What a Blood Bath! Andexxa® Makes a Splash! Current Trends in Anticoagulation Reversal

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What a Blood Bath!
Andexxa® Makes a Splash!
Current Trends in Anticoagulation Reversal

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Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.
Objectives

- Discuss various pharmacological management and reversal options for direct acting oral anticoagulation agents
- Review the mechanism of action and dosing of prothrombin complex concentrate (Kcentra®) and andexanet alfa (Andexxa®)
- Review available studies in practice facilitating the approval of andexanet alfa
- Evaluate and compare literature regarding the safety and efficacy of prothrombin complex concentrate and andexanet alfa for the reversal of oral anticoagulation
## Classification of Anticoagulants

<table>
<thead>
<tr>
<th>Route</th>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Vitamin K antagonist</td>
<td>Warfarin (Coumadin®)</td>
</tr>
<tr>
<td></td>
<td>Direct thrombin inhibitor</td>
<td>Dabigatran (Pradaxa®)</td>
</tr>
<tr>
<td></td>
<td>Factor Xa inhibitors</td>
<td>Apixaban (Eliquis®)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Betrixaban (Bevyxxa®)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edoxaban (Savaysa®)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban (Xarelto®)</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Thrombin/Factor Xa inhibitors</td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin (Lovenox®)</td>
</tr>
<tr>
<td></td>
<td>Direct thrombin inhibitors</td>
<td>Bivalirudin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Argatroban</td>
</tr>
<tr>
<td></td>
<td>Factor Xa Inhibitor</td>
<td>Fondaparinux (Arixtra®)</td>
</tr>
</tbody>
</table>
Mechanism of DOACs

Intrinsic system (surface contact)

Extrinsic system (tissue damage)

Tissue factor

Heparins

Vitamin K antagonists

Direct thrombin inhibitors

Factor Xa inhibitors

Direct Oral Anticoagulants

- Estimated over 6 million patients in the United States are treated with anticoagulants
- DOACs are now the most widely prescribed oral anticoagulants
- Major bleeding reported in 2.1% to 3.6% of patients in phase III trials
- Apixaban and rivaroxaban are among the top ten drugs contributing to emergency department visits in the United States
Management of DOAC-Related Bleed

1. Assess and identify severity of bleed
2. Manage and control bleed
3. Determine whether and when to restart anticoagulation

DOAC Reversal Agents

Idarucizumab (Praxbind®)
Dabigatran (Pradaxa®) Reversal

- Idarucizumab (Praxbind®)
- Mechanism of action: Humanized monoclonal antibody fragment that binds specifically to dabigatran and its metabolites
  - Binds with affinity 350 times greater than that of thrombin

Idarucizumab (Praxbind®)

- **Dosing:** 2.5 grams IV over 5 to 10 minutes for 2 doses
  - Second vial no later than 15 minutes following administration of first vial
- **Onset of action within minutes/hemostasis restored within 12 hours**
- **Renal elimination**
RE-VERSE AD

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., et al.

- Two groups of patients:
  - Uncontrollable or life-threatening bleed
  - Surgery or invasive procedure that could not be delayed

- Primary outcome: maximum percentage reversal of diluted thrombin time or the ecarin clotting time (ECT)

Inclusion criteria:
- ≥18 years old
- On dabigatran

Exclusion criteria:
- Group A:
  - Patients with minor bleeding
  - Patients with no clinical signs of bleeding
  - Hypersensitivity to reversal agent
- Group B:
  - Low risk procedure
  - Elective procedure
  - Hypersensitivity to reversal agent

Idarucizumab reversed anticoagulation rapidly and completely in more than 98% of patients

- Reversal maintained for 24 hours
- Cessation of bleeding within 2.5 hours
- Surgery enabled in 197 of 202 patients
- 4.8% of patients had thrombotic event within 30 days

