Anticoagulation Reversal

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Pharmacist Objectives

1. Discuss mechanisms of coagulation and anticoagulation
2. Evaluate literature surrounding common anticoagulation reversal products
3. Apply knowledge of anticoagulation reversal products to a patient case
Pharmacy Technician Objectives

1. Identify oral anticoagulant medications
2. Identify common anticoagulation reversal products
3. Describe the importance of anticoagulation reversal
Disclosure

I have nothing to disclose concerning possible financial or personal relationships with any commercial entities in relation to this presentation.
Background – Anticoagulation

• Anticoagulation is commonly used for stroke prevention in patients with atrial fibrillation and for the treatment of venous thromboembolism
  – Atrial fibrillation affects 2.7-6.1 million Americans
  – Venous thromboembolism affects about 1 million Americans

• Significant number of people on anticoagulation

Background – Anticoagulation

• Risk of major bleeding is ~15-25 per 1000 person years
  – On average 5 million people on anticoagulation
  – Major bleeds per year: ~100,000

• Food and Drug Administration – Adverse Event Reporting System
  – Greater than 20,000 reported adverse events
  – Serious injuries (n=18,978) and deaths (n=3,018)
  – Majority of reported events: Hemorrhages (n=17,218; 78.3%)
Pharmacotherapy Timeline

- **Unfractionated Heparin**
- **Warfarin**
- **Low Molecular Weight Heparins**
  - Fondaparinux
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Betrixaban

- **Parenteral Direct Thrombin Inhibitors**
- **Parenteral Direct Factor Xa Inhibitors**
- **Vitamin K Antagonists**
  - Protamine
  - Prothrombin Complex Concentrate
  - FEIBA®
  - rFVIIa
  - Idarucizumab
  - Andexanet alfa

**Timeline**

- 1930
- 1940
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
- 2020

**References**

Patient Assessment

- Patient status
- Anticoagulation/indication
- Time of last dose/half-life (renal function)
- Laboratory assessment

## Laboratory Testing

<table>
<thead>
<tr>
<th></th>
<th>aPTT</th>
<th>PT/INR</th>
<th>Anti-Xa</th>
<th>TT and dTT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
<td>↑</td>
<td>↑↑↑↑</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Rivaroxaban, Apixaban</strong>*</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>--</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>↑↑</td>
<td>↑</td>
<td>--</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

*Apixaban’s effect on INR is less pronounced than rivaroxaban*
## Bleeding Severity

<table>
<thead>
<tr>
<th>Clinically relevant non-major bleeding</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Requiring medical intervention</td>
<td>• Life threatening bleed</td>
</tr>
<tr>
<td>• Hospitalization or increased level of care</td>
<td>• Symptomatic bleeding in critical site (e.g. intracranial, retroperitoneal)</td>
</tr>
<tr>
<td>• Prompting a face to face evaluation</td>
<td>• Bleeding causing a decrease in Hgb of ≥2 g/dL or requiring PRBCs transfusion of ≥2 units</td>
</tr>
</tbody>
</table>

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General Management

• Hold anticoagulation
• Manual compression, local therapy, pressure/packing
• Activated charcoal, if appropriate
• Supportive care
  – Volume resuscitation
  – Inotropes/vasopressors
  – Correct hypothermia and acidosis
  – Massive transfusion protocol (balanced hemostatic resuscitation)
  – Ionized calcium monitoring
• Management of comorbidities

Anticoagulation Reversal

Major bleeding
• Limit expansion
• Improves outcomes
• Reduce mortality

✔ Warfarin
?
DOACs

Reversal is desirable in a patient with serious or life-threatening bleeding who remains actively **anticoagulated**

Anticoagulation Reversal

Risks associated with reversal

• Provoking thrombosis and ischemia
  – Life threatening ischemia, thrombosis, or severe disseminated intravascular coagulopathy

• Hematoma expansion
  – Cerebral venous thrombosis with concomitant intraparenchymal hemorrhage

Coagulation Cascade – Warfarin

Inhibits Factors: II, VII, IX, X and proteins C and S

## Warfarin Reversal

<table>
<thead>
<tr>
<th>Asymptomatic INR elevation</th>
<th>Hold warfarin, vitamin K (if needed)</th>
</tr>
</thead>
</table>
| Major /life-threatening bleeding | Vitamin K + 4F-PCC  
Vitamin K + FFP  
- Suggested if 4F-PCC is not available* |

