New Approaches for Reversing Oral Factor Xa Inhibitors

AGENDA

11:30 a.m. – 11:35 a.m.
Welcome and Introductions
William E. Dager, Pharm.D., BCPS (AQ-Cardiology), FASHP, FCCM, FCCP, FCSHP, MCCM

11:35 a.m. – 11:50 a.m.
Direct-acting Oral Factor Xa Inhibitors: Current Reversal and Treatment Strategies for DOAC-related Bleeding
William E. Dager, Pharm.D., BCPS (AQ-Cardiology), FASHP, FCCM, FCCP, FCSHP, MCCM

11:50 a.m. – 12:15 p.m.
Overview of Key Clinical Trials: Reviewing the Evidence on Reversal of DOACs
Mark Cipolle, M.D., Ph.D., FACS, FCCM

12:15 p.m. – 12:40 p.m.
Clinical Considerations in Reversal of DOACs: Focus on Wise and Correct Use
Jessica Rimsans, Pharm.D., BCPS

12:40 p.m. – 1:00 p.m.
Faculty Discussion, Frequently Asked Questions

A Midday Symposium and Live Webinar conducted at the 2018 ASHP Midyear Clinical Meeting and Exhibition

Monday, December 3, 2018
11:30 a.m. – 1:00 p.m. PT
Room 252, 200 Level, ACC North
Anaheim Convention Center
Anaheim, California

Provided by ASHP
Supported by an educational grant from Portola Pharmaceuticals
New Approaches for Reversing Oral Factor Xa Inhibitors: Examining the Evidence

William E. Dager, Pharm.D., BCPS (AQ-Cardiology), FASHP, FCCM, FCCP, FCSHP, MCCM, Activity Chair

Mark Cipolle, M.D., Ph.D., FACS, FCCM

Jessica Rimsans, Pharm.D., BCPS

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Disclosures

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• In this activity, no persons associated with this activity have disclosed any relevant financial relationships.

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Learning Objectives

- Review currently available agents for reversing direct-acting oral anticoagulants (DOACs).
- Explain the risk factors for bleeding complications with DOACs as well as strategies for minimizing them.
- Review current and emerging data for the treatment of bleeding in patients on DOAC therapy.
- Illustrate using patient cases clinical situations for which reversal of DOAC therapy is warranted, including how it may be implemented.

Current Reversal and Treatment Strategies for Anti-Xa DOAC-Related Bleeding

William E Dager, Pharm.D., BCPS (AQ Cardiology), FASHP, FCCM, FCCP, FCSHP, MCCM
Pharmacist Specialist – UC Davis Medical Center
Sacramento, California
# New Approaches for Reversing Oral Factor Xa Inhibitors: Examining the Evidence

## Oral Anti-Xa Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>&gt; 80%</td>
<td>&gt; 50%</td>
<td>62%</td>
<td>34%</td>
</tr>
<tr>
<td>Time to peak Cp</td>
<td>3 hr (Delayed by food)</td>
<td>3 hr</td>
<td>1.5 hr</td>
<td>3-4 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>5-9 hr (Elderly 11-13 hr)</td>
<td>9-14 hr</td>
<td>8-10 hr</td>
<td>19-27 hr</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>36%</td>
<td>25%</td>
<td>35%</td>
<td>5-7%</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>CYP 3A4 or P-gp modifiers</td>
<td>CYP 3A4 or P-gp modifiers</td>
<td>P-gp modifiers</td>
<td>P-gp modifiers</td>
</tr>
</tbody>
</table>

CYP - cytochrome P450; P-gp - P glycoprotein; hr – hours; Cp = peak plasma concentration


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## What is the situation? Goals of therapy?