DOAC Reversal Agents

Prothrombin complex concentrate (Kcentra®)
PCC General Information

- Purified, lyophilized, non-activated 4-factor concentrate prepared from human plasma

- Contains the following:
  - Factor II
  - Factor VII
  - Factor IX
  - Factor X
  - Protein C and S

PCC General Information

- Approved indication: Vitamin K antagonist reversal in patients with
  - Acute major bleeding
  - Need for urgent surgery/invasive procedure
- Weight-based dosing:

<table>
<thead>
<tr>
<th>INR</th>
<th>PCC Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 2 to &lt;4</td>
<td>25 units/kg (Max 2500 units)</td>
</tr>
<tr>
<td>INR 4 to 6</td>
<td>35 units/kg (Max 3500 units)</td>
</tr>
<tr>
<td>INR ≥6</td>
<td>50 units/kg (Max 5000 units)</td>
</tr>
</tbody>
</table>

- Administered IV at a rate of 0.12 ml/kg/minute
- Warnings/precautions:
  - Thromboembolic events
  - Hypersensitivity reactions
  - Contains heparin (contraindicated in patients with Heparin Induced Thrombocytopenia)

PCC for DOAC Reversal

- Off-label

- Initial dosing recommendation from European Heart Rhythm Association: 50 units/kg IV (additional 25 units/kg if clinically necessary)
  - 12 healthy subjects received rivaroxaban for 2.5 days all achieving immediate reversal
  - 15 healthy subjects received apixaban for 3.5 days all achieving immediate reversal

# Fixed Dose PCC

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient: 200 units and 500 units</td>
<td>Extra-cranial hemorrhage treated with 1040 units: Successful clinical outcome in 91% of patients</td>
<td>Variable dosing: 88% positive clinical response</td>
<td>1500 units reversed INR to less than 2.0 in 92.3% of patients and less than 1.5 in 71.8% of patients</td>
</tr>
<tr>
<td>Reversed INR in all patients: 1000 units and 1500 units</td>
<td>1040 units fixed dose: 96% positive clinical response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Ongoing PROPER3 trial evaluating variable vs. fixed dosing (1000 units) in vitamin K antagonist related extra-cranial bleeding**
UPRATE Study

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

Ammar Majeed,1-4 Anna Ågren,1,3 Margareta Holmström,1,3 Maria Bruzelius,1,3 Roza Chaireti,3,5,6 Jacob Odeberg,1,3,7 Eva-Lotta Hempel,1,3 Maria Magnusson,6,8,9 Tony Frisk,10 and Sam Schulman11,12

- Published in 2017 assessing the use of PCC for apixaban and rivaroxaban reversal
- Fixed dose PCC regimen of either 1,500 or 2,000 IV units based on weight

UPRATE Study

Population: patients with acute and active major bleeding while on rivaroxaban or apixaban
- Last dose within 24 hours

Excluded patients:
- Reduced hemoglobin without source
- Preoperative reversal
- Acute coronary syndrome or ischemic stroke in past 30 days
- Other hemostatic agents administered
UPRATE Study

- Prothrombin complex concentrate dosing
  - <65 kg: 1500 units IV
  - >65 kg: 2000 units IV

- Efficacy/safety assessment:

<table>
<thead>
<tr>
<th>Non-intracerebral hemorrhage (ICH) bleeding</th>
<th>Intracerebral hemorrhage (ICH) bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Hemoglobin trend</td>
<td>▪ Follow up CT within 24 hours</td>
</tr>
<tr>
<td>▪ Transfusion of blood products</td>
<td>▪ Change in neurological status</td>
</tr>
<tr>
<td>▪ Need for surgery or intervention</td>
<td>▪ Surgical intervention</td>
</tr>
<tr>
<td>▪ Administration of other hemostatic agents</td>
<td></td>
</tr>
</tbody>
</table>