* 4F-PCC recommended over FFP is supported by ACC, ASH, ACCP

### Fixed vs. variable (INR/weight-based) 4F-PCC for warfarin reversal

4F - PCC = 4 Factor - Prothrombin complex concentrate  
FFP = Fresh frozen plasma

Vitamin K

- Restores hepatic carboxylation
- Administered oral, IV → IV preferred in major bleeding
- INR reduction
  - 1-2 hrs (IV), peaks at 12-24 hrs
  - 6-10 hrs (oral), peaks at 24-48 hrs
- Dosing: Major bleeding – 10 mg IV
- IM/SQ Vitamin K – not recommended

Fresh Frozen Plasma

- Replacement of clotting factors
  - 1 unit = typically 250-300 mL
  - Typical dose is 10-15 mL/kg
- **Cannot** achieve INR < 1.5 with FFP alone
- Requires thawing → 15-60 min
- Onset: INR < 2 within 15 min., Duration: 6-12 hrs
- Adverse effects: thrombosis (3-8%), volume overload (TACO/TRALI)

TACO = Transfusion associated circulatory overload; TRALI = Transfusion related acute lung injury
# Prothrombin Complex Concentrate

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Components</th>
<th>FDA Approval</th>
<th>Thromboembolic Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>4F-PCC</td>
<td>Kcentra</td>
<td>Factors II, VII, IX, X and Proteins C and S *Contains heparin</td>
<td>Reversal of warfarin-related coagulopathy</td>
</tr>
<tr>
<td>aPCC</td>
<td>FEIBA</td>
<td>Mainly activated factor VII, and primarily inactivated factors II, IX, X, and protein C</td>
<td>Hemophilia (coagulation factors VIII or IX deficiencies)</td>
</tr>
</tbody>
</table>

*Contains heparin

# Warfarin Reversal Recommendations

- **4-Factor Prothrombin Complex Concentrate**

<table>
<thead>
<tr>
<th>American College Cardiology: Anticoagulation Reversal</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4F-PCC:</strong> Variable dosing (INR/weight based)</td>
<td>Consensus statement</td>
</tr>
<tr>
<td>• INR 2-5, 25 units/kg</td>
<td></td>
</tr>
<tr>
<td>• INR 4-6, 35 units/kg</td>
<td></td>
</tr>
<tr>
<td>• INR &gt;6, 50 units/kg</td>
<td></td>
</tr>
<tr>
<td><strong>4F-PCC:</strong> Fixed-dose</td>
<td></td>
</tr>
<tr>
<td>• 1000 units for any major bleed</td>
<td></td>
</tr>
<tr>
<td>• 1500 units for ICH</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurocritical Care/Society of Critical Care Medicine: ICH</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4F-PCC:</strong> Variable dosing (INR/weight based)</td>
<td>Strong</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>American Society of Hematology: VTE</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4F-PCC:</strong> No specific dosing recommendation</td>
<td>Conditional</td>
</tr>
</tbody>
</table>

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**References:**
## Fixed Dose 4F-PCC: Warfarin Reversal Major Bleed

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>N=39</td>
<td>N=37</td>
<td>N=61</td>
</tr>
</tbody>
</table>
| **4F-PCC Dosing*** | 1,500 units (emergent reversal) | 1,500 units (urgent or emergent reversal) | Variable dose (N=31) Fixed dose (N=30)  
• 1,000 units |
| Bleed Type   | ICH: 71.8%          | ICH: 45.6%          | ICH: 100%           |
| Results      | INR < 1.5: 71.8%    | INR < 1.5: 75%      | Variable vs. fixed dose  
INR < 1.5: 76% vs. 53%  
INR < 1.6: 81% vs. 73%  
Mortality: 26% vs. 27% |
|              | INR < 2: 92.3%      | Thrombosis: 0%      | Mortality: 0%       |
|              | Thrombosis: 0%      | Mortality: 25%      |                     |
|              | Mortality: 25%      |                     |                     |

