Disclosure

Under guidelines established by the Accreditation Council for Pharmacy Education, disclosure must be made regarding financial relationships with commercial interests within the last 12 months.

☐ I have no relevant financial relationships or affiliations with commercial interests to disclose.
Objectives

At the completion of this activity, pharmacists will be able to:

- Discuss novel oral anticoagulant risk of hemorrhage
- Select appropriate reversal agent for hemorrhage associated with novel oral anticoagulants
- Examine available evidence for use of andexanet alfa

At the completion of this activity, pharmacy technicians will be able to:

- Discuss pharmacology of novel anticoagulants including common and severe side effects.
- Identify reversal agents for hemorrhage associated with novel oral anticoagulants.

Pre-Assessment

Which factor-Xa inhibitor is contraindicated in NVAF patients with CrCl > 95 mL/min due to increased risk in ischemic stroke?

A. Edoxaban
B. Apixaban
C. Warfarin
D. Betrixaban
Pre-Assessment

□ What is the name of the available reversal agent for dabigatran?
   A. 4F-PCC
   B. Phytonadione
   C. Idarucizumab
   D. Andexanet alfa

Pre-Assessment

□ Inhibiting tissue factor pathway inhibitor (TFPI) was an unintended consequence of coagulation factor Xa (recombinant), inactivated. Which side effect of coagulation factor Xa (recombinant), inactivated is thought to be caused by TFPI inhibition?
   A. Sepsis
   B. Bleeding
   C. Thrombosis
   D. Fever
Definitions

- NVAF = non-valvular atrial fibrillation
- VTE = venous thromboembolism
- ICH = intracranial hemorrhage
- LMWH = low-molecular-weight heparin
- VKA = vitamin-K antagonist
- ISTH = International Society for Thrombosis and Haemostasis
- NPSG = National Patient Safety Goal
- 4F-PCC = 4-factor prothrombin complex concentrate
- DOAC = direct-acting oral anticoagulants
- ISMP = Institute of Safe Medication Practices
- Hgb = hemoglobin
- PRBC = packed red blood cells
- TFPI = Tissue Factor Pathway Inhibitor

History

- Warfarin and aspirin as mainstay for stroke prevention and VTE treatment for decades
  - Routine laboratory monitoring
  - Lengthy onset and offset of anticoagulant effect
  - Numerous drug and food interactions
  - High incidence of bleeding complications
- FDA-approved 5 new oral anticoagulants since 2010
  - 3 new reversal agents
Anticoagulant Adverse Effects

- CDC found anticoagulants account for 17.6% of all ED visits for outpatient adverse drug effects
  - More than any other class of drugs!
- NPSG July 2019
  - Anticoagulant safety now includes DOACs


Timeline

[Timeline showing a sequence of anticoagulant drugs from 1954 to 2018]

- 1954: Warfarin (Coumadin)
- 2010: Dabigatran (Pradaxa)
- 2011: Rivaroxaban (Xarelto)
- 2012: Apixaban (Eliquis)
- 2015: Edaravaban (Savvyx)
- 2017:Betrixaban (Bevyxxa)
- 2018: Anticoagulant Factor Xa
  - Recombinant Inactivated (Human) (Kanetka)
  - 2015: Idarucizumab (Praxbind)
Clotting Cascade

DOAC Generalizations

- All noninferior to LMWH/VKA for recurrent VTE
  - Lower (apixaban, rivaroxaban) or similar (edoxaban, dabigatran) bleeding rates
- All at least as effective as VKA for stroke prevention in NVAF
  - Less ICH, reduced mortality
  - Increased risk of GI bleeding (except apixaban)
- Betrixaban labeled for VTE prophylaxis only
- Dosing varies widely based on indication, renal function, drug interactions, etc
Dabigatran

- Only oral-direct thrombin inhibitor
- Similar or increased risk of bleeding vs warfarin
- GI side-effects
- Most reliant on renal elimination
- Drug-interactions (P-glycoprotein)
- RE-ALIGN trial stopped early for HARM
- Dilute Thrombin Time or Ecarin Clotting Time

**WARNING**
Premature discontinuation of dabigatran increases the risk of thrombotic events. Spinal/Epidural hematoma may occur if receiving neuraxial anesthesia or spinal puncture.

