Learning Objectives

1. Discuss the pathophysiology and clinical assessment of a patient with Factor Xa inhibitor-associated intracranial hemorrhage (ICH)
2. Review the pharmacology of Factor Xa inhibitors and reversal agents
3. Compare evidence for andexanet alfa and 4-factor prothrombin complex concentrate and apply to a patient with ICH
Assessment Questions

1. What is the role of Factor Xa (FXa) in the coagulation cascade?
   a. Converts plasmin to plasminogen
   b. Binds to the FXa receptor on platelets
   c. Complexes with FVa to convert prothrombin to thrombin
   d. The initial step in the extrinsic pathway
   e. The initial step in the common pathway
   f. Both c and e

2. What systolic blood pressure (SBP) goal is associated with less hematoma expansion in patients with acute intracranial hemorrhage due to oral anticoagulants?
   a. SBP <160 mmHg within 4 hours
   b. SBP <160 mmHg within 1 hour
   c. SBP between 140 – 179 mmHg within 24 hours
   d. SBP between 140 – 179 mmHg within 6 hours

3. True/False: Andexanet alfa for reversal of FXa inhibitor acute major bleeding has a higher rate of hemostatic efficacy compared to 4-factor prothrombin complex concentrate.
   a. True
   b. False

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Faculty (Speaker) Disclosure: Ashley E. Lock has indicated she has no relevant financial relationships to disclose relative to the content of her presentation.
Background

I. Oral anticoagulation (OAC)
   A. Direct oral anticoagulants
      i. Factor Xa (FXa) inhibitors: rivaroxaban, apixaban, edoxaban, betrixaban
      ii. Direct thrombin inhibitor (DTI): dabigatran
   B. FXa inhibitor mechanism of action: directly inhibits free and clot-bound factor Xa, decreasing thrombin generation and subsequent fibrin production, thereby preventing platelet aggregation
      i. See Appendix A for Factor Xa inhibitors
   C. Epidemiology
      i. Predominant indications for OAC: atrial fibrillation (AF), venous thromboembolism (VTE)
      ii. Use of direct oral anticoagulants (DOACs) has increased compared to warfarin
         1. Decrease in major bleeding
         2. Fewer drug and food interactions
         3. Absence of required coagulation monitoring with DOACs
      iii. OACs account for 17.6% of emergency department visits due to adverse effects, the highest rate of all drug classes
   D. Risk factors for major bleeding on anticoagulation therapy
      i. Age >65 years old
      ii. Recent surgery or trauma
      iii. History of stroke
      iv. Uncontrolled hypertension
      v. Renal or hepatic failure
      vi. Concomitant medications: antiplatelets, nonsteroidal anti-inflammatory drugs
      vii. Anticoagulation intensity (especially at initiation of therapy)

II. Intracranial hemorrhage (ICH)
   A. Epidemiology
      i. Primary ICH (without anticoagulation) mortality: 30 – 55%
      ii. Every 1-mL increase in hematoma volume increases death and disability by 7%
      iii. ICH occurs 8 times more frequently in patients on OAC
      iv. OAC-ICH is associated with higher mortality than primary ICH (67%)
      v. Incidence of OAC-ICH: 0.25 – 1.1% annually
      vi. Mean age of patients with OAC-ICH: 60 – 70 years old
   B. Prognosis
      i. Predictors of poor prognosis: elderly, large hematoma volume (≥40 mL), intraventricular involvement, depressed mental status, hematoma expansion
III. Pathophysiology of clot formation

A. Vessel injury
B. Vessel spasm
C. Platelet activation
  i. Purpose: form platelet plug at injury site
  ii. Occurs through exposed collagen and thrombin generation
  iii. Result: activated platelets express receptors (GPIIb/IIIa), allowing platelet aggregation via cross-linked fibrinogen
D. Coagulation cascade
  i. Purpose: reinforce platelet plug
  ii. Intrinsic and extrinsic pathways lead to the common pathway
  iii. In vivo: vessel injury exposes tissue factor (TF) to circulating Factor VII (FVII), activating it to FVIIa (Figure 1)
    1. FVIIa/TF complex initiates the common pathway
      a. Directly: activates Factor X to Factor Xa (FXa)
      b. Indirectly: activates Factor IX (FIXa), which complexes with FVIIIa to activate Factor X
    2. FXa/FVa complex converts prothrombin to thrombin
    3. Thrombin converts fibrinogen to fibrin
  iv. Result: fibrin strands strengthen platelet plug

Figure 1. Coagulation cascade in vivo

Figure 2. Coagulation cascade common pathway
Management of Oral Anticoagulant Intracranial Hemorrhage (OAC-ICH)