*other reversal agents given: Vitamin K, FFP

Variable Vs. Fixed Dose 4F-PCC: Warfarin Reversal

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Prospective observational two-cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Evaluate 4F-PCC dosing strategies to achieve INR &lt; 2</td>
</tr>
<tr>
<td>Sample Size</td>
<td>N= 240</td>
</tr>
<tr>
<td>Inclusion</td>
<td>4F-PCC for warfarin reversal</td>
</tr>
<tr>
<td></td>
<td>Major or clinically relevant bleeding (non-ICH patients)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Fixed dosed: N=101</td>
</tr>
<tr>
<td></td>
<td>• 1,040 units</td>
</tr>
<tr>
<td></td>
<td>Variable: N=139</td>
</tr>
<tr>
<td></td>
<td>• INR/weight-based</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Fixed vs. variable dosing</td>
</tr>
<tr>
<td></td>
<td>Target INR: 91.7% vs. 94.7%</td>
</tr>
<tr>
<td></td>
<td>Clinical success: 96% vs. 88%</td>
</tr>
<tr>
<td></td>
<td>Mortality: 14% vs. 26%</td>
</tr>
<tr>
<td></td>
<td>Thrombosis: 1% vs. 1.4%</td>
</tr>
</tbody>
</table>

## PROPER3 Trial – Ongoing Trial

### PROthrombin complex concentrate: Prospective Evaluation and Rationalization

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>Confirm non-inferiority of fixed PCC dosing vs. variable dosing in extracranial bleeding emergencies</th>
</tr>
</thead>
</table>
| **Intervention**       | Fixed dose: 1000 units Factor IX PCC  
Variable dosing: INR/weight base |
| **Outcomes**           | Primary: Hemostatic efficacy  
Secondary: INR, total PCC dose, thromboembolic events, and mortality |

Meet JR

JR is a 72 year old male. PMH significant for CHF, DM, history of DVT. Patient is on warfarin 5mg daily, except 2.5mg MWF. Patient presents to the ED with 3 day history of black tarry stool. He is hemodynamically unstable and not responding to supportive measures.

Labs: INR = 7; Hgb = 5.2 mg/dL (baseline 8.9 mg/dL)
Meet JR

Team wants to give vitamin K, what do you recommend?
A. 10 mg IV vitamin K
B. 10 mg oral vitamin K
C. 10 mg SQ vitamin K
D. Vitamin K not indicated
Meet JR

Would you give 4F-PCC to this patient?

A. Yes
B. No
Management of Upper Gastrointestinal Bleed

- **Warfarin associated acute GI bleed**
  - Active bleeding/shock
    - Vitamin K and 4F-PCC indicated
  - Bleeding without hemodynamic compromise
    - Vitamin K, consider 4F-PCC*
  - Minor rectal bleeding
    - Monitor, consider oral vitamin K

* Dependent on INR and endoscopy timing
Management of Upper Gastrointestinal Bleed

International Consensus Group: 2019 Update

• In patients with acute upper GI bleeds on anticoagulation, we suggest not delaying endoscopy
  – Conditional recommendation – very low quality of evidence

• Future research
  – Effectiveness of targeted reversal vs. nonreversal of anticoagulant therapy in patients with UGIB with access to early endoscopy

Summary Warfarin Reversal

- Reversal is indicated in patients with major bleeding
- IV vitamin K should be given for sustained reversal
- 4F-PCC should be given for rapid reversal
  - Fixed or variable 4F-PCC dosing are recommended
  - Similar safety and efficacy profile
- On-going trials to assess optimal 4F-PCC dosing for warfarin reversal
Coagulation Cascade – Dabigatran

Inhibits Factor: IIa

Idarucizumab

• Humanized monoclonal antibody fragment
• Binds dabigatran and metabolites, neutralizes anticoagulation effect
  – Dabigatran has 350x more affinity to idarucizumab than for thrombin
  – Antibodies have no clinically significant procoagulant effect
• Indication: Reversal of anticoagulant effects of dabigatran
  – Emergency surgery/urgent procedures
  – Life-threatening or uncontrolled bleeding

# RE-VERSED AD

## Study design
Multicenter, prospective, open-label study

## Intervention
- **5g of IV idarucizumab**
  - Group A: Uncontrolled bleeding (n=301)
  - Group B: Urgent procedure (n=202)