Rivaroxaban

- New CAD indication (COMPASS trial)
- Lower major bleeding in VTE, but increased GIB in NVAF
- p-GP and CYP3A4 interactions
- Once-daily dosing
- Prothrombin time or Anti-Xa

**WARNING**
Premature discontinuation of rivaroxaban increases the risk of thrombotic events. Spinal/Epidural hematoma may occur if receiving neuraxial anesthesia or spinal puncture.
Apixaban

- Consistently decreased event rate and lower bleeding rates than warfarin
- Least dependency on renal elimination
  - Pharmacokinetic data supported renal dosing
- p-GP and CYP3A4 interactions
- Twice-daily dosing

**WARNING**
Premature discontinuation of apixaban increases the risk of thrombotic events.
Spinal/Epidural hematoma may occur if receiving neuraxial anesthesia or spinal puncture.

Edoxaban

- Lower major bleeding in VTE, but similar bleeding in NVAF
- Like dabigatran, parenteral anticoagulation ≥ 5 days THEN begin VTE treatment with edoxaban
- p-GP interactions

**WARNING**
Reduced efficacy in NVAF patients with CrCl > 95 mL/min
Premature discontinuation of edoxaban increases the risk of thrombotic events.
Spinal/Epidural hematoma may occur if receiving neuraxial anesthesia or spinal puncture.
Betrixaban

- VTE prophylaxis only
- APEX trial found significantly less VTE vs LMWH in hospitalized medical patients without an increase in bleeding
  - RRR = 0.26 [0.04-0.42], P = .023
- p-GP interactions

**WARNING**
Spinal/Epidural hematoma may occur if receiving neuraxial anesthesia or spinal puncture.

---

**DOAC Bleed Rates**

![Bar chart comparing bleed rates for DOACs and Warfarin for AF and VTE trials.]

- **Major Bleeding**
- **GI Bleeding**
- **ICH**

**4 Phase III AF DOAC Trials**
- DOACs: 2.39
- Warfarin: 2.8

**6 Phase III VTE DOAC Trials**
- DOACs: 1.17
- Warfarin: 0.32

**References**
19 Reversal Agents

20 General Management

- Assess bleed (any of following = major bleed)
  - Critical site of life-threatening
  - Hemodynamic instability
  - Clinically overt bleeding with Hgb decrease ≥ 2 g/dL or requiring administration of ≥2 units PRBCs
- Stop oral anticoagulant
- Provide local therapy/manual compression
- Supportive care
- Assess and manage comorbidities that could be contributing to bleed
- Consider surgical/procedural management

4-Factor Prothrombin Complex Concentrate (4F-PCC)

- Blood coagulation factor replacement product
  - Factors II, VII, IX, X, protein C and S
  - Administer with vitamin K concurrently*
- Lyophilized powder in single-use vials
  - Potency and Dosing per Factor IX nominal strength
    - 500 IU/20 mLs
    - 1000 IU/40 mLs
- Onset: minutes
- Duration: 6-8 hours*

<table>
<thead>
<tr>
<th>Pretreatment INR</th>
<th>Units/kg</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 2-3.9</td>
<td>25</td>
<td>2500 units</td>
</tr>
<tr>
<td>INR 4-6</td>
<td>35</td>
<td>3500 units</td>
</tr>
<tr>
<td>INR &gt; 6</td>
<td>50</td>
<td>5000 units</td>
</tr>
</tbody>
</table>

Administer by intravenous infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min).