Figure 3. OAC-ICH management pathway\textsuperscript{13}

I. Assessment of bleed severity\textsuperscript{13}
   A. Primary assessment (i.e. airway, breathing, circulation, disability, exposure)
   B. Bleeding at a critical site (i.e. intracranial, intraocular, spinal, pericardial tamponade, hemothorax, intra-abdominal, retroperitoneal)
   C. Decrease in hemoglobin $\geq 2$ g/dL or receipt of $\geq 2$ units packed red blood cells (PRBCs)
   D. Signs and symptoms\textsuperscript{13}
      i. Active hemorrhage at critical site
      ii. Altered mental status with or without neurologic deficit
      iii. Hemodynamic instability
      iv. Respiratory failure
      v. Pallor, skin mottling, cool extremities, or paresthesias
   E. History of present illness
      i. Determine time of last dose of oral FXa inhibitor\textsuperscript{13}
         1. Drug is eliminated within 3 – 5 half-lives
         2. Consider renal and hepatic impairment – increases elimination half-life
   F. Imaging
      i. Computed tomography (CT) scan of head, chest x-ray, and ultrasound
   G. Coagulation monitoring\textsuperscript{13,14}
      i. Coagulation assays, such as: prothrombin time (PT), international normalized ratio (INR), activated partial prothromboplastin time (aPTT), and thrombin time (TT), are poor indicators of bleed severity\textsuperscript{14}
      ii. INR does not correlate with degree of anticoagulation with oral FXa inhibitors
      iii. Do not delay treatment of major bleed while awaiting coagulation results in patients with suspected OAC-ICH
      iv. Anti-FXa activity levels are used to monitor FXa inhibitors and enoxaparin
         1. ISTH recommends reversal of serious bleed with DOAC levels $>50$ ng/mL or $>30$ ng/mL in patients undergoing high bleed risk procedures\textsuperscript{13}
         2. Not widely available\textsuperscript{15}
II. Control

A. Discontinue the anticoagulant

B. Supportive measures

i. Endotracheal intubation

ii. Resuscitation with intravenous fluids and/or blood products

iii. Intracranial pressure management to achieve ICP <22 mmHg

1. Neurosurgical hematoma evacuation

iv. Hypertonic intravenous fluids (e.g. 3% sodium chloride, mannitol)

C. Decontamination

i. Consider activated charcoal if anticoagulant dose taken within 2 hours of oral FXa inhibitor ingestion

   1. Dose: 1 g/kg (maximum: 50 g) oral or enteral once

   2. Not recommended in patients with aspiration risk

   3. Intubated patients: do not administer activated charcoal if the patient has an un-cuffed endotracheal tube or during gastric suctioning

ii. Hemodialysis: not indicated, FXa inhibitors are highly protein bound and minimally dialyzable

D. Blood pressure management

i. SBP threshold should be maintained ≥100 mmHg for age 50 – 69 years, and ≥110 mmHg for age 15 – 49 or >70 years

ii. Most ICHs present with acutely elevated SBP, which is associated with increased risk of hematoma expansion and mortality

   1. INTERACT-I: intensive BP control (SBP <140 mmHg) within 6 hours of spontaneous ICH (sICH) onset reduces incidence of hematoma expansion

   2. ATACH-II: BP control to SBP <140 mmHg is safe in sICH

iii. Fast-acting antihypertensive agents are recommended to acutely lower blood pressure (e.g. nicardipine, clevidipine, labetalol)

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<table>
<thead>
<tr>
<th>Design</th>
<th>Multi-center, observational cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>N = 146 patients with spontaneous ICH; rivaroxaban 110 (75.3%), apixaban 21 (14.4%), dabigatran 15 (10.3%)</td>
</tr>
<tr>
<td>SBP reduction at 4 hours</td>
<td>SBP &lt;160 mmHg at 4 hours after admission was associated with lower risk of HE</td>
</tr>
<tr>
<td>Hematoma expansion</td>
<td>No significant association between 4F-PCC administration and HE (RR = 1.057, 95% CI 0.565 – 1.977)</td>
</tr>
<tr>
<td>Baseline anti-FXa activity</td>
<td>Strong positive association between anti-FXa level &gt;118 ng/mL and HE</td>
</tr>
<tr>
<td>N = 40/131; AUC 0.711 (95% CI 0.645-0.777; p &lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) 4F-PCC dose</td>
<td>2,000 (1,500 – 3,000) units</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>29/146 (19.9%)</td>
</tr>
</tbody>
</table>

HE = hematoma expansion; ICH = intracranial hemorrhage; IQR = interquartile range; SBP = systolic blood pressure
E. Hemostatic efficacy
   i. Definitions of hemostatic efficacy vary widely among OAC reversal studies
   ii. International Society of Thrombosis and Hemostasis (ISTH) provides standardized criteria for major bleeding (Appendix B)

F. Factor Xa inhibitor reversal

Reversal Agents

I. 4-factor prothrombin complex concentrate (4F-PCC) (Kcentra®)
   A. Contains factors II, VII, IX, X, Proteins C and S, and heparin
   B. FDA-approved for reversal of vitamin K antagonist-induced coagulation factor deficiency in the setting of urgent surgery, invasive procedure, or acute major bleeding
      i. Current standard of care for FXa inhibitor reversal (off-label indication)
   C. Mechanism of action
      i. Provides a high concentration of non-activated clotting factors, which are activated during hemorrhage, to indirectly overcome anticoagulant effects of FXa inhibitors
   D. Dosing for FXa inhibitor reversal
      i. 50 units/kg (FIX component) IV if OAC-ICH occurred within 3-5 half-lives of drug exposure or in patients with liver failure (low-quality evidence)
   E. Pharmacokinetics and pharmacodynamics
      i. In the setting of VKA reversal, 4F-PCC decreases INR rapidly to ≤1.3 within 30 minutes of initiation
      ii. Clotting factor half-lives