## Results
- **Group A:** Cessation of bleeding median time: 2.5 hours
- **Group B:** Periprocedural hemostasis: 93.4%

<table>
<thead>
<tr>
<th>Thrombotic events (90 days)</th>
<th>Mortality (90 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Group A: 6.3%</td>
<td>• Group A: 18.8%</td>
</tr>
<tr>
<td>• Group B: 7.4%</td>
<td>• Group B: 18.9%</td>
</tr>
</tbody>
</table>

Alterative Reversal Agent to Idarucizumab

Anticoagulation Forum: Reversal of DOACs

• If idarucizumab is not available, we suggest treatment with aPCC 50 units/kg
  – Limited data
  – Small sample size: N=14
  – Hemostasis achieved (good/moderate): 100%
  – Thrombosis events: 0%

Meet TB

TB is a 64 year old male who presented to the ED for slurred speech and right sided weakness. CT is positive for ICH and patient is on dabigatran 150mg twice daily for atrial fibrillation. Timing of last dose is unknown.
Meet TB

What reversal agent would you recommend?

A. Reversal is not indicated
B. Activated charcoal
C. Idarucizumab
D. aPCC
Summary of Dabigatran Reversal

• Idarucizumab is approved for dabigatran reversal
  – Emergency surgery/urgent procedures
  – Life-threatening or uncontrolled bleeding

• Idarucizumab does not have a clinically significant procoagulant effect

• If Idarucizumab is not available, aPCC is an alternative option
Coagulation Cascade – Factor Xa inhibitors

Inhibits Factor: Xa (apixaban, edoxaban, rivaroxaban)
# Reversal Recommendations – Factor Xa inhibitors

<table>
<thead>
<tr>
<th>Organization</th>
<th>Life Threatening/Critical Organ Bleed</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEST: Atrial fibrillation</td>
<td>Suggest specific reversal agents over PCC</td>
<td>Not graded</td>
</tr>
</tbody>
</table>
| American College Cardiology: Anticoagulation reversal | First line: Andexanet alfa  
Second line: 4F-PCC 50 units/kg | Not graded |
| AHA/ACC/HRS: Atrial fibrillation | Andexanet alfa may be useful | IIA, B-NR |
| American Society of Hematology: VTE | Either Andexanet alfa or 4F-PCC in fixed dosing or 4F-PCC 25-50 units/kg | Conditional |
| Anticoagulation Forum: Anticoagulation reversal | Suggest: Andexanet alfa  
If andexanet alfa unavailable: 4F-PCC 2,000 units | Not graded |
| UpToDate DOAC Bleed Management | Either Andexxa or 4F-PCC (25-50 units/kg or 2,000 units) | Not graded |

Anticoagulation Reversal

Major bleeding
• Limit expansion
• Improves outcomes
• Reduce mortality

Unclear if reversal of DOACs improves outcomes
• Reversal vs. watchful waiting due to short half-life of DOACs

✔ Warfarin

? DOACs

Andexanet alfa: Mechanism of Action

- Andexanet alfa is a decoy protein that preferentially binds factor Xa inhibitors
Andexanet alfa: Anti-Factor Xa Levels

C Apixaban Study, Andexanet Bolus plus Infusion

D Rivaroxaban Study, Andexanet Bolus plus Infusion

Andexanet alfa: Pharmacology

Inhibition of TFPI-FXa: Potential prothrombotic mechanism

TFPI = Tissue factor pathway inhibitor
Reversal of Factor Xa Inhibitors by Andexanet Alfa May Increase Thrombogenesis Compared to Pretreatment Values

D. Thrombokinnetogram for Rivaroxaban

Generation of more thrombin than the patient would have naturally produced
## Annexa - 4 Clinical Trial

### Study design
- Multicenter, prospective, open-label, single group

### Purpose
- Determine the effect of andexanet alfa on anti-factor Xa activity and hemostatic efficacy

### Sample size
- n=352 (safety), n=254* (efficacy)

### Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 18 years of age</td>
<td>• Planned surgery within 12 hours</td>
</tr>
<tr>
<td>• Acute major bleeding</td>
<td>• ICH in patient with a GCS &lt;7</td>
</tr>
<tr>
<td>• Dose of anticoagulation within 18 hours</td>
<td>• Estimated hematoma volume of more than 60 mLs</td>
</tr>
<tr>
<td>• *Baseline anti factor Xa of at least 75 ng/mL</td>
<td>• Expected survival of less than 1 month</td>
</tr>
<tr>
<td>• *Confirmed major bleeding at presentation</td>
<td>• Thrombotic event within previous 2 weeks</td>
</tr>
</tbody>
</table>

