Objectives for Pharmacists

• Review current strategies for the management of bleeding due to direct oral anticoagulants.
• Describe the characteristics and clinical trial data behind new reversal agents.
• Identify anticoagulation reversal agents in the pipeline.

Objectives for Pharmacy Technicians

• List currently available medications used to reverse bleeding caused by direct oral anticoagulants.
• Describe how new reversal agents are stored, prepared, and administered.
• Identify anticoagulation reversal agents in the pipeline.

Which of the following agents undergoing clinical trials may reverse the anticoagulant effects of factor Xa inhibitors, but NOT factor IIa inhibitors?

A. Aripizine (PER977)
B. Andexanet alfa (PRT064445)
C. Antihemophilic factor, PEGylated (BAX855)
D. Clazakizumab (ALD518)

Anticoagulation Guideline Recommendations

• Management of Atrial Fibrillation
  – dabigatran, rivaroxaban, or apixaban.
  • Level of Evidence: B
• Venous Thromboembolism Disease (VTE)
  – dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy.
  • Grade 2B
  – The risk that a major bleed will be fatal appears to be no higher for the direct oral anticoagulants (DOACs) than for VKA therapy.
DOAC Mechanisms of Action

Anticoagulant Effect of DOACs

Patient Case

56 year old female
PMH: DVT
Meds: rivaroxaban 20 mg PO daily
CC: MVA
Dx: retroperitoneal hemorrhage (major bleed) — requires immediate surgical intervention

Which of the following would you recommend to try and reverse her rivaroxaban?
A. Hemodialysis
B. 4-factor prothrombin complex concentrate (KCENTRA*)
C. Idarucizumab (PRAXBIND*)
D. Cryoprecipitate

Reversal for Major Bleeding or Urgent Invasive Procedure

Stop drug activated charcoal (<2 hr)

Concentrated Clotting Factor Products

None of the concentrated clotting factor products are FDA-approved for reversal of bleeding due to DOACs.
What is the only FDA-approved medication for reversal of dabigatran?

A. Aripazine (PER977)
B. 4-factor prothrombin complex concentrate (KCENTRA®)
C. Activated 4-factor prothrombin complex concentrate (FEIBA VH®)
D. Idarucizumab (PRAXBIND®)

**DIRECT ANTIDOTE**

**REVERSAL OF DABIGATRAN**

**idarucizumab (PRAXBIND®)**

- Humanized antibody fragment.
- ≈350-fold higher affinity to dabigatran versus dabigatran for thrombin.

**idarucizumab (BI655075) phase 1 trial**

- Placebo-controlled, double-blind
- Healthy males age 18-45 years (n=47)
  - BMI 18.5-29.9 kg/m²
- Dabigatran 220 mg PO daily x 3 days
- 3:1 ratio to idarucizumab or placebo
  - Idarucizumab: 1g, 2g, 4g, 5g + 2.5g
- Endpoints
  - adverse events
  - laboratory values
**idarucizumab – phase 1 trial**


**idarucizumab – phase 3 trial**

**RE‐VERSE AD**

- Outcomes
  - Reversal (%) of the anticoagulant effect of dabigatran after idarucizumab
  - Clinical and safety outcomes


**REVERSE AD**

<table>
<thead>
<tr>
<th>Group</th>
<th>dTT 4h</th>
<th>dTT 24h</th>
<th>ECT 4h</th>
<th>ECT 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>98%</td>
<td>90%</td>
<td>89%</td>
<td>72%</td>
</tr>
<tr>
<td>B</td>
<td>93%</td>
<td>81%</td>
<td>88%</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Percentage of patients with dabigatran concentrations near lower limit.**

- Group A
  - Cessation of bleeding at 11.4 h
- Group B
  - 92% intra-operative hemostasis


**idarucizumab (PRAXBIND®)**

- Mechanism
  - Noncompetitive inhibitor
- Onset - minutes
- Labs - dTT, ECT, aPTT, TT
- Half-life - 4.4-8.1 h
- Interactions - none
- Storage - refrigerated
- Stability - 2 years
- Cost - $3500 (WAC)
- Repeat dosing?
- Co-administration of factor products?