Safety assessment: arterial or venous thromboembolism and 30-day mortality

UPRATE Results

- 84 total patients (39 apixaban and 45 rivaroxaban)
  - 70.2% ICH
- 26 patients (30.9%) had ineffective hemostatic effect post PCC
  - 61.5% suffered from ICH
- Death occurred in 15 patients (18%)
  - 13 patients (86.7%) had ICH
- Thromboembolism in 3 patients (2.4%)
  - 1 patient on thromboprophylaxis

UPRATE Conclusions

- Limitations:
  - Observational study
  - No control group for comparison
  - Subjective effectiveness

- Majority of patients treated with 2,000 units PCC for the management of major bleeding event on rivaroxaban or apixaban achieved effective bleeding control

Published in 2018 assessing the use of PCC for apixaban and rivaroxaban reversal

Fixed dose of 2,000 units studied

Inclusion criteria:
- Received 2,000 units of PCC for major bleeding on apixaban or rivaroxaban
- No other hemostatic agents

Exclusion criteria:
- Drop in hemoglobin without source
- Acute coronary syndrome or stroke within 30 days
66 patients (29 apixaban and 37 rivaroxaban)
- 55% ICH

10 patients (15%) did not achieve hemostatic efficacy

5 patients (8%) experienced thromboembolism within 30 days
- 0 of the 4 patients with thromboembolism during first 12 days were on anticoagulation
- 62% of patients were restarted on anticoagulation within 5 days

Study Conclusions

- Limitations:
  - Retrospective recruitment of patients
  - No control group for comparison
  - Not all patients received 2000 units
  - Subjective effectiveness

- Good hemostatic efficacy was achieved in 65% of patients and moderate hemostatic efficacy was achieved in 20% of patients

DOAC Reversal Agents

Andexanet Alfa (Andexxa®)
Andexanet Alfa General Information

- **Indication**: FDA accelerated approval in May 2018 for the reversal of anticoagulation in patients treated with apixaban (Eliquis®) or rivaroxaban (Xarelto®) in the setting of:
  - Life-threatening or uncontrolled bleeding
  - Emergency surgery

Andexanet Alfa General Information

Mechanism of action

- Recombinant modified human factor Xa decoy protein
  - Catalytically inactive (no coagulation activity)
  - Binds to factor Xa inhibitors at their site with a higher affinity than endogenous factor Xa
    - 1:1 stoichiometric ratio
    - Sequesters the inhibitor within the vascular space allowing endogenous factor Xa to be active

ANNEXA-A/ANNEXA-R trial

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., et al.

- ANNEXA-A and ANNEXA-R trials published in 2015 evaluated the ability of andexanet alfa to reduce anti-factor Xa levels in healthy volunteers
  - Compared andexanet alfa to placebo
  - Compared bolus to bolus with infusion

Randomized, double-blind, placebo controlled trial

Healthy volunteers

Primary endpoint: percent change in anti-factor Xa activity from baseline to post-administration
Trial design

**ANNEXA-A**
- Apixaban 5 mg twice daily for 3.5 days
- Low dose andexanet alfa regimen administered on day four, 3 hours after the last apixaban
  - Bolus vs. bolus with infusion

**ANNEXA-R**
- Rivaroxaban 20 mg daily for 4 days
- High dose andexanet alfa regimen administered on day four, 4 hours after the last rivaroxaban
  - Bolus vs. bolus with infusion

ANNEXA-R Results

ANNEXA-A/ANNEXA-R

Safety Data

- No serious safety events and no thrombotic events reported
- One patient discontinued treatment after 35 minutes – allergic reaction
- No antibodies to factor X or factor Xa developed

ANNEXA-A/ANNEXA-R Conclusions

- Andexanet alfa effectively reverses the anticoagulant effects of apixaban and rivaroxaban within minutes of administration.