<table>
<thead>
<tr>
<th>Clotting factor/protein</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>60</td>
</tr>
<tr>
<td>Factor VII</td>
<td>4 – 6</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24</td>
</tr>
<tr>
<td>Factor X</td>
<td>48 – 72</td>
</tr>
<tr>
<td>Protein C</td>
<td>8</td>
</tr>
<tr>
<td>Protein S</td>
<td>30</td>
</tr>
</tbody>
</table>

F. Clinical efficacy and safety of 4F-PCC in OAC-ICH
   i. 4F-PCC corrects INR faster than plasma for warfarin reversal

<table>
<thead>
<tr>
<th>Design</th>
<th>Multi-center, open-label, noninferiority trial (N = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR reduction to ≤1.3 at 0.5 hours</td>
<td>62.2% vs. 9.6% (difference 52.6%, 95% CI 39.4 – 65.9)</td>
</tr>
<tr>
<td>Effective hemostasis</td>
<td>72.4% vs. 65.4% (difference 7.1%, 95% CI -5.8 – 19.9)</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>7.8% vs. 6.4%</td>
</tr>
<tr>
<td>Mortality at 30 days</td>
<td>5.8% vs. 4.6%</td>
</tr>
</tbody>
</table>
ii. Thrombotic event risk with 4F-PCC for warfarin reversal: ~1.8 – 9.1%\textsuperscript{21}

iii. Literature for 4F-PCC in FXa inhibitor-associated ICH limited by several factors:
   1. Small sample size
   2. Heterogeneity in outcomes
   3. Varying criteria for hemostatic efficacy
   4. Thrombotic event follow-up time
   5. Lack of control groups

<table>
<thead>
<tr>
<th>Study (n\textsuperscript{a})</th>
<th>% ICH\textsuperscript{b}</th>
<th>4F-PCC dose</th>
<th>Hemostatic efficacy</th>
<th>Thrombotic events</th>
<th>Mortality</th>
<th>Functional outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger, et al. 2019 (n = 22)</td>
<td>100% ICH</td>
<td>25 units/kg</td>
<td>94.7%</td>
<td>9.1% (14 days)</td>
<td>18.2% (in-hospital)</td>
<td>-</td>
</tr>
<tr>
<td>Majeed, et al. 2017 (n = 84)</td>
<td>70.2% ICH</td>
<td>26.7 units/kg</td>
<td>72.9%</td>
<td>2.4% (30 days)</td>
<td>32% (30-day)</td>
<td>-</td>
</tr>
<tr>
<td>Dybdahl, et al.\textsuperscript{c} 2019 (n = 62)</td>
<td>100% tICH</td>
<td>50 units/kg</td>
<td>-</td>
<td>1.6% (in-hospital)</td>
<td>11/38 (29%) (in-hospital)</td>
<td>AM-PAC: ~50%</td>
</tr>
<tr>
<td>Harrison, et al.\textsuperscript{c} 2018 (n = 14)</td>
<td>14.2% tICH</td>
<td>25 – 50 units/kg</td>
<td>-</td>
<td>0% (30 days)</td>
<td>14.2% (in-hospital)</td>
<td>-</td>
</tr>
<tr>
<td>Sheikh-Taha, et al. 2019 (n = 29)</td>
<td>72.4% ICH</td>
<td>50 units/kg</td>
<td>72.4%</td>
<td>3.4% (30 days)</td>
<td>20.7% (in-hospital)</td>
<td>-</td>
</tr>
<tr>
<td>Gerner, et al. 2017 (n = 146)</td>
<td>100% sICH</td>
<td>≤25 – ≥50 units/kg</td>
<td>-</td>
<td>-</td>
<td>19.9% (in-hospital)</td>
<td>mRS 0 – 3 at 90 days: 31.1%</td>
</tr>
<tr>
<td>Grandhi, et al. 2015 (n = 18)</td>
<td>44.4% tICH</td>
<td>3,177 units mean dose</td>
<td>94.4%</td>
<td>5.6% (90 days)</td>
<td>33.3% (in-hospital)</td>
<td>mRS ≤2 at 90 days: 33.3%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Number of patients on non-vitamin K antagonists
\textsuperscript{b}Type of ICH not reported in all studies
\textsuperscript{c}Study design included a comparator group

AM-PAC = activity measure for post acute care; ICH = intracranial hemorrhage; mRS = modified Rankin scale (Appendix C); sICH = spontaneous ICH; tICH = traumatic ICH

II. Andexanet alfa (Andexxa\textsuperscript{\textregistered}) (ADX)
   A. Mechanism of action
      i. Recombinant modified human FXa decoy protein that binds with direct FXa inhibitors, low molecular weight heparin, and activated antithrombin III\textsuperscript{15,29}
      ii. ADX also binds to the endogenous anticoagulant tissue factor pathway inhibitor, which could contribute to procoagulant effects\textsuperscript{13,29}
         1. Thrombin levels remain elevated 22 hours after ADX administration\textsuperscript{29}
B. FDA-approved in May 2018, under accelerated approval given the lack of a standard of care agent for FXa inhibitor reversal.

i. FDA Accelerated Approval Program (AAP) expedites approval for drugs treating serious diseases in which there is an unmet medical need.

