Reversal of Newer Anticoagulants

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www.fshp.org

Objectives

Pharmacists
I. Compare and contrast mechanisms, roles in therapy, and adverse effect profiles of the new oral anticoagulants
II. Summarize available evidence based literature for the reversal of the new oral anticoagulants
III. Select the most appropriate agent for reversal of new oral anticoagulants in clinical practice

Technicians
I. Identify brand/generic names of newer anticoagulants
II. State the common conditions that newer anticoagulants are used to manage
III. Explain the common adverse effects of anticoagulants

Disclosure

I have no conflicts of interests to declare regarding the content of this presentation.

Epidemiology

Venous thrombosis embolism (VTE) defined as deep vein thrombosis and pulmonary embolism (DVT/PE)

Affects an estimated 300,000-600,000 individuals in the U.S. annually

Frequency of VTE increases with age
- 1 in 100 in those 80 years or older

Overall rate is higher among African Americans and Caucasians
Blood Clot Formation

Atrial Fibrillation

Epidemiology

- Atrial Fibrillation
  - Structural/electrical abnormalities that change atrial tissue and cause abnormal impulse formation
  - Affects an estimated 2.7-6.1 million people in the United States
    - Causes 15%-20% of ischemic strokes
  - Incidence increases with age
    - 1 in 4 adults 40 years or older

Epidemiology

- Morbidity and mortality
  - Approximately 60,000-100,000 Americans die of DVT/PE annually
    - 10-30% die within one month of DVT diagnosis
    - Sudden death occurs in 25% of PE patients
  - One-half of PE patients have long-term complications
  - Following anticoagulation therapy about 1/3 of patients have a recurrence in 10 years
Clotting Cascade for New Oral Anticoagulants

Table 1: FDA Approved Indications for New Oral Anticoagulants (NOAC)\(^6,7,8,9\)

<table>
<thead>
<tr>
<th>FDA Indications</th>
<th>Pradaxa(^a)</th>
<th>Xarelto(^a)</th>
<th>Savaysa(^a)</th>
<th>Eliquis(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke prevention in nonvalvular atrial fibrillation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DVT/PE treatment</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Reduction in risk of recurrent DVT/PE after initial therapy after initial therapy</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>DVT prophylaxis following replacement surgery of hip or knee</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Pill Identification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison of New Oral Anticoagulants: Metabolism and Bleeding Risk

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa(^a)</th>
<th>Xarelto(^a)</th>
<th>Savaysa(^a)</th>
<th>Eliquis(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6.5%</td>
<td>&gt;80%</td>
<td>62%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 hours</td>
<td>5-9 hours</td>
<td>10-14 hours</td>
<td>10-14 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% renal</td>
<td>60% renal</td>
<td>50%</td>
<td>27% renal</td>
</tr>
<tr>
<td><strong>Plasma protein binding</strong></td>
<td>24-31%</td>
<td>92-95%</td>
<td>55%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>P-gp inducers/inhibitors</td>
<td>P-gp inducers/inhibitors</td>
<td>P-gp inducers/inhibitors</td>
<td>P-gp inducers/inhibitors</td>
</tr>
</tbody>
</table>
Pradaxa® (dabigatran) is **not** dialyzable, due to its low plasma protein binding.

A) True  
B) False
Bleeding Risk of New Oral Anticoagulants

### ARISTOTLE Trial

<table>
<thead>
<tr>
<th>Bleeding Event</th>
<th>Apixaban (n=9088)</th>
<th>Warfarin (n=9052)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>327 (3.6%)</td>
<td>462 (5.1%)</td>
<td>0.69 (0.60-0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>105 (1.16%)</td>
<td>119 (1.31%)</td>
<td>0.89 (0.70-1.15)</td>
<td>0.37</td>
</tr>
<tr>
<td>Intracranial</td>
<td>52 (0.57%)</td>
<td>122 (1.35%)</td>
<td>0.42 (0.30-0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>2356 (25.9%)</td>
<td>3060 (33.8%)</td>
<td>0.71 (0.68-0.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Major bleeding: decrease in hemoglobin of 2gm/dL or transfusion ≥2 units packed red cells, occurring in a critical site or resulting in death.