**AGENTS IN THE PIPELINE**

**REVERSAL OF DIRECT ORAL ANTICOAGULANTS**
**andiexanet alfa (PRT064445)**

- Recombinant decoy protein, catalytically inactive and unable to bind to phospholipid membrane


**andiexanet alfa – phase 3 trials**

- Placebo-controlled, double-blind
- Healthy adults age 50-75 years
- 2 part studies
  - Part 1: IV bolus only
  - Part 2: IV bolus followed by 2 hour infusion
- Endpoints
  - Change (%) in anti-factor Xa activity
  - Drug concentrations, thrombin generation


**andiexanet alfa**

- **ANNEXA-A**
  - Apixaban 5 mg PO BID 3.5 days
  - Andexanet alfa (n=48)
  - 400 mg IV bolus (30 mg/min)
  - 400 mg IV bolus, 480 mg infusion (2 hours)
- Placebo (n=17)

- **ANNEXA-R**
  - Rivaroxaban 10 mg PO daily 4 days
  - Andexanet alfa (n=53)
  - 800 mg IV bolus (30 mg/min)
  - 800 mg IV bolus, 960 mg infusion (2 hours)
- Placebo (n=27)


**ANNEXA-A and ANNEXA-R**

- Factor Xa activity and thrombin generation restored
- Reduced unbound DOAC (apixaban and rivaroxaban)
  - NO thrombotic events seen
- Bolus and/ or infusion administration
- Biomarkers of anticoagulation return to placebo levels after 1 to 3 hours
- ANNEXA-4, phase 3b study underway [NCT02329327]


**ANNEXA-A and ANNEXA-R**

- 400 mg IV bolus (30 mg/min)
- 400 mg IV bolus, 480 mg infusion (2 hours)
- 800 mg IV bolus (30 mg/min)
- 800 mg IV bolus, 960 mg infusion (2 hours)


**ANNEXA-A and ANNEXA-R**

- 400 mg IV bolus (30 mg/min)
- 400 mg IV bolus, 480 mg infusion (2 hours)
- 800 mg IV bolus (30 mg/min)
- 800 mg IV bolus, 960 mg infusion (2 hours)
andexanet alfa

- Mechanism – recombinant decoy protein
- Dosing – differs based on DOAC agent
- Administration – IV bolus rate 30 mg/min
- Onset – minutes
- Half-life – approximately 1 h
- Interactions – unknown
- Storage – refrigerated
- Supplied – 50 mg/vial lyophilized powder (10 mg/mL)
- Potential to reverse edoxaban, LMWH, fondaparinux

arpizone (PER977, ciraparantag)

- Small, synthetic, water-soluble, cationic molecule
- Non-covalent hydrogen bonding – charge-charge interactions

### aripizone (PER977, ciraparantag) phase 1 trial

<table>
<thead>
<tr>
<th>Dose</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PER977 5 mg or placebo</td>
<td>EDX + PER977 5 mg or placebo</td>
</tr>
<tr>
<td>PER977 15 mg or placebo</td>
<td>EDX + PER977 15 mg or placebo</td>
</tr>
<tr>
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<td>EDX + PER977 25 mg or placebo</td>
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<td>PER977 300 mg or placebo</td>
<td>EDX + PER977 300 mg or placebo</td>
</tr>
</tbody>
</table>

### aripizone (PER977, ciraparantag) phase 1 trial

- “...baseline hemostasis was restored from the anticoagulated state within 10 to 30 minutes after administration of 100 to 300 mg of PER977 and was sustained for 24 hours.”

### aripizone (PER977, ciraparantag)

- Mechanism – hydrogen bonding directly to anticoagulant
- Dosing – to be determined
- Administration – IV bolus rate 50 mg/min
- Onset – minutes
- Half-life – approximately 1.5 h
- Interactions – unknown
- Storage – room temperature
- Potential to reverse all DOACs, UFH, LMWH, fondaparinux
- Phase 2 study underway [NCT02207257]
### Activity of Reversal Agents

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Idarucizumab</th>
<th>Andexanet alfa</th>
<th>Aripazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>X</td>
<td>n/a</td>
<td>X</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>n/a</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Apixaban</td>
<td>n/a</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>n/a</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>UFH</td>
<td>n/a</td>
<td>n/a</td>
<td>X</td>
</tr>
<tr>
<td>LMWH</td>
<td>n/a</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>n/a</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

Some data inferred based on mechanisms of action versus actual study data.

### Future Anticoagulant Reversal Proposed Protocol

1. Stop drug activated charcoal (<2 hr.)
2. dabigatran
   - idarucizumab 5 g
3. rivaroxaban
   - aripazine (PER977) 100-300 mg?
4. apixaban
5. edoxaban
   - andexanet alfa 400-800 mg IV bolus followed by 480-960 mg infusion?
   - aripazine (PER977) 100-300 mg?

### Of the following anticoagulant reversal agents, FDA-approved or undergoing clinical trials, which is stored at room temperature?

A. Aripizine (PER977)
B. Andexanet alfa (PRT064445)
C. 4-factor prothrombin complex concentrate (KCENTRA®)
D. Idarucizumab (PRAXBIND®)

### Which of the following agents undergoing clinical trials may reverse the anticoagulant effects of factor Xa inhibitors, but NOT factor IIa inhibitors?

A. Aripizine (PER977)
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