1. Approval is based on surrogate endpoints (e.g. laboratory values, radiographic imaging, or physical signs) rather than clinical outcomes.
2. AAP requires drug companies to perform Phase 4 trials to confirm clinical benefit.

C. Indication: apixaban or rivaroxaban reversal due to life-threatening or uncontrolled bleeding.

D. Black box warning: VTE, myocardial infarction, ischemic stroke, cardiac arrest, or sudden death.

E. Dosing

i. Considerations: specific FXa inhibitor ingested, FXa inhibitor dose, time of last FXa inhibitor dose.

<table>
<thead>
<tr>
<th>Table 5. Andexanet alfa dosing regimens</th>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Low dose</td>
</tr>
<tr>
<td>High dose</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6. Andexanet alfa dose based on rivaroxaban or apixaban dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FXa inhibitor</strong></td>
</tr>
<tr>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Apixaban</td>
</tr>
<tr>
<td>Apixaban</td>
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<tr>
<td>Apixaban</td>
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</tbody>
</table>

ii. Safety and efficacy of repeat doses have not been determined.

F. Pharmacokinetics and pharmacodynamics

i. Onset of action: rapid decrease in anti-FXa activity within 2 minutes.

ii. Elimination half-life: 3 – 4 hours.

iii. Pharmacodynamic half-life: 1 hour.

1. Infusion following the bolus is necessary to extend duration of action.

III. Pharmacoeconomics

<table>
<thead>
<tr>
<th>Table 7: Cost comparison with 4F-PCC</th>
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<tbody>
<tr>
<td><strong>Reversal agent</strong></td>
</tr>
<tr>
<td><strong>Price per unit dose</strong></td>
</tr>
<tr>
<td><strong>Total cost per treatment</strong></td>
</tr>
<tr>
<td>High Dose: $59,400</td>
</tr>
</tbody>
</table>
### IV. Guidelines

**Table 8. Guidelines on FXa inhibitor reversal**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocritical Care Society (2016)</td>
<td>4F-PCC 50 units/kg if ICH occurred within 3-5 half-lives or in the context of liver failure</td>
</tr>
<tr>
<td>American College of Cardiology (2017)</td>
<td>4F-PCC 50 units/kg is reasonable for emergency reversal in life-threatening bleed</td>
</tr>
<tr>
<td>CHEST (2018)</td>
<td>Use a specific reversal agent when available</td>
</tr>
<tr>
<td>AHA/ACC/HRS (2019)</td>
<td>ADX can be useful for reversal of rivaroxaban and apixaban for life-threatening or uncontrolled bleeding</td>
</tr>
</tbody>
</table>

AHA/ACC/HRS = American Heart Association/American College of Cardiology/Heart Rhythm Society

**Clinical Question**

Is andexanet alfa as safe and efficacious as 4 factor prothrombin complex concentrate for reversal of Factor Xa inhibitor-associated intracranial hemorrhage?


**Table 9.**

<table>
<thead>
<tr>
<th>Objective</th>
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<tbody>
<tr>
<td>Evaluate efficacy and safety of andexanet alfa in patients with acute major bleeding occurring while taking a factor Xa inhibitor</td>
</tr>
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<table>
<thead>
<tr>
<th>Methods</th>
</tr>
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<tbody>
<tr>
<td>Multi-center, prospective, open-label cohort study conducted at 63 sites in North America and Europe from April 2015 – May 2018</td>
</tr>
<tr>
<td>Only patients with ICH were enrolled from July 2016 – August 2017</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion:</strong></td>
</tr>
<tr>
<td>Age ≥18 years old</td>
</tr>
<tr>
<td>Acute major bleeding: bleeding with hemodynamic instability or in a critical area, decrease in Hgb ≥2 g/dL or Hgb ≤8 g/dL</td>
</tr>
<tr>
<td>Received apixaban, rivaroxaban, or edoxaban at any dose or enoxaparin ≥1 mg/kg/day in the last 18 hours</td>
</tr>
<tr>
<td><strong>Exclusion:</strong></td>
</tr>
<tr>
<td>Planned surgery within 12 hours after ADX (except minimally invasive procedures)</td>
</tr>
<tr>
<td>ICH with GCS &lt;7 or hematoma &gt;60 mL</td>
</tr>
<tr>
<td>Expected survival &lt;1 month</td>
</tr>
<tr>
<td>Thrombotic event 2 weeks before enrollment</td>
</tr>
<tr>
<td>Use of VKA, dabigatran, PCC, rFVIIa, whole blood, or plasma in the previous 7 days</td>
</tr>
</tbody>
</table>
### Intervention
- Dosing: ADX bolus over 15-30 minutes followed by a 2-hour infusion
  - Low dose regimen: bolus 400 mg over 15 minutes, infusion 480 mg
  - High dose regimen: bolus 800 mg over 30 minutes, infusion 960 mg
- See Table 6. Andexanet alfa dose based on rivaroxaban or apixaban dose
- Anti-FXa activity and unbound fraction of FXa inhibitor measured before and during ADX treatment and at 4, 8, and 12 hours after the end of treatment
- Patients were followed for \( \geq 30 \) days or until death