- **Urgent**
- **Semi-Urgent**
- **Not so Urgent**

Reversing an Oral Anti-Xa Anticoagulant

- **Assessment**
  - Urgency → patient setting, surgery?
  - Anticoagulant – last dose, how much is involved
    - Assay: Anti-Xa, INR
  - Your role and what agents are available
  - Continuous Process
- **Withhold anticoagulation**
- **Pharmacological intervention**
  - Topical agents
  - Andexanet alfa
  - Prothrombin concentrate concentrate (PCC) (? Titrate to effect)
  - Plasmapheresis ? – Case report (Anti-Xa ↓ 0.8 to 0.3 IU/mL in 2 hours)
- **Replace blood losses**
- **Optimize management of comorbid situations**

---

**DOAC – Agent Unclear**

**Bleeding or need for urgent reversal**

- **Thrombin Time High**
  - Anti-Xa Low
  - ↑ aPTT > PT ( assay dependent)
  - Dabigatran
  - Urgent
  - Administer antidote
    - Consider adding hemostatic agent if urgent – life threatening bleed

- **Assessment**
  - Amount of drug (↑ INR/PT etc)
  - Thrombin time/Anti-Xa
  - Bleeding risk
  - Charcoal if ingestion recent
  - Med Rec: Dosing QD/BID

**Rivaroxaban**

- **Thrombin Time Low**
  - Anti-Xa High
  - ↑ PT > aPTT ( assay dependent)

- **Apixaban**
- **Edoxaban**
- **Betrixaban**

- **Supportive management**
  - Underlying condition
  - Transfuse
  - Need for invasive procedure

- **Semi-urgent**
  - Watch

- **Consider antidote**
  - Hemostatic agent if clinically necessary (low dose titrate to effect)
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Efficacy Outcomes (n=47)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in anti-Xa activity</td>
<td>~89%</td>
</tr>
<tr>
<td>Change in hemostatic efficacy through 12 hours</td>
<td>79% of patients achieved good or excellent hemostasis post-andexanet alfa</td>
</tr>
<tr>
<td>(Visual 1 and 4 hr; CNS bleed – &lt;20% mass effect by 12 hours)</td>
<td>• Excellent 66%</td>
</tr>
<tr>
<td></td>
<td>• Good – 13%</td>
</tr>
</tbody>
</table>

Time from admission to dose administration: 4.8 +/- 1.8 hr

Does this create a negative outcome bias?


Potential INR Response with Higher DOAC Serum Concentrations

Andexanet alfa

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Recombinant truncated human factor Xa variant (decoy) that temporarily shuts down the activity of factor Xa (Does not remove it).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding</td>
<td>Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor-activated antithrombin</td>
</tr>
<tr>
<td>Target affinity</td>
<td>Affinity for direct factor Xa inhibitors. No effect on dabigatran</td>
</tr>
<tr>
<td>Onset</td>
<td>2 min</td>
</tr>
<tr>
<td>Half-life</td>
<td>Terminal = 6 hr</td>
</tr>
<tr>
<td>Elimination</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cost</td>
<td>$25,000 – $50,000 or more (CMS: New technology add-on payment (NTAP) - FY2019 $14,062)</td>
</tr>
</tbody>
</table>


Safety Outcomes (n=67)

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day thromboembolic events (TE)</td>
<td>18%</td>
</tr>
<tr>
<td>Antibodies to factor X, factor Xa, andexanet alfa</td>
<td>No issues</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>15%</td>
</tr>
</tbody>
</table>

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Andexanet Alfa: Reversing Oral Anti-Xa Agents

Use of PCC or aPCC* with Anti-Xa DOAC Bleeding

- No randomized comparisons to antidotes
- Doses variable (8 – 100 units/kg)
- Single doses and low doses in GI bleeds have worked
  - Onset seems to be rapid
- No clear advantage – aPCC* over PCC with anti-factor Xa agents (except heparin allergy)
- Thrombosis has been reported - ? If incidence higher
- Mortality rates vary

* = activated prothrombin complex concentrates (aPCC)


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### PCC or aPCC with Anti-Xa DOAC Bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANEXXA-4 (Safety Population) (n=67)</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>Majeed et al (n=84) – 4 factor PCC (1500-2000 IU)</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Schulman et al (n=66) – 4 factor PCC (2000 IU)</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Dager et al (n=48) – activated 4 factor PCC Low Dose – 10 ± 3.6 units/kg</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Moderate Dose – 24 ± 2.1 units/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santibanez M et al. (n=42 all DOAC with 38 on a Anti-Xa Agent) – 4 factor PCC 25 units/kg (88%)*</td>
<td>Not Reported</td>
<td>7%*</td>
</tr>
</tbody>
</table>

* 14 day VTE event rate for all 42 patients on a DOAC including 4 receiving Dabigatran


### Overall Goals

- Stop or control the bleeding
- Stabilize any comorbid conditions and observe
- Identify contributing factors
- Evaluate anticoagulation plan (Restarting/prophylaxis)
- Make any needed adjustments
As frontline providers caring for patients on DOACs who are bleeding, our biggest challenges are:

1. deciding who needs urgent reversal
2. knowing when, or if, to resume anticoagulation
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It’s all about balance!