- Bolus with continuous infusion dosing results in prolonged suppression of anti-factor Xa activity.
Andexanet Alfa Dosing Regimens

- **Two dosing regimens**
  - **Low dose:**
    - 400 mg IV bolus administered at 30 mg/minute
    - 4 mg/minute IV infusion 2 minutes after for up to 120 minutes
  - **High dose:**
    - 800 mg IV bolus administered at 30 mg/minute
    - 8 mg/minute IV infusion 2 minutes after for up to 120 minutes

- **Andexanet alfa available as 100 mg and 200 mg vial**
## Regimen Selection

<table>
<thead>
<tr>
<th>FXa inhibitor</th>
<th>FXa inhibitor last dose</th>
<th>Timing of FXa inhibitor last dose before andexanet alfa initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>≤5 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mg/unknown</td>
<td>High dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg/unknown</td>
<td>High dose</td>
</tr>
</tbody>
</table>
**IV Bolus Preparation**

**200 mg vials:** Reconstitute the 200 mg vial of ANDEXXA with 20 mL of Sterile Water for Injection USP (SWFI).

- Use a 20-mL (or larger) syringe and 20-gauge (or higher) needle.

- To ensure dissolution of the cake or powder, gently swirl each vial until complete dissolution of powder occurs (A). Do not shake (B); shaking could lead to foaming. Typical dissolution time for each vial is approximately 3 to 5 minutes. If dissolution is incomplete, discard the vial and do not use the product.

- Use 60-mL or larger syringe with a 20-gauge (or higher) needle to withdraw the reconstituted ANDEXXA solution from each of the vials until the required dosing volume is achieved. Note the total volume withdrawn into the syringe.

- Slowly inject the SWFI directing the solution onto the inside wall of the vial to minimize foaming.

- To reduce the total reconstitution time needed during preparation, reconstitute all required vials in succession.

- Upon reconstitution, the parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration.

- Transfer the ANDEXXA solution from the syringe into an empty polyolefin or polyvinyl chloride IV bag with a volume of 250 mL or less.

- Discard the syringe and needle.

- Discard the vials, including any unused portion.
ANNEXA-4 Trial

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Mark Crowther, M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., John H. Lawrence, M.D., Patrick Yue, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., et al., for the ANNEXA-4 Investigators

- Patients enrolled from April 2015 to May 2018
  - Preliminary results published September 2016 (67 patients)
  - Final results published April 2019

ANNEXA-4 Trial

- Multicenter, prospective, open-label, single-group study
- Received within 18 hours one of the following:
  - Apixaban
  - Rivaroxaban
  - Edoxaban
  - Enoxaparin at least 1 mg/kg/day
- Acute major bleeding

ANNEXA-4 Acute Major Bleeding

- Life-threatening bleeding with signs/symptoms of hemodynamic compromise
- Bleeding associated with hemoglobin decrease of at least 2 g/dL
- Bleeding in a critical area or organ
- July 2016 to August 2017 only patients with intracranial hemorrhage were enrolled

## ANNEXA-4 Exclusion Criteria

<table>
<thead>
<tr>
<th>ANNEXA-4 Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned surgery within 12 hours</td>
</tr>
<tr>
<td>Intracranial hemorrhage in patient with Glasgow Coma Scale score of less than 7</td>
</tr>
<tr>
<td>Estimated hematoma volume greater than 60 mL</td>
</tr>
<tr>
<td>Expected survival of less than 1 month</td>
</tr>
<tr>
<td>Thrombotic event within 2 weeks of enrollment</td>
</tr>
<tr>
<td>Vitamin K antagonist, dabigatran, PCC, recombinant factor VIIa, whole blood, or plasma administered within last 7 days</td>
</tr>
</tbody>
</table>

Dosing based on time since anticoagulant for rivaroxaban only

- <8 hours = low dose regimen
- ≥8 hours = high dose regimen

Primary outcomes:

- Percent change in anti-factor Xa activity
- Rate of excellent or good hemostatic efficacy 12 hours post infusion
- Safety outcome of death, thrombotic event, development of antibodies