### Outcomes

#### Efficacy:
- Co-primary outcomes:
  - Percent change in anti-FXa activity after ADX
  - Percentage of patients with excellent or good hemostatic control 12 hours after completion of ADX infusion (Appendix D)

#### Safety:
- Mortality
- Thrombotic events
- Antibody development to ADX, native FX, or FXa

### Statistical Analysis
- Effective hemostasis presented with 95% confidence interval calculated with the binomial test
- Association between hemostatic efficacy and change in anti-FXa activity evaluated with ROC curves
- Continuous variables reported as mean and standard deviation or median and IQR
- Categorical variables reported as frequencies

### Results
- Safety population (all patients who received ADX): ICH 227 (64%), GIB 90 (26%)
- Mean age 77 years
- Indications for anticoagulation: AF 481 (79.4%), VTE 107 (17.7%)
- Most patients were on rivaroxaban (n = 228, 37.6%) and apixaban (n = 328, 54.1%)

<table>
<thead>
<tr>
<th>N = 606</th>
<th>Efficacy Population (n = 254)</th>
<th>Safety Population (n = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcomes</strong></td>
<td><strong>Efficacy Population (n = 254)</strong></td>
<td><strong>Safety Outcomes</strong></td>
</tr>
<tr>
<td>% Reduction in anti-FXa activity</td>
<td>Apixaban (n = 134) 92% (95% CI, 91 – 93)</td>
<td>Thrombotic events within 30 days</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban (n = 100) 92% (95% CI, 88 – 94)</td>
<td>Time of event n = 34 (10%)</td>
</tr>
<tr>
<td>Hemostatic efficacy at 12 hours</td>
<td>Overall (n = 249): 82% (95% CI, 77 – 87)</td>
<td>&lt;5 days 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 – 14 days 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 – 30 days 12</td>
</tr>
<tr>
<td></td>
<td>Excellent: 171 (68.7%)</td>
<td>Mortality within 30 days</td>
</tr>
<tr>
<td></td>
<td>Good: 33 (13.3%)</td>
<td>Cause of death n = 49 (14%)</td>
</tr>
<tr>
<td></td>
<td>Poor: 45 (18.1%)</td>
<td>Cardiovascular 35</td>
</tr>
<tr>
<td>Antibody development</td>
<td>No patients developed antibodies to FX, FXa, or ADX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No significant correlation seen between hemostatic efficacy and reduction in anti-FXa activity during ADX treatment</td>
<td></td>
</tr>
</tbody>
</table>
Author’s Conclusions

- In patients with FXa inhibitor-associated acute major bleed, andexanet alfa significantly decreased anti-FXa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours.

Reviewer’s Critique

Strengths:

- Multi-center, prospective study
- Adjudication committee verified major bleed criteria and outcomes
- Independent committee reviewed safety data – important for a manufacturer-driven study

Limitations:

- Single-arm, open-label study design
- Excluded patients with GCS < 7
- Anti-FXa activity not patient-centered
- BP control not reported in ICH patients
- Time to ADX not reported

Reviewer’s Conclusion

- Though anti-FXa activity decreased with ADX treatment, it did not correlate with hemostatic efficacy.
- Risk of thromboembolism cannot be fully described without a control group.
- Rate of thromboembolism is relatively higher than what is reported in studies with 4F-PCC.
- Future randomized controlled trials are necessary to elucidate the efficacy and safety of ADX in reversal of oral FXa inhibitors.

ADX = andexanet alfa; AF = atrial fibrillation; FX = factor X; FXa = activated factor X; GCS = Glasgow coma score; GIB = gastrointestinal bleed; Hgb = hemoglobin; ICH = intracranial hemorrhage; IQR = interquartile range; PCC = prothrombin complex concentrate; rFVIIa = recombinant activated factor VII; ROC = receiver-operating-characteristic; VKA = vitamin K antagonist


Objective

Determine efficacy and safety of 4F-PCC for reversal of FXa inhibitors in traumatic ICH.

Methods

- Retrospective cohort study conducted at two trauma centers in Ohio.
- Data collected from the institutional trauma database and EMR from March 2015 – August 2017.
- Institutional protocol utilized by trauma surgeons and neurosurgeons to determine need for FXa inhibitor reversal of traumatic ICH with 4F-PCC.

Patient Population

Inclusion:

- Trauma patients with ICH diagnosis and taking oral FXa inhibitor prior to admission.
- ICH confirmed by head CT.

Exclusion:

- None listed.

Intervention

- Patients who received 4F-PCC for FXa inhibitor reversal compared to those who did not receive 4F-PCC for FXa inhibitor reversal.
- Institutional protocol:
  - INR ≥ 1.5: 4F-PCC 50 units/kg, max dose 5,000 units.
  - INR ≤ 1.4: 4F-PCC not recommended.