**WARNING**
ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

---

4F-PCC vs plasma for VKA reversal in Acute Major Bleeding (2013)
randomized, controlled, non-inferiority trial comparing 4F-PCC to plasma

<table>
<thead>
<tr>
<th></th>
<th>4F-PCC</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemostatic Efficacy at 24 hours</strong></td>
<td>72.4 % excellent or good</td>
<td>65.4 % excellent or good</td>
</tr>
<tr>
<td>(n=202)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rapid INR Reduction at 30 minutes (&lt;1.3)</strong></td>
<td>62.2 % (95% CI, 52.6 to 71.8)</td>
<td>9.6 % (95% CI, 3.9 to 15.3)</td>
</tr>
<tr>
<td>(n=202)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious Adverse Events</strong></td>
<td>32 (31.1 %) 2 treatment-related</td>
<td>26 patients (23.9 %) 4 treatment-related</td>
</tr>
<tr>
<td>(n=212)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thromboembolic Events</strong></td>
<td>8 (7.8 %) 4 treatment-related</td>
<td>7 (6.4 %) 3 treatment-related</td>
</tr>
<tr>
<td>(n=212)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality at 30 days</strong></td>
<td>6 (5.8 %) 1 treatment-related</td>
<td>5 (4.6 %)</td>
</tr>
<tr>
<td>(n=212)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 4-Factor Prothrombin Complex Concentrate (4F-PCC)

#### 4F-PCC vs plasma for VKA reversal in Urgent Surgical/Procedural needs (2015)
randomized, controlled, non-inferiority trial comparing 4F-PCC to plasma

<table>
<thead>
<tr>
<th></th>
<th>4F-PCC</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostasis during surgical or invasive procedure (n=168)</td>
<td>78/87 (90 %)</td>
<td>61/81 (75 %)</td>
</tr>
<tr>
<td></td>
<td>14.3% (2.8 to 25.8) (95 % CI) (p=0.0142)</td>
<td></td>
</tr>
<tr>
<td>Rapid INR Reduction at 30 minutes (≤1.3) (n=168)</td>
<td>48/87 (55 %)</td>
<td>8/81 (10 %)</td>
</tr>
<tr>
<td></td>
<td>45.3% (31.9 to 56.4) (95 % CI) (p=&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Events (n=176)</td>
<td>22/88 (25 %)</td>
<td>23/88 (26 %)</td>
</tr>
<tr>
<td></td>
<td>3 treatment-related</td>
<td>3 treatment-related</td>
</tr>
<tr>
<td>Thromboembolic Events (n=176)</td>
<td>6/88 (7 %)</td>
<td>7/88 (8 %)</td>
</tr>
<tr>
<td></td>
<td>−1.1% (-10 to 8) (95 % CI) (p=0.77)</td>
<td></td>
</tr>
<tr>
<td>Mortality at 45 days (n=176)</td>
<td>3/88 (3 %)</td>
<td>8/88 (9 %)</td>
</tr>
<tr>
<td></td>
<td>1 treatment-related</td>
<td></td>
</tr>
</tbody>
</table>


---

### Meta-Analysis of PCC for DOAC acute bleeding management

<table>
<thead>
<tr>
<th>Pooled Outcome</th>
<th>4F-PCC (N=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective major bleeding management (ISTH criteria) (n=150)</td>
<td>0.69 (95% CI 0.61 to 0.76)</td>
</tr>
<tr>
<td>Effective major bleeding management (NON-ISTH criteria) (n=190)</td>
<td>0.77 (95% CI 0.63 to 0.92)</td>
</tr>
<tr>
<td>Mortality (n=249)</td>
<td>0.16 (95% CI 0.07 to 0.26)</td>
</tr>
<tr>
<td>Thromboembolic Events (n=240)</td>
<td>0.04 (95% CI 0.01 to 0.08)</td>
</tr>
</tbody>
</table>

Idarucizumab

- Humanized, monoclonal antibody binding to dabigatran and metabolites
- Supplied as cartons of (2) single-dose 2.5 gram/50 mL vials
- Recommended dose: 5 gram IV infusion
  - Consecutively infuse (2) 2.5 gram vials no more than 15 minutes apart OR bolus injection (2) 2.5 gram vials
- Onset: minutes
- Duration: ~24 hours