# ANNEXA-4 Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Safety (N=352)</th>
<th>Efficacy (N=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age - yr</strong></td>
<td>77.4 ± 10.8</td>
<td>77.1 ± 11.1</td>
</tr>
<tr>
<td><strong>Indication for anticoagulation – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Atrial fibrillation</td>
<td>280 (80)</td>
<td>201 (79)</td>
</tr>
<tr>
<td>- Venous thromboembolism</td>
<td>61 (17)</td>
<td>46 (18)</td>
</tr>
<tr>
<td>- Other</td>
<td>11 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td><strong>Factor Xa inhibitor – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rivaroxaban</td>
<td>128 (36)</td>
<td>100 (39)</td>
</tr>
<tr>
<td>- Apixaban</td>
<td>194 (55)</td>
<td>134 (53)</td>
</tr>
<tr>
<td>- Enoxaparin</td>
<td>20 (6)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>- Edoxaban</td>
<td>10 (3)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Site of bleeding – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Gastrointestinal</td>
<td>90 (26)</td>
<td>62 (24)</td>
</tr>
<tr>
<td>- Intracranial</td>
<td>227 (64)</td>
<td>171 (67)</td>
</tr>
<tr>
<td>- Other</td>
<td>35 (10)</td>
<td>21 (8)</td>
</tr>
</tbody>
</table>

ANNEXA-4 Efficacy Results

- Anti-factor Xa activity at end of bolus administration
  - Apixaban 92% reduction
  - Rivaroxaban 92% reduction

- Hemostatic efficacy:

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients/Total No.</th>
<th>Percent with Excellent or Good Hemostasis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>204/249</td>
<td>82 (77–87)</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>79/99</td>
<td>80 (72–88)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>109/131</td>
<td>83 (77–90)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>13/15</td>
<td>87 (69–100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>101/127</td>
<td>80 (73–87)</td>
</tr>
<tr>
<td>Female</td>
<td>103/122</td>
<td>84 (78–91)</td>
</tr>
<tr>
<td>Site of bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>51/60</td>
<td>85 (76–94)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>135/168</td>
<td>80 (74–86)</td>
</tr>
<tr>
<td>Other</td>
<td>18/21</td>
<td>86 (71–100)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>23/28</td>
<td>82 (68–96)</td>
</tr>
<tr>
<td>65–75 yr</td>
<td>57/66</td>
<td>86 (78–95)</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>124/155</td>
<td>80 (74–86)</td>
</tr>
<tr>
<td>Andexanet dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>172/208</td>
<td>83 (78–88)</td>
</tr>
<tr>
<td>High</td>
<td>32/41</td>
<td>78 (65–91)</td>
</tr>
</tbody>
</table>

34 (10%) patients had at least 1 thrombotic event during 30-day follow up

- 34 (100%) occurred prior to restart of oral anticoagulant
- 26 (76%) occurred prior to restart of any anticoagulant at any dose

ANNEXA-4 Limitations

- 41 of 249 patients received the high dose regimen
  - 99 patients were on rivaroxaban
- No comparison – single group cohort
- Patients on average had a Glasgow Coma Score (GCS) of 14 and hematoma volume of <10 mL
- Excluded patients with surgery within 12 hours
- Subjective primary outcome

ANNEXA-4 Conclusions

- Andexanet alfa reduced anti-factor Xa levels and achieved hemostasis in the majority of patients
- Increased risk of thrombotic events
  - May be dependent on restart of anticoagulation
Anticoagulation Reversal Recommendations
Guidance from the American Journal of Hematology

- Reversal agents only indicated if bleeding is life-threatening or not controlled by supportive measures.

- Reversal agents should only be administered pre-operatively if the surgery cannot be performed or delayed.