- 75-year-old man on dabigatran for atrial fibrillation slipped on the ice going to the gym
- PT/INR and aPTT NORMAL
- Thrombin Time (TT) >180
- Urgent craniectomy

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Comparison of bleeding rates between DOACs and warfarin: atrial fibrillation

- Randomized trials – DOAC bleeding
  - Major bleeding = 2-3% per year with DOAC
  - Intracranial hemorrhage (ICH) = 0.1 to 0.5% per year with DOAC
- “Real world” N >50,000
  - Dabigatran vs. warfarin
    - Major bleeding: 1.6 vs. 3.5 per 100,000 patient days
    - ICH: 0.8 vs. 2.1 per 100,000 patient days

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Comparison of bleeding rates between DOACs and warfarin: venous thromboembolism (VTE)

- Meta-analysis of 5 trials
  - N= 24,555
  - Bleeding rates with DOACs
    - Fatal 0.06%
    - Nonfatal ICH 0.09%
    - GI bleed 0.35%
  - Relative Risk compared with warfarin = 0.5 (0.41-0.88)


Management of Major Bleeding Events in Patients Treated with Dabigatran for Nonvalvular Atrial Fibrillation: A Retrospective Multicenter Review

- 191 cases reviewed
  - 118 (62%) GI bleed
  - 36 (19%) ICH
  - 36 “other locations”
  - Excluded patients enrolled in idarucizumab trial
- 12 (6%) deaths
  - 8 GI bleed
  - 2 ICH
- Red blood cell (RBC) and fresh frozen plasma (FFP) administration was common
- 6% received purified coagulation factors


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Efficacy and Harms of DOACs in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of VTE

- Reviewed 19 studies
- DOACs were equivalent or superior to Vitamin K antagonist (VKA) in managing thrombotic risk
- GI bleeding in elderly on dabigatran was higher compared with VKA

**GI bleeding in non-elderly, ICH, clinically relevant bleeding and fatal bleeding were ALL LOWER in DOACs compared with VKA!**


87-year-old woman on rivaroxaban in MVC

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Preinjury Warfarin Worsens Outcome in Elderly Patients Who Fall From Standing

<table>
<thead>
<tr>
<th>Mortality Rate</th>
<th>+warf % (n=537)</th>
<th>-warf % (n=2254)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>8.6</td>
<td>5.7</td>
<td>1.54 (1.09–2.19)</td>
<td>0.015</td>
</tr>
<tr>
<td>Abbreviated Injury Score (AIS) Head &lt;4</td>
<td>2.4</td>
<td>3.9</td>
<td>1.63 (0.55–4.79)</td>
<td>0.377</td>
</tr>
<tr>
<td>AIS Head (4 &amp; 5)</td>
<td>23.7</td>
<td>16.0</td>
<td>1.63 (1.03–2.58)</td>
<td>0.035</td>
</tr>
<tr>
<td>&amp; GCS (14-15)</td>
<td>13.5</td>
<td>6.4</td>
<td>2.30 (1.12–4.70)</td>
<td>0.019</td>
</tr>
<tr>
<td>&amp; GCS (9-13)</td>
<td>38.9</td>
<td>30.2</td>
<td>1.47 (0.48–4.49)</td>
<td>0.496</td>
</tr>
<tr>
<td>&amp; GCS (≤ 8)</td>
<td>57.9</td>
<td>65.5</td>
<td>0.72 (0.25–2.09)</td>
<td>0.549</td>
</tr>
</tbody>
</table>

- warf = non-warfarin group; + warf = warfarin group

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Results
- n=67 safety analysis,
  n = 47 efficacy analysis
- Mean age 77
- Mean time to bolus 4.8±1.8 hr from presentation

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

- Hemostatic efficacy excellent or good
  - Rivaroxaban (n=26) 81% (61-93)
  - Apixaban (n=20) 75% (51-91)
  - GI bleed (n=25) 84% (64-96)
  - ICH (n=20) 80% (56-94)

- Safety
  - No infusion reactions or antibodies developed
  - Thrombotic events in 12 patients (18%)
  - 6 of 10 deaths cardiovascular causes!!