Outcomes
Efficacy:
- Primary outcome: in-hospital mortality
- Secondary outcomes:
  - Functional recovery using AM-PAC daily activity score
  - Hospital LOS
  - ICU LOS

Safety:
- In-hospital events:
  - VTE
  - Ischemic stroke or TIA
  - MI

Statistical Analysis
- Demographic and clinical data evaluated using descriptive statistics, mean ± standard deviation for continuous variables and frequencies and percentages for categorical variables
- Means compared between independent groups using two-sample t-test or Wilcoxon tests
- ANCOVA used to compare continuous outcomes between groups while controlling for ISS
- Chi-square test used to compare percentages between groups
- Logistic regression used to compare percentages while controlling for ISS

Results
- Mean age 79.1 yrs, predominantly female (64.5%)
- Patients similar at baseline except those who received 4F-PCC had significantly higher baseline ISS than those who did not receive 4F-PCC (17.6 ± 8.9 vs. 12.1 ± 6.4; p = 0.019)
- Provider adherence to reversal protocol: 62.3%
  - In-hospital mortality higher in protocol compliant patients with 4F-PCC: 29% vs. 5%; p = 0.038
- Patients on apixaban 31 (50%), rivaroxaban 31 (50%)

<table>
<thead>
<tr>
<th>N = 62</th>
<th>4F-PCC (n = 35)</th>
<th>No Reversal (n = 27)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>22.9%</td>
<td>3.7%</td>
<td>0.034*</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM-PAC score⁶</td>
<td>17.1 ± 3.27</td>
<td>16.2 ± 4.48</td>
<td>0.46</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>2.5 ± 3.19</td>
<td>1.4 ± 3.77</td>
<td>0.0024³</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>6.4 ± 5.58</td>
<td>5.2 ± 5.61</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Safety Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>1 (2.9%)</td>
<td>0 (0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Ischemic stroke/TIA</td>
<td>0 (0)</td>
<td>4 (14.8%)</td>
<td>0.019⁷</td>
</tr>
<tr>
<td>MI</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

⁶Difference not statistically significant after controlling for ISS in logistic regression model (p = 0.20)
⁷Scores correlate with 50.11% and 53.32% functional impairment at hospital discharge, respectively
³Difference not statistically significant after controlling for ISS in ANOVA (p = 0.64)
⁷Difference not statistically significant after controlling for ISS in logistic regression model (p = 0.94)

Subgroup analysis:
- No difference in mortality between groups by neurosurgical intervention, gender, antiplatelet use, or site of injury
- Higher mortality in the 4F-PCC group among patients 65 – 79 years old (31% vs. 0%; p = 0.036)
- Discharge disposition not significantly different between groups (p = 0.70)

Author’s Conclusions
- Clinical effectiveness of 4F-PCC for oral FXa inhibitor reversal remains unknown
- Thrombotic events are uncommon with 4F-PCC
- Larger, multi-center, RCTs are necessary to determine safety and efficacy of 4F-PCC for reversal of oral FXa inhibitors

Reviewer’s Critique
**Strengths:**
- First study to include a comparator group to 4F-PCC in traumatic ICH patients
- Assessed patient functional outcomes – patient-centered outcome
- Confirmed ICH with head CT – internal validity
- Performed subgroup analysis and controlled for ISS with logistic regression

**Limitations:**
- Retrospective study with small sample size
- Institutional protocol utilized INR cutoff to determine need for 4F-PCC
- Follow-up time limited to hospital stay
- Time of last dose FXa inhibitor not reported
- Hematoma expansion on CT and BP control not reported
- Did not study hemostatic efficacy

**Reviewer’s Conclusion**
- 4F-PCC for reversal of FXa inhibitor-associated traumatic ICH may not provide a mortality benefit over no reversal with 4F-PCC, though type II error should be considered
- Rate of thrombotic events is low with 4F-PCC, though events may not have been detected due to lack of follow-up past hospital discharge
- Multi-center, randomized controlled trials are necessary to determine safety and efficacy of 4F-PCC

---


<table>
<thead>
<tr>
<th>Objective</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess achievement of effective clinical hemostasis using 4F-PCC in patients on chronic apixaban and rivaroxaban with major bleeding</td>
<td></td>
</tr>
</tbody>
</table>

**Methods**
- Retrospective chart review conducted at a tertiary teaching center in Huntsville, Alabama
- Data collected from electronic medical records from June 2016 – June 2018

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion:</th>
<th>Exclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding while on apixaban or rivaroxaban who received 4F-PCC</td>
<td>Patients needing reversal for emergency surgery or procedure</td>
</tr>
<tr>
<td>o Major bleeding defined using ISTH criteria</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**
- Patients received a single dose of 4F-PCC 50 units/kg (max dose 5,000 units)
- Patients followed until death or discharge

**Outcomes**

<table>
<thead>
<tr>
<th>Efficacy:</th>
<th>Safety:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: clinical hemostasis</td>
<td>Thrombotic events:</td>
</tr>
<tr>
<td>Secondary outcomes:</td>
<td>o VTE</td>
</tr>
<tr>
<td>o In-hospital mortality</td>
<td>o Stroke or TIA</td>
</tr>
<tr>
<td>o Hospital LOS</td>
<td>o Myocardial infarction</td>
</tr>
<tr>
<td>o Patients on concomitant drugs interacting with apixaban or rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>(i.e. aspirin, SSRI, NSAIDs, prasugrel, clopidogrel, omega 3)</td>
<td></td>
</tr>
</tbody>
</table>
Statistical Analysis