REVERSE-AD
Multicenter, prospective, open-label case series of 503 patients reversing dabigatran in life-threatening bleeding or need for urgent surgery

<table>
<thead>
<tr>
<th>Primary Efficacy Outcomes</th>
<th>Group A (N= 310, n=203) (uncontrollable bleeding)</th>
<th>Group B (N= 202, n=197) (urgent procedure/surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median % reversal of anticoagulant effect in 4 hours (n=461)</td>
<td>100% (95% CI, 100 to 100)</td>
<td></td>
</tr>
<tr>
<td>Restoration of hemostasis</td>
<td>• 67.7 % (134) confirmed bleeding cessation in 24 hours • Median time to hemostasis: 2.5 hours (95% CI, 2.2 to 3.9)</td>
<td>• 93.4 % normal hemostasis • 5.1 % mildly abnormal • 1.5 % moderately abnormal • Median time to procedure: 1.6 hours</td>
</tr>
</tbody>
</table>
Reappearance of dabigatran was observed in 114 of 497 patients (23%). 10 patients experienced recurrent or continual bleeding. 9 of 503 patients received more than 5 grams of Idarucizumab. 7 received a second dose, 1 received (two) additional doses, 1 received a second dose in error.

Andexanet alfa
Coagulation factor Xa (recombinant), inactivated-zhzo

- Original 2015 submission rejected due to lack of manufacturing details
- Received FDA approval in May 2018
  - Conditional on post-marketing clinical benefit
  - Generation-2 manufacturing line approved December 2018
  - ANEXXA-4 trial published February 2019

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Andexanet alfa
Coagulation factor Xa (recombinant), inactivated-zhzo

- Reversal of *rivaroxaban* or *apixaban* for life-threatening or uncontrolled bleeding
- Acts a decoy protein to bind Factor Xa inhibitors
  - Also inhibits the activity of Tissue Factor Pathway Inhibitor (TFPI)
- Supplied as cartons of (4) single-use 100 mg vials

---

WARNING
THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS

---
### Andexanet alfa

**Coagulation factor Xa (recombinant), inactivated-zhzo**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial IV Bolus</th>
<th>Following IV Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose</td>
<td>400 mg at a target rate of 30 mg/min</td>
<td>4 mg/min for up to 120 min</td>
</tr>
<tr>
<td>High Dose</td>
<td>800 mg at a target rate of 30 mg/min</td>
<td>8 mg/min for up to 120 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor Xa inhibitor</th>
<th>Last Dose</th>
<th>Dose &lt; 8 hours or Unknown</th>
<th>≥ 8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>≤ 10 mg</td>
<td>Low Dose</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&gt;10 / Unknown</td>
<td>High Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>≤ 5 mg</td>
<td>Low Dose</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>&gt;5 mg / Unknown</td>
<td>High Dose</td>
<td></td>
</tr>
</tbody>
</table>

---

**Anti-Factor Xa activity increases to placebo levels ~2 hours after andexanet alfa infusion**

“It is possible that further refinements in the administration of andexanet could lead to more complete reversal of anti-factor Xa activity and improved clinical outcomes.”

---

Multicenter, prospective, open-label, single-group cohort study of 352 patients with acute major bleeding reversing factor Xa inhibitors

**Inclusion:**
- ≥ 18 years, acute major bleeding, received apixaban, rivaroxaban, edoxaban, enoxaparin (treatment dose) within previous 18 hours,

**Exclusion:**
- Planned surgery within 12 hours of andexanet, ICH with GCS < 7, ICH with hematoma volume > 60 mL, expected survival of less than 1 month, thrombotic event in prior 2 weeks, use of VKA, dabigatran, PCC, Factor VIIa, whole blood, or plasma in prior 7 days

Many protocol deviations – enrollment criteria, dosing protocol, primary endpoint, etc