Update for ANNEXA-4

- Safety analysis n=227
- Efficacy analysis n=137
- Reducing anti-Xa levels and hemostatic efficacy are similar to initial *N Engl J Med* report

- Safety
  - Thrombotic events
    - 6 (2.6%) within 3 days
    - 24 (11%) within 30 days
  - Anticoagulation restarted in 129 (57%) in 30 days and only in 9 patients before thrombotic event
  - 27 (12%) deaths by day 30, 11 cardiovascular

Connolly, SJ. Presentation at American College of Cardiology. March 2018. Orlando, FL.
Management of rivaroxaban- or apixaban-associated major bleeding with PCCs: a cohort study

- 25 centers in Sweden coordinated by Karolinska University Hospital
- Enrolled consecutive patients prospectively needing “prompt” reversal for major bleeding
- Predefined protocol utilizing 1500-2000 units of PCC4, a second dose was given in 3 patients
- Assessment of efficacy performed by 2 independent coagulation specialists using International Society Thrombosis and Hemostasis (ISTH) criteria
- Primary safety endpoint was arterial or venous thromboembolism


Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study

- Results
  - Evaluated 39 apixaban and 45 rivaroxaban patients
  - ICH n=59, GI bleed n=13
  - 12.5 hours from last dose to treatment with PCC
  - Hemostatic effectiveness
    - Overall 69%
    - ICH 73%, non-ICH 60%
    - Trauma 73%, atraumatic 67%
  - Safety
    - 32% mortality rate
    - Two strokes with one death attributed to PCC4
    - 4% thrombotic complications

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PCC for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study

- 9 Canadian centers
- Apixaban and rivaroxaban
- Most received fixed dose of 2000 units
- Results
  - N=66, ICH 55%, GI bleed 24%, trauma 38%
  - Hemostatic efficacy (Sarode criteria)
    - Overall 65% good, 20% moderate
    - ICH 76%
  - Safety
    - 9 deaths (14%)
    - 5 thromboembolic events (8%)


Andexanet Alfa or PCC4 for Reversal of Bleeding Associated with Xa-inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>ANNEXA-4 (n=67)</th>
<th>Majeed et al (n=84)</th>
<th>Schulman et al (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal agent</td>
<td>Andexanet alfa</td>
<td>PCC4</td>
<td>PCC4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77.1±10.0</td>
<td>75.0±10.9</td>
<td>76.9±10.4</td>
</tr>
<tr>
<td>ICH</td>
<td>42%</td>
<td>70%</td>
<td>55%</td>
</tr>
<tr>
<td>Time since last dose (hours)</td>
<td>R 12.8±4.2</td>
<td>12.5 (9-16)</td>
<td>16.9 (12-21)</td>
</tr>
<tr>
<td></td>
<td>A 12.1±4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness for CNS bleeds</td>
<td>16 (80%)</td>
<td>43 (73%)</td>
<td>25 (76%)</td>
</tr>
<tr>
<td>excellent or good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>12 (18%)</td>
<td>3 (4%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Death</td>
<td>10 (15%)</td>
<td>27 (32%)</td>
<td>9 (14%)</td>
</tr>
</tbody>
</table>
“The similar effectiveness results in our study and in ANNEXA-4 could, if true, be because both methods are effective or, alternatively, because reversal has minimal or no effect on the outcome. The latter could, in turn, be due to too late administration (intracranial hemorrhage—the damage is already done) or that the anticoagulation effect is rapidly vanishing with the short half-life of the Xa inhibitors.”