Principles and Measures for Management of Anticoagulant-related Bleeding

**General Principles**
- Stop anticoagulant
- Hemodynamic and hemostatic resuscitation
- Volume replacement
- Transfusion of blood products
- Supportive measures for life threats (e.g., ventilation)
- Reversal of anticoagulation, antiplatelet medication if indicated
- AABB recommendations for transfusion, use anticoagulant reversal if long delay in bleeding

**Vitamin K Analogs**
- PCCs: Prothrombin complex concentrate

**Recombinant Factor VIIa (rFVIIa)**

**Activated Charcoal**

**Activated Protein C**

**Epinephrine**

**Praxbind® (Idarucizumab)**

**Adjunctive Measures**
- Consider Fibrinolytic Therapy

Reversal Strategies of New Oral Anticoagulants

### Reversal Strategies

- **Prastaro®**
- **Fibrinogen Factor (FFP)**
- **Prothrombin Complex Concentrates (PCC)**
- **Recombinant Factor VIIa (rFVIIa)**
- **Humanized Monoclonal Antibody**
- **Praxbind® (Idarucizumab)**
Activated Charcoal

**Indication**
Acute poisoning

**Mechanism**
Adsorbs toxic substances, thus inhibiting GI absorption and preventing systemic toxicity

**Formulation**
Oral liquid

**Adverse Reactions**
Fecal discoloration, constipation, vomiting

**Administration**
Flavoring agents or thickening agents can enhance palatability
The container should be agitated before administration

**Onset**
Depends upon ingestion

**Storage and Handling**
Room temperature

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Fresh Frozen Plasma

- Restores all coagulation factors
- Contains coagulation factors in normal serum concentrations
  - Significantly lower amounts of clotting factors II, VII, IX, and X
- Must be thawed, ABO type matching required, large volume of administration
  - Dose: 10-20mL/kg
- Associated with fluid overload, infectious disease, transfusion related acute lung injury

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Prothrombin Complex Concentrates (PCC)

- Concentrated plasma products that contain clotting factors in varying amounts
- Formulations can include:
  - 3-Factor products (II, IX, and X)
  - 4-Factor products (II, VII, IX, and X)
- May also contain coagulation inhibitors to mitigate thrombotic risk
- Proposed mechanism for reversal: large amounts of factor X may decrease inhibitory effects of factor Xa inhibitors

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  - Significantly lower amounts of clotting factors II, VII, IX, and X
- Must be thawed, ABO type matching required, large volume of administration
  - Dose: 10-20mL/kg
- Associated with fluid overload, infectious disease, transfusion related acute lung injury
**Bebulin®/ Profilnine®**

**Indication:** Control and prevention of bleeding episodes in adult patients with hemophilia B; Warfarin associated hemorrhage

**Mechanism:** Replaces deficient clotting factor including factor IX

**Formulation:**
- **Bebulin®**
  - Reconstituted solution
  - Contains factors II, IX, X, and low levels of VII and heparin
- **Profilnine SD®**
  - Reconstituted solution
  - Contains factors II, IX, X, and low levels of VII

**Adverse Reactions:** Nausea/vomiting, headache, fever, thrombosis, somnolence, pyrexia, chills, hypotension and DIC

**Preparation:** Reconstitute with diluent provided with kit

**Administration:** Solution should be infused at room temperature

**Rate:**
- Bebulin: 2 mL/minute
- Profilnine: 10 mL/minute

**Onset:** Less than 30 minutes

**Storage and Handling:** Store at refrigerated temperature. Do not freeze

**FDA Approval:**
- Bebulin® April 7, 2011
- Profilnine SD® July 20, 1981

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**Kcentra®**

**Indication:** Urgent reversal of acquired coagulation factor deficiency induced vitamin K antagonist therapy in adult patients with acute major bleeding

**Mechanism:** Prothrombin complex concentrate provides an increase in the levels of the vitamin K-dependent coagulation factors (II, VII, IX, and X) with the addition of protein C and protein S.