---


### Primary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Andexanet alfa (n=254, 72%)</th>
<th>Apixaban (n=134)</th>
<th>Rivaroxaban (n=100)</th>
<th>Enoxaparin (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change from baseline Anti-Xa activity (n=250*)</td>
<td>92% (95% CI, 91 to 93)</td>
<td>92% (95% CI, 88 to 94)</td>
<td>75% (95% CI, 66 to 79)</td>
</tr>
<tr>
<td>% excellent or good hemostatic efficacy at 12 hours (n=249*)</td>
<td>83% (95% CI, 77 to 90)</td>
<td>80% (95% CI, 72 to 88)</td>
<td>87% (95% CI, 69 to 100)</td>
</tr>
</tbody>
</table>

ANNEXA-4

Multicenter, prospective, open-label, single-group cohort study of 352 patients with acute major bleeding reversing factor Xa inhibitors

<table>
<thead>
<tr>
<th>Primary Safety Outcomes</th>
<th>Andexanet alfa (n=352, 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6 days after bolus</td>
</tr>
<tr>
<td>≥1 Thrombotic event within 30 days (n=34, 10%)</td>
<td>11</td>
</tr>
<tr>
<td>Death within 30 days (n=49, 14%)</td>
<td>8</td>
</tr>
<tr>
<td>Restart of any anticoagulation (n=220, 62%)</td>
<td>145 (41%)</td>
</tr>
</tbody>
</table>


---

**Coagulation factor Xa (recombinant), inactivated-zhzo**

- Acts as a decoy for Factor Xa inhibitors to bind
- Lacks natural procoagulant properties of endogenous Factor Xa
- Also binds and inhibits Tissue Factor Pathway Inhibitor (TFPI)
  - Unanticipated procoagulant property

Balancing Risk and Benefit

<table>
<thead>
<tr>
<th>Efficacy and Safety Comparison for reversing bleed on DOAC</th>
<th>4F-PCC</th>
<th>Idarucizumab</th>
<th>Andexanet alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective major bleeding management (ISTH criteria)</td>
<td>69 – 77 %</td>
<td>67 – 93 %</td>
<td>80 – 87 %</td>
</tr>
<tr>
<td>Thromboembolic Events</td>
<td>4 %</td>
<td>5 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Death at 30 or 45 days</td>
<td>16 %</td>
<td>13 %</td>
<td>14 %</td>
</tr>
</tbody>
</table>

Consider:
- Rebound of anticoagulant
- Emergent need/availability
- Cost
- Patient population
- Need for surgery
- Restarting Anticoagulation

Reversal Agent Comparison

- **4F-PCC**
  - Off-label for DOAC reversal
  - Limited evidence
  - Dosing errors may occur

- **Idarucizumab**
  - Dabigatran only
  - Dosing errors may occur

- **Andexanet alfa**
  - Thrombotic event rate
  - Cost
    - $29,700 - $59,400

**4F-PCC vs Andexanet alfa**
Randomized, controlled trial in ICH with DOAC
EXPECTED 2023
Post-Assessment

39. Which factor-Xa inhibitor is contraindicated in NVAF patients with CrCl > 95 mL/min due to increased risk in ischemic stroke?
   A. Edoxaban
   B. Apixaban
   C. Warfarin
   D. Betrixaban

Post-Assessment

40. What is the name of the available reversal agent for dabigatran?
   A. 4F-PCC
   B. Phytonadione
   C. Idarucizumab
   D. Andexanet alfa
Post-Assessment

☐ Inhibiting tissue factor pathway inhibitor (TFPI) was an unintended consequence of coagulation factor Xa (recombinant), inactivated-zhzo. Which side effect of coagulation factor Xa (recombinant), inactivated-zhzo is thought to be caused by TFPI inhibition?
   A. Sepsis
   B. Bleeding
   C. Thrombosis
   D. Fever

Conclusion

☐ DOACs have variable rates hemorrhage
   □ Overall, lower incidence than warfarin

☐ Reversal agents for DOACs are now available

☐ Newly-approvedandexanet alfa (coagulation factor Xa (recombinant), inactivated-zhzo) offers reversal agent for apixaban or rivaroxaban
References