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Some Exclusions in Sarode Bleeding Trial

- Expected survival <3 days
- Expected surgery <1 day
- Acute trauma for which reversal alone would not be expected to control the bleeding
- History of thrombotic event within 3 months
- Sepsis
- Large vessel rupture
- Preexisting fatal disease life expectancy <2 months
- ICH
  - Glasgow Coma Score (GCS) <7
  - ICH >30 mL
  - Subdural hematoma >1 cm or shift >5 mm
  - Infratentorial hemorrhage
  - Epidural hemorrhage
  - Intraventricular hemorrhage


Exclusions for ANNEXA-4

- ICH volume >60 mL or GCS <7
- Expected survival <1 month
- Expected to undergo surgery in <12 hr
- Major thrombotic event within 2 weeks of hemorrhage
- Received VKA, dabigatran, PCC, blood within 7 days

ICH patients in ANNEXA-4

- 28 (42%) of 67 patients enrolled with an ICH
- Baseline GCS: 14.1 ± 1.7
- Intracerebral hemorrhage:
  - Hematoma volume:
    - ≤10 mL: 8 (57%) of 14
    - 11-60 mL: 6 (43%) of 14
- Subdural hemorrhage:
  - Maximal thickness:
    - ≤10 mm: 8 (73%) of 11


Resumption of anticoagulation
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Restarting Anticoagulation Treatment After Intracranial Hemorrhage in Patients with Atrial Fibrillation and the Impact of Recurrent Stroke, Mortality, and Bleeding

- Three Danish nationwide registries 1997-2013
- 1752 patients with 1 year follow-up
- VKA 65%, VKA + antiplatelet 33%, DOAC 2%
- Primary outcome: ischemic stroke/systemic embolism (SE)/all cause mortality
- Compared three groups
  - Resumed oral anticoagulation (OAC)
  - Resumed antiplatelet therapy
  - No resumption of anticoagulation or antiplatelet therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No treatment</th>
<th>OAC treatment</th>
<th>Antiplatelet Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke/systemic embolism and all cause mortality event rate</td>
<td>27.3% (23.6-31.6)</td>
<td>13.6% (10.1-18.3)</td>
<td>25.7% (20.7-31.9)</td>
</tr>
<tr>
<td>Recurrent ICH event rate</td>
<td>8.6% (6.6-11.2)</td>
<td>8.0% (5.4-11.8)</td>
<td>5.3% (3.3-8.4)</td>
</tr>
</tbody>
</table>

OAC=oral anticoagulation

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Restarting Anticoagulation Treatment After Intracranial Hemorrhage in Patients with Atrial Fibrillation and the Impact of Recurrent Stroke, Mortality, and Bleeding

![Graph showing survival probability over years with OAC Rx, Antiplatelet Rx, and No Rx lines.]


Ischemic Events: OAC stopped for ICH
19 German Centers

![Graph showing incidence of ischemic events over months with no OAC resumption and OAC resumption lines.]


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Hemorrhage Events: OAC stopped for ICH
19 German Centers

Survival Rate: OAC stopped for ICH
19 German Centers

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Christiana Care Health System AC and AT Resumption

<table>
<thead>
<tr>
<th>Trauma</th>
<th>Full anticoagulation should be resumed after bleeding stopped based on thrombotic risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High risk: within 4 days</td>
</tr>
<tr>
<td></td>
<td>Moderate risk: within 1-2 weeks</td>
</tr>
<tr>
<td></td>
<td>Low risk: Consider within 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td>Withhold dual antiplatelet therapy (DAPT) for 24 hours to assess bleed</td>
</tr>
<tr>
<td></td>
<td>For all patients on aspirin indications listed in Table 1, we recommend resuming aspirin (81mg) 24 hours after bleeding stops</td>
</tr>
<tr>
<td></td>
<td>For patients with a DES &lt;12 mo, BMS &lt;3 mo, or intracranial stent &lt;12 mo–restart second agent within 1-2 weeks</td>
</tr>
<tr>
<td>Intracranial or intraspinal hemorrhage: Traumatic and Spontaneous</td>
<td>Trauma: Re-evaluate reason for anticoagulation: Antithrombotics vs Antiplatelets</td>
</tr>
<tr>
<td></td>
<td>Anticoagulation should be resumed after bleeding stopped based on thrombotic risk:</td>
</tr>
<tr>
<td></td>
<td>High risk: resume 7-10 days after bleeding event</td>
</tr>
<tr>
<td></td>
<td>Moderate risk: resume within 2-3 weeks</td>
</tr>
<tr>
<td></td>
<td>Low risk: resume within 3-4 weeks</td>
</tr>
<tr>
<td></td>
<td>Spontaneous: Identify/Secure underlying lesion: aneurysm/AVM</td>
</tr>
<tr>
<td></td>
<td>*Neurologic consultations prior to re-initiation of full anticoagulation</td>
</tr>
</tbody>
</table>