**Formulation:** Reconstituted solution

**Contains clotting factors II, VII, IX, and X, proteins C and S**

**Adverse Reactions:** Headache, nausea/vomiting, arthralgia, and hypotension

**Preparation:** Reconstitute with 20mL of diluent provided with kit

**Administration:**
- Administer at room temperature at a rate of 0.12 mL/kg/minute (~3 units/kg/minute). Do not exceed 8.4 mL/minute (~210 units/minute). Do not allow blood to enter into syringe; Must be used within 4 hours of reconstitution
- **Onset:** Rapid; significant INR decline within 10 minutes

**Storage and Handling:** Store between 2°C - 25°C. Do not freeze

**FDA Approval:** April 29, 2013

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**ISMP Alert**

- Misleading label leads to dosage errors
  - Base dosing on actual potency
  - Varies from 20-31 Factor IX units/mL
  - Normal potency is ~500 units per vial

“Safety requires a state of mindfulness”

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**Fresh frozen plasma is associated with transfusion related acute lung injury.**

A) True

B) False
Activated Prothrombin Complex Concentrate (aPCC)

**FEIBA®**

**Indication**
Spontaneous bleeding episodes or surgical interventions in hemophilia A and B patients

**Mechanism**
Multiple interactions of the components in FEIBA restore the impaired thrombin generation of hemophilia patients with inhibitors. Shortens aPTT of plasma containing Factor VII inhibitor

**Formulation**
Reconstituted solution
500 units; 1000 units; 2500 units

**Adverse Reactions**
Anemia, diarrhea, hepatitis B antibody positive

**Preparation**
Reconstitute with 20mL or 50mL of diluent provided with kit

**White, off white or pale green freeze dried powder**

**Administration**
IV injection or drip infusion only; maximum infusion rate: 2 units/kg/minute. Following reconstitution, complete infusion within 3 hours.

**Onset**
Rapid (peak at 15-30 minutes)

**Storage and Handling**
Store at room temperature. Do not freeze

**FDA Approval**
May 27, 2009

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Novoseven RT®

**Indication**
Indicated for the treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B, congenital Factor VII deficiency, Glanzmann’s

**Mechanism**
Replaces deficient activated coagulation factor VII

**Formulation**
Reconstituted solution
1mg; 2mg; 5mg; 8mg

**Contains activated factor VII**

**Adverse Reactions**
Thrombotic events, were most common in clinical trials

**Preparation**
Reconstitute with diluent provided

**Administration**
IV administration only as a bolus over 2 to 5 minutes

Administer within 3 hours after reconstitution

**Onset**
Less than 30 minutes

**Storage and Handling**
Prior to reconstitution store between 2°-25° C. Do not freeze.

**FDA Approval**
August 6, 2010

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**Prothrombin Complex Concentrates and Hemophilia Agent Composition**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Components</th>
<th>Dose</th>
<th>Time to Effect (min)</th>
<th>Duration (hr)</th>
<th>Cost (AWP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3F-PCC</td>
<td>Bebulin</td>
<td>Factors II, IX, X, low concentration factor VII, heparin</td>
<td>25-90 units/kg</td>
<td>10</td>
<td>6-8</td>
</tr>
<tr>
<td>Profilnine SD</td>
<td>Factors II, IX, X, and low concentration factor VII</td>
<td>20-50 units/kg</td>
<td>10</td>
<td>6-8</td>
<td>$1.19 /IU</td>
</tr>
<tr>
<td>Activated 4F-PCC</td>
<td>FEIBA</td>
<td>Factors II, VII, IX, X</td>
<td>50-100 units/kg</td>
<td>15</td>
<td>8-12</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>NovoSeven RT</td>
<td>Activated rFVIIa</td>
<td>15-90 mcg/kg</td>
<td>10</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

AWP: average wholesale price, IU: international units
Trials Patients Treatment

1. Endpoint Results

Apixaban
Induced Alterations in Hemostasis by different coagulation factor concentrates
PlosONE.20013;8(11): e78696

10 healthy volunteers rFVIIa (Novoseven) 270 μg/kg
aPCC (FEIBA) 75 U/kg
4F-PCC (Beriplex) 50 IU/kg

