Anticoagulation Reversal – Use of Specific Reversal Agents

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Objectives

• Summarize clinical controversies surrounding the use of reversal agents (antidotes) for anticoagulation reversal

• Explain the advantages and disadvantages associated with using reversal agents (antidotes) as the primary treatment approach for anticoagulation reversal

I do not have any financial conflicts of interest related to this presentation
Outline

• Brief overview of available anticoagulant reversal agents

• Review available literature and guideline recommendations

• Compare and contrast the use of PCC vs. specific antidotes for DOAC related bleeding
Reversal Options for DOAC Bleeding

• Plasma derived products
  – Fresh frozen plasma
  – Prothrombin complex concentrate (PCC)
    • 3 and 4 factor products

• Specific antidotes
  – Idarucizumab
  – Andexanet alfa
<table>
<thead>
<tr>
<th><strong>Available Reversal Antidotes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idarucizumab</strong></td>
</tr>
<tr>
<td><strong>Anticoagulant(s) Reversed</strong></td>
</tr>
<tr>
<td><strong>Chemical Structure</strong></td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
</tr>
<tr>
<td><strong>Pharmacokinetics/Pharmacodynamics</strong></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
</tr>
</tbody>
</table>
# Idarucizumab

## REVERSE-AD Trial

**Idarucizumab for Dabigatran Reversal – Full Cohort Analysis**

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, prospective, open-label study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Adults patients receiving dabigatran</td>
</tr>
<tr>
<td></td>
<td>• Group A - patients with uncontrollable or life-threatening bleeding</td>
</tr>
<tr>
<td></td>
<td>• Group B – patients undergoing surgery that could not be delayed for at least 8 hours</td>
</tr>
<tr>
<td></td>
<td>No major exclusions</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>5 grams IV idarucizumab (no placebo)</td>
</tr>
<tr>
<td></td>
<td>• Second dose allowed if continued bleeding</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Maximum percent reversal of the anticoagulant effect of dabigatran, assessed with diluted thrombin time or ecarin clotting time</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td>Adverse events (thrombosis, hypersensitivity)</td>
</tr>
</tbody>
</table>

# Idarucizumab

**REVERSE-AD Trial**

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=301)</th>
<th>Group B (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median, range)</strong></td>
<td>79 (24-96)</td>
<td>77 (21-96)</td>
</tr>
<tr>
<td><strong>Indication, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>288 (95.7)</td>
<td>190 (94.1)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>5 (1.7)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td><strong>Time since last dose, hours (median, range)</strong></td>
<td>14.6 (1.5-90.4)</td>
<td>18 (2.6-105.8)</td>
</tr>
<tr>
<td><strong>Elevated ECT or DTT at baseline, n (%)</strong></td>
<td>276 (91.7)</td>
<td>185 (91.6)</td>
</tr>
</tbody>
</table>

ECT = ecarin clotting time  
DTT = diluted thrombin time  
• Clinical outcome – cessation of bleeding within 24 hours
  – 134/203 (67.7%) in group A
  – 184/197 (93.4%) in group B

• Mortality (30 days)
  – 13.5% in group A vs. 12.6% in group B

• Thrombosis (90 days)
  – 6.3% group A vs. 7.4% group B

• Serious Adverse Event (5 days)
  – 23.3% of patients

Andexanet alfa (ANNEXA-A/R Trial)

# Andexanet alfa

## ANNEXA-4 Trial

**Andexanet alfa for acute major bleeding associated with factor Xa inhibitors**

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, prospective, open-label, single group study</th>
</tr>
</thead>
</table>
| Patients | 63 Centers in North America and Europe  
- Adults patients who received apixaban, rivaroxaban, edoxaban, or enoxaparin within the past 18 hours, **AND**  
- Acute major bleeding (life threatening, hemoglobin drop > 2 g/dl, bleeding in a critical organ)  
**Exclusion** – surgery planned within 12 hours, ICH + GCS < 7, recent thrombosis, expected survival < 30 days |
| Intervention | Andexanet 400-800 mg IV bolus, then 4-8mg/min infusion  
- If last dose > 7 hours ago or unknown, low dose used |
| Primary Outcome | Change in anti-Xa activity  
Clinical hemostasis efficacy during the first 12 hours |
| Secondary Outcomes | Adverse events (thrombosis, infusion reactions, immune)  
Mortality |

ICH = Intracranial hemorrhage  
GCS = Glasgow Coma Scale

## ANNEXA-4 Trial

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Safety Population (n=352)</th>
<th>Efficacy Population (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean, standard dev.)</strong></td>
<td>77.4 ± 10.8</td>
<td>77.1 ± 11.1</td>
</tr>
<tr>
<td><strong>Indication, n (%)</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>Time from hospitalization till dose, hours (mean)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>4.5 ± 3.6</td>
<td>4.7 ± 4.0</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>4.7 ± 3.1</td>
<td>4.7 ± 3.4</td>
</tr>
<tr>
<td><strong>Factor Xa inhibitor used, n (%)</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>Type of bleeding, n (%)</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>