- Data evaluated using descriptive statistics, mean and standard deviation for continuous variables and frequencies and percentages for categorical variables

Results

- Mean age 73.8 yrs, predominantly female (55.2%)
- Patients on apixaban 13 (44.8%), rivaroxaban 16 (55.2%)
- Indications for anticoagulation: AF 23 (79.3%), VTE 5 (17.2%), hip replacement 1 (3.4%)
- Bleeding site: ICH 21 (72.4%), GIB 4 (13.8%)
- Majority of patients (96.6%) received last dose of FXa inhibitor on the day of hospital admission
- Received additional hemostatic treatment (i.e. PRBCs, FFP, platelets): 9 (31%)

<table>
<thead>
<tr>
<th>N = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
</tr>
<tr>
<td>Clinical hemostasis</td>
</tr>
<tr>
<td>ICH</td>
</tr>
<tr>
<td>GIB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary Outcomes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Hospital LOS (mean [range])</td>
</tr>
<tr>
<td>Patients on concomitant drugs interacting with apixaban or rivaroxaban</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Safety Outcome</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic events</td>
</tr>
</tbody>
</table>

Author’s Conclusions

- Use of 4F-PCC appears to be effective in attaining clinical hemostasis in patients on apixaban or rivaroxaban with major bleeding
- 4F-PCC may be an alternative for patients with major bleeding if andexanet alfa is not available

Reviewer’s Critique

**Strengths:**
- Guideline-recommended 4F-PCC dose
- Standardized criteria for hemostasis
- Recorded concomitant drugs affecting clinical hemostasis
- Verified time of last dose within 3-5 half-lives to assess need for FXa inhibitor reversal

**Limitations:**
- Small sample size
- Retrospective study with no comparator group
- Follow-up time limited to hospital stay
- Time of 4F-PCC administration not reported
- ICH type and severity not reported
- Hematoma expansion on CT not reported

**Reviewer’s Conclusion**

- 4F-PCC may achieve hemostatic efficacy for FXa inhibitor-associated major bleeding
- Future, comparative studies are necessary to further define efficacy and safety of 4F-PCC
- Presence of concomitant agents affecting hemostasis should be considered when managing patients on apixaban or rivaroxaban with major bleeding
- Conclusions cannot be drawn about the rate of thromboembolism with 4F-PCC given the small sample size and limited follow-up duration

AF = atrial fibrillation; CT = computed tomography; DVT = deep vein thrombosis; FXa = activated factor X; GIB = gastrointestinal bleed; ICH = intracranial hemorrhage; ISTH = International Society of Thrombosis and Hemostasis; LOS = length of stay; NSAID = nonsteroidal anti-inflammatory drug; PE = pulmonary embolism; SSRI = selective serotonin reuptake inhibitor; TIA = transient ischemic attack; VTE = venous thromboembolism; 4F-PCC = four factor prothrombin complex concentrate
Summary

1. There is insufficient evidence to recommend ADX over 4F-PCC in FXa inhibitor-associated ICH, based on the following patient-centered outcomes:

   **Table 12. Summary of patient-centered outcomes**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ADX versus 4F-PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostatic efficacy</td>
<td>82% vs. 78.4% ± 13.6</td>
</tr>
<tr>
<td></td>
<td>No clinically significant difference in hemostatic efficacy</td>
</tr>
<tr>
<td>Thrombotic risk</td>
<td>10% vs. 3.06% ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Clinically significant higher thrombotic risk with ADX</td>
</tr>
<tr>
<td>Mortality</td>
<td>14% vs. 24.2% ± 3.2</td>
</tr>
<tr>
<td></td>
<td>Clinical significance unclear</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>Unable to assess, not evaluated by ANNEXA-4 and most 4F-PCC studies</td>
</tr>
<tr>
<td>Cost</td>
<td>ADX significantly more expensive than 4F-PCC</td>
</tr>
<tr>
<td></td>
<td>Cost-difference ~$45,000</td>
</tr>
</tbody>
</table>

*a* 4F-PCC values listed as mean ± standard deviation of the study outcomes summarized in Table 4  
*b* Note that ANNEXA-4 and the majority of 4F-PCC trials lacked comparator groups. It is unknown whether the rates of these outcomes would be higher or lower compared to placebo.  
*c* The studies driving high mortality rate in the 4F-PCC group included ICH patients, regardless of GCS, whereas ANNEXA-4 excluded ICH patients with GCS <7.  