Clotting assays, measure TG, CFT, thrombin peak, lag phase, time peak to determine reversal

rVIIa and aPCC normalized prolongation to reach peak TG,
rVIIa/aPCC significantly reversed lag phase and thrombin peak (p<0.01),
rVIIa/aPCC significantly reduced CT and CFT (p<0.01)

aPCC shows potential and may be 1st line

Impact of 3F-PCC on anticoagulatory effects of Edoxaban
Thrombosis Research 136(2015) 825-831

24 healthy volunteers Single-dose 60mg or single-dose 180mg of Edoxaban, followed by placebo or 25 IU/kg 3F-PCC or 50 IU/kg 3F-PCC

Evaluate reversal of 25-50 IU/kg doses of 3F-PCC using prothrombin time as the primary PD marker and ETP

No apparent reversal of PT prolongation, but ETP was completely reversed

Reversal of Rivaroxaban and Dabigatran by PCC
Circulation. 2011;124:1573-1579

12 healthy male volunteers Dabigatran 150mg twice daily or Rivaroxaban 20mg twice daily for 2.5 days
Received either PCC 50 IU/kg or Saline on Day 3

Reversal of anticoagulant effect by measuring PT and ETP (rivaroxaban) and APTT, ETP, lag time, thrombin time, ecarin clotting time (dabigatran)

Rivaroxaban: PCC completely reversed prothrombin time (12.8±1.0; p<0.001), and normalized ETP (114±26; p<0.001)
Dabigatran: 4F-PCC did not significantly reverse APTT, ETP lag time, thrombin time,
ecarin clotting time

Reversal of Rivaroxaban induced anticoagulation by PCC, aPCC, and rFVIIa
Thromb Res. 2014;133:671-681

Healthy volunteers Rivaroxaban diluted to simulate a 20mg dose and hypothetical overdose aPCC (FEIBA) 0.2 U/mL, 0.4 U/mL, 0.7 U/mL
4F-PCC (Beriplex) 0.4 U/mL, 0.2 U/mL, 0.7 U/mL
rFVIIa (Novoseven) 5μg/mL, 15μg/mL, 50μg/mL

Reversal of anticoagulant effects by measuring PT, CT, TG lag time, maximum concentration, ETP

PCC: decreased prothrombin time by 15-20% (p<0.001)
aPCC/rFVIIa significantly shortened clotting time (p<0.001)
aPCC/rFVIIa significantly reversed lag time (p<0.001)
PCC significantly reversed ETP(p<0.01)
aPCC significantly increased ETP (p<0.01)

Kcentra® has a normal potency of ~500 units per vial, but has varying amounts of Factor IX from 20-31 units/mL.

A) True
B) False

Humanized Monoclonal Antibody

Praxbind® (idarucizumab)

<table>
<thead>
<tr>
<th>Administration</th>
<th>Sr 2.5g/mL in saline. Give immediately after IV bolus and induction. An intravenous drip.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>Sr 5g (2.5g/50mL) idarucizumab. Administration should begin promptly or within 1 hour.</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>Give solution 1 hour before Praxbind administration or 2 hours before Praxbind administration.</td>
</tr>
<tr>
<td>Duration</td>
<td>Sr 5g (2.5g/50mL) idarucizumab. Administration should begin promptly or within 1 hour.</td>
</tr>
<tr>
<td>Indication</td>
<td>Sr Emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Sr Binds to dabigatran and its acylglucuronide metabolites with higher affinity and neutralizes the anticoagulant effect</td>
</tr>
<tr>
<td>Formulation</td>
<td>Sr Sterile, preservative free, colorless to slightly yellow, clear to slightly opalescent solution available as: Injection: 2.5g/mL solution in a single use vial</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Sr Headache, hypokalemia, delirium, constipation, pyrexia, and pneumonia</td>
</tr>
<tr>
<td>Preparation</td>
<td>Sr Once solution has been removed from the vial, administration should begin promptly or within 1 hour</td>
</tr>
<tr>
<td>Administration</td>
<td>Sr The recommended dose of Praxbind® by intravenous infusion containing 2.5g/mL idarucizumab to clinical effects. Praxbind® was administered as one 3mg intravenous infusion over 5 minutes.</td>
</tr>
<tr>
<td>Drug Storage</td>
<td>Sr Immediate and should be used within 30 minutes.</td>
</tr>
<tr>
<td>Refrigeration</td>
<td>Sr Store in the refrigerator. Do not freeze or freeze.</td>
</tr>
</tbody>
</table>