Clinical Considerations in Reversal of DOACs: Focus on Wise and Correct Use

Jessica Rimsans, Pharm.D., BCPS
Clinical Pharmacy Specialist
Hemostatic Antithrombotic Stewardship
Brigham and Women’s Hospital
Boston, Massachusetts
What is the American College of Cardiology recommended dose of PCC4 or aPCC for life threatening ICH associated with factor Xa inhibitors?

- a. 12.5 units/kg
- b. 30 units/kg
- c. 25 units/kg
- d. 50 units/kg
- e. 100 units/kg

What is the recommended dose of andexanet alfa for a patient presenting with ICH whose last dose of apixaban 5 mg was 10 hours ago?

- a. Bolus 400 mg
- b. Bolus 200 mg then a 2 hour infusion of 480 mg
- c. Bolus 800 mg then a 2 hour infusion of 960 mg
- d. Bolus 400 mg then a 2 hour infusion of 480 mg
- e. Bolus 480 mg then a 2 hour infusion of 400 mg
Patient Case: PP

- PP is an 81 YOM with a history of CAD, s/p DES implant 2009, AF, hypertension, s/p right occipital ventriculoperitoneal shunt placed in 2008.
- On rivaroxaban 20 mg QD (last dose 9 pm night prior to admission) and ASA.
- CT scan was performed which demonstrated a large right basal ganglia hemorrhage with IVH and hydrocephalus.
- At OSH: INR 2.3 and patient was given PCC4 50 units/kg + vitamin K 10 mg IV, and platelets.
- Unresponsive upon transfer to our emergency department (ED).
- At our hospital: Anti-Xa (LMWH/UFH) was 4.74 IU/mL.
  - New CT reveals hematoma expansion with mild mass effect and right-to-left midline shift of 5 mm.
- The ED team stat-pages the pharmacist to discuss treatment options given new findings.

Three Main Questions

- What is the urgency and reason for reversal?
- What treatment options are available?
- What patient-specific factors should be considered?
Available Treatment Options for DOAC Reversal

**FDA Approved Options**
- Idarucizumab for dabigatran reversal only
- Andexanet alfa for apixaban and rivaroxaban only
- PCC4 for VKA-reversal only

**Non-FDA Approved Options**
- PCC3
- PCC4
- aPCC (Factor VIII inhibitor bypassing activity, FEIBA)
- Recombinant activated factor VII
- Plasmapheresis
- Hemodialysis for dabigatran reversal only

**Factor Xa Inhibitor Reversal**

- **Andexanet alfa** is FDA Approved for patients with **life threatening major bleeding** on apixaban or rivaroxaban

- **PCC4** and **aPCC** are options to consider for Factor Xa inhibitor reversal for both **life threatening bleeding** and those requiring **urgent surgery/procedures**

- Withholding the factor Xa inhibitor will promote clearance in those with normal renal function

New Approaches for Reversing Oral Factor Xa Inhibitors: Examining the Evidence

*aPCC*
- Activated PCC
- Risk of thromboembolic events unclear
- 50 units/kg ~$5300
- Optimal dose unclear
- Fast administration
- Some data available for use in bleeding patients

*PCC4*
- Inactivated PCC
- Risk of thromboembolic events unclear
- 50 units/kg ~$4800
- Optimal dose unclear
- Fast administration
- More data available for use in surgery/bleeding patients

*Andexanet alfa*
- Decoy protein
- 18% thromboembolic events
- $25,000 to $50,000
- Set dosing for factor Xa inhibitors per PI
- Semi-fast administration (2.5 hr)
- No data in surgical patients