2. Management of traumatic and spontaneous ICH is not well-characterized
   
a. Blood pressure control may be more important than 4F-PCC administration in reducing risk of hematoma expansion in spontaneous ICH  
b. Studies on traumatic ICH have shown low rates of in-hospital thrombotic risk and similar mortality and hemostatic efficacy rates compared to ADX  
c. It is unknown the effect that blood pressure control may have on traumatic ICH and risk of hematoma enlargement

3. Anti-FXa activity monitoring does not correlate with hemostatic efficacy and is not widely available among health systems

4. Future, comparative studies with larger sample sizes are necessary to be able to measure incidence of thrombotic events and mortality

5. Data is lacking on the use of concomitant adjunctive therapies (i.e. 4F-PCC, tranexamic acid, DDAVP, whole blood, FFP, platelets, rVIIa) with ADX

Recommendations

1. In patients with FXa inhibitor-associated ICH, 4F-PCC is recommended over ADX at this time  
2. Weight-based dose 4F-PCC 50 units/kg should be utilized  
3. Coagulation monitoring of INR and/or anti-FXa level activity is not recommended  
   a. Decisions to reverse FXa inhibitor-associated ICH should be made based on clinical assessment of bleed severity
4. Goal systolic blood pressure <160 mmHg within 4 hours of admission to reduce hematoma expansion in spontaneous FXa inhibitor-associated ICH\textsuperscript{8,11}

**Future Directions**

1. ANNEXA-4 trial to be extended in sites in Germany and Japan to include more edoxaban patients\textsuperscript{10}
2. Phase 4 randomized, multi-center trial of andexanet alfa compared to usual care, including 4F-PCC, in patients with acute ICH, conducted by Portola Pharmaceuticals\textsuperscript{10,38}
   a. Status: recruiting 440 patients
   b. Study period: January 18, 2019 – November 1, 2023
   c. Inclusion: ICH presenting within 12 hours of onset and 15 hours of FXa inhibitor
3. Ciraparantag (PER977)\textsuperscript{14,39}
   a. Synthetic, water-soluble molecule, reverses all DOACs, UFH, LMWH, and fondaparinux
   b. Currently in Phase II trials, not FDA-approved

**References**

Appendices

Appendix A.* Factor Xa inhibitors\(^{1,41-43}\)

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing: NVAF prophylaxis</strong></td>
<td>5 mg PO BID</td>
<td>20 mg PO daily with evening meal</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td><strong>Dosing: DVT/PE treatment</strong></td>
<td>10 mg PO BID x 7 days, then 5 mg PO BID</td>
<td>15 mg PO BID x 21 days, then 20 mg PO daily with evening meal</td>
<td>60 mg PO daily after 5-10 days of parenteral anticoagulant</td>
</tr>
<tr>
<td><strong>Renal dose adjustment</strong></td>
<td>Yes(^a)</td>
<td>Yes</td>
<td>Yes(^b)</td>
</tr>
<tr>
<td><strong>Hepatic dose adjustment</strong></td>
<td>Not recommended in Child-Pugh class C</td>
<td>Avoid in Child-Pugh class B or C</td>
<td>Not recommended in Child-Pugh class B or C</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>87%</td>
<td>92-95%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>9-14 hrs</td>
<td>7-11 hrs</td>
<td>10-14 hrs</td>
</tr>
</tbody>
</table>

*Betrixaban not included for the purposes of this presentation

\(^a\)Dose adjust to 2.5 mg BID in NVAF patients meeting 2 of 3 criteria: age ≥80 years, weight ≤60 kg, SCr ≥1.5 mg/dL

\(^b\)Avoid edoxaban in patients with creatinine clearance <15 mL/min or >95 mL/min

BID = twice daily; DVT = deep vein thrombosis; NVAF = nonvalvular atrial fibrillation; PE = pulmonary embolism; PO = oral; SCr = serum creatinine
Appendix B. International Society of Thrombosis and Hemostasis (ISTH) criteria

<table>
<thead>
<tr>
<th>Definitions of effective hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-visible bleeding</strong></td>
</tr>
<tr>
<td>Hgb stable at 48 hr after PRBCs and hemostatic agent</td>
</tr>
<tr>
<td>No need for additional treatment at 48 hr</td>
</tr>
<tr>
<td>Invasive procedures are avoided or performed with a normal amount of blood loss</td>
</tr>
<tr>
<td>No neurologic dysfunction or limb loss at discharge or at 30 days</td>
</tr>
</tbody>
</table>

CT = computed tomography; GOS-E = extended Glasgow outcome scale; Hgb = hemoglobin; PRBC = packed red blood cells

Appendix C. Modified Rankin Scale (mRS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Degree of disability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
<td>N/A</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms</td>
<td>Able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability</td>
<td>Unable to carry out all previous activities but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability</td>
<td>Requiring some help but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability</td>
<td>Unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability</td>
<td>Bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Appendix D. Hemostatic efficacy criteria

<table>
<thead>
<tr>
<th>Type of major bleed</th>
<th>ANNEXA-4*</th>
<th>Sarode, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH: Excellent</td>
<td>≤20% increase in hematoma volume vs baseline on repeat CT at 1 and 12 hrs post-infusion</td>
<td>≤20% increase in hematoma volume vs baseline on repeat CT at 3 and 24 hrs</td>
</tr>
<tr>
<td>ICH: Good</td>
<td>≤35% increase in hematoma volume vs baseline on repeat CT at 12 hrs post-infusion</td>
<td>&gt;20% but ≤35% increase in hematoma volume vs baseline on repeat CT at 24 hrs</td>
</tr>
</tbody>
</table>

*Adapted from criteria used by Sarode, et al. 2013