## Andexanet alfa

### ANNEXA-4 Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of bolus</th>
<th>End of infusion</th>
<th>4 hours</th>
<th>8 hours</th>
<th>12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban anti-Xa</td>
<td>211.8</td>
<td>14.2 (-92%)</td>
<td>16.5 (-90%)</td>
<td>121.7</td>
<td>101.4</td>
<td>85.5 (-62%)</td>
</tr>
<tr>
<td>(median, % change baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban anti-Xa</td>
<td>149.7</td>
<td>11.1 (-92%)</td>
<td>11.5 (-92%)</td>
<td>97.2</td>
<td>104.6</td>
<td>91.2 (-39%)</td>
</tr>
<tr>
<td>(median, % change baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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### Safety Outcome (30 days)

<table>
<thead>
<tr>
<th>Safety Outcome (30 days)</th>
<th>Safety Population (n=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic Event, n (%)</td>
<td>34 (10)</td>
</tr>
<tr>
<td>Event before restart anticoagulant</td>
<td>26 (7)</td>
</tr>
<tr>
<td>Event after restart anticoagulant</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Death within 30 days, n (%)</td>
<td>49 (14)</td>
</tr>
<tr>
<td>Restart anticoagulant (yes), n (%)</td>
<td>220 (62)</td>
</tr>
</tbody>
</table>

Direct Comparison of PCC vs. Specific Reversal Agents?
So What Do The Experts Say?
Guideline Recommendations

• **2016 Neurocritical Care Society and SCCM Statement**
  - Factor Xa inhibitors – Suggest 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure (conditional rec, low-quality evidence)
  - Direct thrombin inhibitors – Suggest 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred, if Idarucizumab is not available (conditional rec, low-quality evidence)

• **2016 ESC Atrial Fibrillation Guidelines**
  - For severe or life threatening bleeding, consider specific antidote or PCC if no antidote available.

• **2018 CHEST Atrial Fibrillation Guidelines**
  - For serious bleeding, give DOAC specific reversal agent or PCC if reversal agent is not available

Guideline Recommendations

• 2017 ACC Consensus Document on Management of Bleeding
  – For severe bleeding with dabigatran, recommend idarucizumab. If not available, consider 4F-PCC or aPCC 50 units/kg IV
  – For severe bleeding with Factor Xa inhibitors, recommend 4F-PCC 50 units/kg

• 2019 Guidance From Anticoagulation Forum
  – For severe bleeding with dabigatran, recommend idarucizumab. If not available, suggest treatment with aPCC 50 units/kg
  – For severe bleeding with Factor Xa inhibitors, recommend Andexanet. If not available, suggest treatment with four factor PCC 2000 units

• 2019 AHA/ACC/HRS Atrial Fibrillation Focused Update
  – Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure (I B-NR)
  – Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life threatening or uncontrolled bleeding (IIa B-NR)

PCC – The **Good**, the Bad, the Ugly

- Good data for warfarin related bleeding
- Readily available, lower drug acquisition cost
- Compared to FFP, much less volume with administration
PCC — The Good, the Bad, the Ugly

• Lack of evidence in “real” patients
  – 8/17 studies in healthy volunteers
  – 2/17 studies were prospective, major bleeds (37 patients)

• Most studies used different endpoints
  – Only 4 studies evaluated clinical hemostasis

• Which product do we use? What dose?
  – 3 factor vs. 4 factor
  – Weight based vs. fixed dose

• “Low” rates of thromboembolism (3-9%)
  – Difficult to truly assess with small sample sizes
A Few Clinical Conundrums

• Repeat dosing
  – What guides decision to re-dose?

• Obese patients
  – Fixed dose ok?

• Restarting anticoagulation
  – Thrombosis occurred in patients who did not have anticoagulation restarted (30 days)
63-year-old female patient with metastatic endometrial cancer presents with intractable vomiting and progressive headache
CT head shows 40mm right parietal intra-parenchymal hemorrhage with ventricular extension
History of DVT, on rivaroxaban 20 mg daily (last dose 11 hours ago)

1. Does this qualify as a severe, life threatening bleed?
2. Do we need any other information to make a decision?
3. What intervention should be choose? (Drug, dose)

### Complete Blood Count (CBC)
- 5.6
- 9.2
- 182
- 29

### Chemistry Panel
- 135
- 97
- 17
- 183
- 4.6
- 23
- 1

- PO₄: 3.4 mg/dL
- Magnesium: 1.4 mg/dL
- Ca: 11.5 mg/dL

### Other
- Tbili: 0.4 mg/dL
- Alk phos: 61 International units/L
- ALT: 19 International units/L
- AST: 28 International units/L
- Alb: 3.7 g/dL
- PT: 17.7 seconds
- INR: 1.43
- aPTT: 30.7 seconds
Learning Assessment Question

• Which of the following anticoagulants have commercially available reversal agents?

A. Dabigatran
B. Rivaroxaban
C. Apixaban
D. All of the above
Learning Assessment Question

• Which of the following anticoagulants have commercially available reversal agents?

A. Dabigatran
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Learning Assessment Question

• Which factors(s) may describe the elevated rates of thrombosis in patients receiving reversal agents?

A. Delay in restarting anticoagulation
B. Faster correction of coagulation effects of medication
C. Volume of drug being administered
D. All of the above
Learning Assessment Question

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Rebuttal/Closing Thoughts

• Should be used in severe, life threatening bleeds
  – Can bleeding be stopped with other measures first?
  – Cost significant, but urgent need

• Better data in “real” patients
  – Most of studies with PCC/aPCC are in healthy volunteers/retrospective studies
  – Guidelines recommend specific reversal agents first

• Accepted drug selection and dosing with antidotes
  – Consider when to restart anticoagulation to minimize thrombosis
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.