Both PCCs have not been evaluated for effect on anti-factor Xa levels and bleeding/hematoma expansion


*Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.*

**Andexanet Alfa** coagulation factor Xa (recombinant), inactivated

- Recombinant modified human factor Xa decoy protein that is catalytically inactive but that retains the ability to bind factor Xa inhibitors in the active site with high affinity

- FDA approved May 2018
  - Only for life threatening bleeding with rivaroxaban and apixaban
  - Different dosing strategy for agent, dose, and time since last dose

*Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.*
New Approaches for Reversing Oral Factor Xa Inhibitors: Examining the Evidence

Andexanet Alfa Dosing

- Different dosing strategy for agent, dose, and time since the last dose
  - dependent on family/patient involvement

<table>
<thead>
<tr>
<th>Factor Xa inhibitor</th>
<th>FXa inhibitor dose</th>
<th>Timing of FXa inhibitor last dose before coagulation Factor Xa (andexanet alfa)</th>
<th>Dose</th>
<th>Initial IV bolus</th>
<th>Follow-up IV infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>&lt;8 hours or unknown</td>
<td>Low dose</td>
<td>400 mg at a target rate of 15-30 min</td>
<td>4 mg/min for 120 minutes (480 mg)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg, or unknown</td>
<td>≥8 hours</td>
<td>High dose</td>
<td>800 mg at a target rate of 15-30 min</td>
<td>8 mg/min for 120 minutes (960 mg)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>≤5 mg</td>
<td>Low dose</td>
<td>Low dose</td>
<td></td>
<td></td>
</tr>
<tr>
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New Approaches for Reversing Oral Factor Xa Inhibitors: Examining the Evidence

Andexanet Alfa

Other considerations:
- Availability
- Vial size
- Tubing
- One compounded bag vs. two
- Bleeding vs. surgery
- Outside hospital transfer
- Drug levels vs. standard tests
- Formulary addition & stewardship oversight
- Guideline development & education

Availability

Idarucizumab
Andexanet alfa

- Early supply program offered to high-enrolling ANEXXA-4 institutions
- Considerations for loaning/borrowing from other hospitals that do not carry andexanet

https://www.andexxa.com/
https://www.praxbind.com/

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Reconstitution & Administration Considerations for Andexanet Alfa

- Currently available as 100 mg vials
  - 9-18 vials required for the low and high dose
  - 200 mg vials in the pipeline

- Reconstitution
  - Bolus +/- maintenance infusion in one IV bag

- Tubing
  - ½ the dose remains in the line if not flushed post bolus and infusion
  - OSH transfers and pump compatibility between hospitals


Indication for Use of Andexanet Alfa

- Life threatening bleeding on apixaban or rivaroxaban
  - within 18 hr of last dose

- Currently not indicated for:
  - Non life threatening major bleeding
  - Surgery in the next 12 hours or that can be delayed
  - Bleeding managed with supportive measures

Our Experience

• 15 patients as of October 2018
• Many patients would not have met ANNEXA-4 criteria
  – 7 received PCC
  – 1 recent thrombotic event
  – 3 had surgery within 12 hours


Considerations/Indication for Use

• Outside hospital transfer s/p PCC treatment
  – Hematoma expansion on CT
  – Anti-Xa (LMWH/UFH) level remains elevated

• Elevated standard coagulation tests vs. chromogenic drug levels
  – Anti-Xa (LMWH/UFH) vs. drug concentration
  – Not indicated unless evidence of bleeding/expansion
Considerations in Using Andexanet Alfa

- Doses of factor Xa inhibitor greater than 18 hours prior

- Life threatening bleeding on factor Xa inhibitor other than apixaban or rivaroxaban

- Andexanet alfa + surgery
  - Rebound anti-Xa levels 2-4 hr post infusion
  - Consideration for continuous infusion for length of surgery
  - Not approved by FDA at this time

Considerations After Andexanet Alfa Administration

- Rebound in anti-Xa observed 2-4 hours
  - Monitor for re-bleeding and elevated anti-Xa levels
  - Educate clinicians on rebound and timing of procedures

