uncontrolled bleeding with andexanet alfa in patients taking apixaban or rivaroxaban, if available¹,²</td>
<td>• Do not delay administration of reversal agents for life-threatening bleeding while waiting for lab results¹</td>
<td>• Consider activated charcoal for known recent ingestion (within 2-4 hours)³</td>
<td>• Be cautious about potential thromboembolic risk with reversal²,⁴</td>
</tr>
<tr>
<td>• Do reverse life-threatening or uncontrolled bleeding with idarucizumab in patients taking dabigatran, if available¹,³</td>
<td></td>
<td>• Consider hemodialysis for dabigatran removal if drug administered recently and idarucizumab not available¹</td>
<td>• Be cautious about reversal agent re-dosing due to limited safety and efficacy data</td>
</tr>
<tr>
<td>• Do formulate an anticoagulation restart plan¹</td>
<td></td>
<td>• Consider pre-reversal laboratory measurement of DOACs based on assay availability¹</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Last Dose</th>
<th>Time from last dose</th>
<th>Low Dose</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>High Dose</th>
<th>Limited data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>&lt;8 hrs or unknown, ≥8 hrs</td>
<td>Low Dose</td>
<td>High Dose</td>
<td>Low Dose</td>
<td>High Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg or unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>≤25 mg</td>
<td>&lt;8 hrs or unknown, ≥8 hrs</td>
<td>Low Dose</td>
<td>High Dose</td>
<td>Low Dose</td>
<td>High Dose</td>
<td>Limited data</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mg or unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Any Dose</td>
<td>High Dose</td>
<td>High Dose</td>
<td>High Dose</td>
<td>Low Dose</td>
<td>High Dose</td>
<td></td>
</tr>
</tbody>
</table>

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*

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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.

- **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.

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.


**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\(^\text{10}\).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Assays suitable for quantitation of DOAC levels</th>
<th>Screening assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>dTT, ECA, LC-MS/MS</td>
<td>TT, Urine DOASENSE(^\text{®})</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Apixaban anti-Xa, LC-MS/MS</td>
<td>Heparin or LMWH anti-Xa Urine DOASENSE(^\text{®})</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Edoxaban anti-Xa, LC-MS/MS</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Rivaroxaban anti-Xa, LC-MS/MS</td>
<td></td>
</tr>
</tbody>
</table>

Example: A normal thrombin time or negative Urine DOASENSE\(^\text{®}\) 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\(^\text{®}\) indicates the absence of “clinically significant” apixaban, edoxaban, or rivaroxaban levels. Note: DOASENSE\(^\text{®}\) is currently not available in the United States.
References

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