- DOAC overdose without bleeding is not an indication for reversal.
Patients with dabigatran associated major bleeding or requiring emergent surgery should be treated with idarucizumab 5 grams IV

- PCC can be used at 50 units/kg if idarucizumab is not available
- Hemodialysis removes up to 68% but often impractical
Guidance from the American Journal of Hematology – Factor Xa Inhibitors

- Patients with rivaroxaban or apixaban associated bleeding warranting reversal should be treated with andexanet alfa
  - PCC 2,000 units can be used if andexanet alfa is not available

Guidance from the American Journal of Hematology – Factor Xa Inhibitors

- Patients with edoxaban-associated or betrixaban-associated major bleeding warranting reversal should be treated with either high dose andexanet alfa or PCC 2,000 units.

# Andexanet alfa vs. PCC

<table>
<thead>
<tr>
<th>Study result</th>
<th>ANNEXA-4 S - N=352</th>
<th>UPRATE N=84</th>
<th>Schulman et al. N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulant</strong></td>
<td>Xa inhibitors</td>
<td>Xa inhibitors</td>
<td>Xa inhibitors</td>
</tr>
<tr>
<td><strong>Reversal agent</strong></td>
<td>Andexanet alfa</td>
<td>PCC</td>
<td>PCC</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td></td>
<td>1500 units or 2000 units</td>
<td>2000 units</td>
</tr>
<tr>
<td><strong>Age, yrs</strong></td>
<td>77.4 ± 10.8</td>
<td>75 (70.0–83.0)</td>
<td>76.9 ± 10.4</td>
</tr>
<tr>
<td><strong>Intracranial hemorrhage – no, (%)</strong></td>
<td>227 (64)</td>
<td>59 (70.2)</td>
<td>36 (55)</td>
</tr>
<tr>
<td><strong>Efficacy endpoint met – no, (%)</strong></td>
<td>204 (82)</td>
<td>58 (69.1)</td>
<td>56 (85)</td>
</tr>
<tr>
<td><strong>Thromboembolism – no, (%)</strong></td>
<td>34 (10)</td>
<td>3 (3.6)</td>
<td>5 (7.6)</td>
</tr>
</tbody>
</table>

**Abbreviations:**
S = safety
E = efficacy
Investigational Agent

Ciraparantag

(Aripazine-PER977)
Ciraparantag (Aripazine-PER977)

- Direct sequestering of heparin, direct factor Xa and thrombin inhibitors
- Small synthetic water-soluble molecule
- Single dose forms strong ionic, noncovalent bonds and large complex molecules that bind anticoagulation agents
- Under evaluation in Phase II clinical trials

Restarting Anticoagulation
Restarting Anticoagulation

- **Reassess indication for anticoagulation**
  - Paroxysmal atrial fibrillation with CHA2DS2-VASc ≤1
  - Temporary indication (postsurgical prophylaxis, provoked VTE >3 months prior, etc.)

- **Risk/benefit assessment to restart**
  - Reversible factors contributing to bleed
  - High thrombotic risk (Mechanical valve prosthesis, atrial fibrillation, left ventricular assist device, venous thromboembolism)

- **Timing of restart**
  - High re-bleeding risk – initiate parenteral anticoagulant
  - Dependent on thrombotic/bleed risk

1. The ANNEXA-4 trial included patients with severe neurologic compromise as well as those requiring urgent surgery. (T/F)

2. According to a guidance document published in the American Journal of Hematology, a fixed dose of 2000 units of prothrombin complex concentrate is preferred to weight-based dosing in factor Xa inhibitor associated bleeding. (T/F)

3. Reversal agents for direct acting oral anticoagulant associated bleeding, should be administered to patients with bleeds that are life threatening, located in a critical organ, or uncontrolled by supportive measures. (T/F)

4. Investigational drug, ciraparantag is capable of reversing all anticoagulants including warfarin, argatroban, DOACs, heparin, LMWH, and fondaparinux. (T/F)
Andexxa (andexanet alfa) [package insert]. South San Francisco, Ca. Portola Pharmaceuticals