- Medicare New Technology Add on Payment (NTAP) approved October 1, 2018
  - Need to submit appropriate coding
  - Up to $14,062.50
  - Resources available on website

- Restarting anticoagulation when hemostasis achieved
Implementing Use of Andexanet Alfa

- Formulary review
- Guidelines for use
- Electronic medical record decision support
- Education for emergency medicine, hematology, pharmacy, and anesthesiologists

Patient Case: MS

- MS is an 85 YOF who presents with sudden onset of abdominal pain associated with watery diarrhea, chills, and arrives to the ED by ambulance at 10 pm

- Past medical history: severe aortic stenosis w/ preserved ejection fraction, pacemaker, peripheral artery disease, atrial fibrillation 4 months prior, hypertension, diabetes mellitus, hypothyroid

- Current medications: aspirin 81 mg/day, apixaban 2.5 mg twice daily, atorvastatin 40 mg/day, levothyroxine 75 mcg/day, metoprolol 25 mg/day, furosemide 20 mg/day

- On exam: blood pressure 124/72 mmHg, heart rate 77 bpm, Remainder of exam is normal

- Labs: hemoglobin 10.4 g/dL, hematocrit 32.3%, platelets 188 k/uL, Serum creatinine 0.65 mg/dL, PT 14.3 seconds, INR 1.1

- CT: approx. 20 cm length of mid ileum demonstrates circumferential wall thickening, adjacent mesenteric fat stranding→ concern for mesenteric ischemia requiring emergent exploratory laparotomy
Patient Case (continued)

- Upon further discussion, last dose of apixaban was last night, 24-26 hours ago
- Team consults with the pharmacist about how to reverse apixaban to emergently bring this patient to the operating room (OR) for exploratory laparotomy.

What do you recommend?

a. Andexanet alfa 400 mg bolus followed by 480 mg infusion over 2 hours
b. PCC4 25 units/kg
c. Andexanet alfa continuous infusion for the duration of the procedure
d. aPCC 25 units/kg
e. Nothing – withholding the apixaban is sufficient given normal renal function

Outcome

- Last dose ~24 hours prior, normal renal function
- Stat anti-factor Xa (LMWH/UFH) was 1.15 IU/mL
- No data at this time supporting andexanet alfa for surgery
- Allowed PCC4 to be in the OR if bleeding occurred that was not typical for this procedure
- No PCC or transfusion of blood products were required
- Estimated blood loss reported: “minimal; 10 mL”
Key Takeaways

Anticoagulant associated bleeding requires

- Patient assessment
  - Site, Severity, Anticoagulant, Images, Timing, Labs
  - Worsening, Stable, Improving
- Hospital resources
  - Blood factors and/or reversal agents
- Expertise/teamwork
  - Drug prescribing, drug prep, drug administration
- Follow up
  - When to restart anticoagulation

Consider these practice changes.
Which will you consider making after this activity?

1. Educate colleagues on the need for close follow-up and management of patients on anticoagulant therapy.
2. Be proactive in counseling patients on bleeding risk when using DOACs on a long-term basis.
3. Read my institutional protocols for bleeding management in patients experiencing a life-threatening bleed or requiring emergency surgery.
4. Review which DOAC reversal agents are available at my institution (e.g., andexanet alfa, idarucizumab, PCC4).
5. Discuss with colleagues how to assess the need for reversal of the DOACs in special populations.
6. Investigate appropriate use of DOAC reversal agents, including timing of the dose, potential for excessive levels, and adapting to other co-factors.
A patient on a new oral anticoagulant...

- Is going to the OR for an emergent procedure
  - INR is 2.5 and no liver disease or warfarin on board.
  - What if the INR was >6 (with heart failure and acute kidney failure)
- With history of multiple PE has a massive GI bleed, Hgb is 5 and BP dropping
- Who fell yesterday and CT today shows an epidural hemorrhage
- Is stable and has some blood in their stool

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✓ elearning.ashp.org
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✓ Additional instructions in handout

Coming Soon
On-demand archive of today’s presentation
- Available early March 2019

Download the handout at www.ashpadvantagemedia.com/doac-reversal
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