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Idarucizumab for Dabigatran Reversal RE-VERSE AD Trial

**Purpose**
Examine efficacy and safety of idarucizumab for dabigatran reversal

**Design**
Multicenter, prospective cohort study

**Interim analysis, data on 90 of 300 patients**

Each patient received two 2.5 g infusions 15 minutes apart

**Patients**
30 years and older and on dabigatran

Group A: Life-threatening bleed

Group B: Urgent surgery or procedure required

**End Points**
Primary:

- Maximum percentage reversal

Secondary:

- Proportion with normalization of dilute thrombin time
- Proportion with normalization of ecarin clotting time
- Reduction in concentration of unbound dabigatran

**Safety**
- 82 adverse events captured

**Results**
22 patients had dilute thrombin times that were within normal limits and 9 of those patients had normal clotting times excluding these 22 pts from analysis

81 of 90 were assessed with ecarin-clotting time test

All patients received idarucizumab regardless of their inclusion in the efficacy analysis

**Primary Outcome**

- Maximum percentage reversal in Groups A and B was 100%

**Secondary Outcome**

- Group A DTT and ECT: 98% and 89% respectively
- Group B DTT and ECT: 93% and 88% respectively

**Recommendations for the Reversal of New Oral Anticoagulants**

**ISMP Alert**

*Don't confuse idarucizumab with IDAurubicin*

Last month the US Food and Drug Administration (FDA) granted accelerated approval to PRAXBIND (idarucizumab) for use in patients who take PRADAXA (dabigatran) and suffer a life-threatening bleeding event. Hospital pharmacies may stock Pradaxa if dabigatran patients are treated in the hospital or seen in the emergency department. Unfortunately, the drug’s nonproprietary names, idarucizumab, shares its first five letters with the anticancer drug IDAurubicin. This might lead to the selection of the wrong drug from a computer system drop-down menu or selection of the wrong container from its storage location, since both drugs are refrigerated solutions.

**Recommendations for Reversal of New Oral Anticoagulants**

**Pradaxa® Dabigatran**

- **First Line:** Praxbind® Idarucizumab, neutralizes anticoagulant effect
- **Second Line:** aPCC may be beneficial

**Xarelto® Rivaroxaban**

- **First Line**: rFVIIa and aPCC are more effective than 4F-PCC for reversal effects
- **Second Line**: 4F-PCC partially reverses its anticoagulant effect

**Savaysa® Edoxaban**

- **First Line**: 4F-PCC may be suitable for reversal
- **Second Line**: 3F-PCC reverses endogenous thrombin potential

**Eliquis® Apixaban**

- **First Line**: aPCC partially reversed anticoagulant parameters
- **Second Line**: rFVIIa partially reversed its anticoagulant effect
Antidotes Under Development

PER977\textsuperscript{36}
- A small molecule antidote has been shown in preliminary studies to bind directly and specifically to direct thrombin inhibitors, factor Xa inhibitors, and heparins
  - Edoxaban required the lowest dose for full reversal
  - In a study of 80 healthy volunteers given Edoxaban, PER977 normalized blood clotting time in 10 minutes

Andexanet alfa\textsuperscript{37}
- A recombinant “decoy” protein of catalytically inactive, truncated form of factor Xa.
- Binds directly to factor Xa inhibitors at subnanomolar affinity
- In a series of 101 healthy volunteers were given apixaban and rivaroxaban, andexanet was effective at reversal within minutes
- A study evaluating efficacy for patients with factor Xa inhibitor-associated bleeding is ongoing

Clinical Pearls
- Anticoagulation is an important standard therapeutic approach for cardiovascular disease
- Clinical data is very limited, primarily non-human to guide management of bleeding
- The goal for the bleeding patient is to improve the clinical situation
- There are currently 2 novel oral anticoagulant specific reversal agents in clinical development
References

24. Any Questions?
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