### Primary Outcome
- Percent change from baseline: anti-factor Xa activity after andexanet treatment
- Percent of patients with good or excellent hemostatic efficacy 12 hours after treatment

### Secondary Outcomes
- Death
- Thrombotic events
- Development of antibodies to andexanet alfa, factor X, or factor Xa

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Results

• Change in anti-factor Xa activity: ~90% decrease

• Percent of patients with good or excellent hemostatic efficacy at 12 hours
  – Overall 82% (CI 77-87%)
    • 85% GI bleed
    • 80% ICH

• Thrombotic events: 10% (n=34)

• Mortality: 14% (n=49)
Results

- Receiver-Operating-Characteristic Curves for Hemostatic Efficacy
  - Association between anti-factor Xa activity and hemostatic efficacy

AUC, 0.53 (95% CI, 0.44–0.62)
AUC, 0.64 (95% CI, 0.53–0.74)
Andexanet alfa Challenges

• Surgical patients excluded from trial
• Rebound anticoagulation effect
• No relationship between anti- factor Xa levels and hemostatic efficacy
• Potentially prothrombotic
• Preparation time
• Cost
• Ongoing evaluation mandated by the FDA
4F-PCC vs. Andexanet alfa: Clinical Trial

Trial of Andexanet alfa in ICH Patients Receiving an Oral FXa Inhibitor

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, multicenter cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Objectives</td>
<td>Determine the efficacy and safety of andexanet alfa compared to usual care in ICH patients</td>
</tr>
<tr>
<td>Estimated study completion</td>
<td>2023</td>
</tr>
</tbody>
</table>

Similar study design as Annexa - 4
Alterative reversal option: Factor Xa Inhibitors

- 4F-PCC
  - Weight based options
    - Doses range from 25-50 units/kg
  - Fixed dose
    - 2,000 units

- aPCC
  - Weight based
## Summary of Prospective and Retrospective Studies for Factor Xa Reversal

<table>
<thead>
<tr>
<th>Agent/Dosing</th>
<th>Trials</th>
<th>Total N</th>
<th>Favorable Hemostatic Response</th>
<th>Thromboembolism (time frame)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight based 4F-PCC 25-50 units/kg</td>
<td>6 retrospective</td>
<td>173</td>
<td>72% - 95%</td>
<td>2.3 – 5.6% (14 days)</td>
</tr>
<tr>
<td>Fixed dose 4F-PCC (at least 1,500 units)</td>
<td>3 prospective observational, 1 retrospective</td>
<td>230</td>
<td>65% - 75%</td>
<td>2.4 – 8% (30 days)</td>
</tr>
<tr>
<td>aPCC</td>
<td>3 retrospective</td>
<td>101</td>
<td>64% - 92%</td>
<td>10 – 18% (up to 30 days)</td>
</tr>
<tr>
<td>Andexanet alfa</td>
<td>1 Prospective</td>
<td>354</td>
<td>82%</td>
<td>10% (30 days)</td>
</tr>
</tbody>
</table>

Comparisons are not valid due to differences in baseline risk of populations and numerous design differences.
4F-PCC vs. Andexanet alfa
Neurocritical Care Society: Abstract Data

<table>
<thead>
<tr>
<th>Study design</th>
<th>Retrospective, single center cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>N=29</td>
</tr>
</tbody>
</table>
| Intervention | 4F-PCC (~ 28 IU/kg): n=16
Andexanet alfa: n=13 |
| Efficacy endpoint | Degree of hemostasis achieved 6 hours post reversal CT scan stability |
| Safety endpoint | All cause in-hospital mortality |

<table>
<thead>
<tr>
<th></th>
<th>4F-PCC: N=16</th>
<th>Andexanet alfa: N=13</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable CT scan, n (%)</td>
<td>10 (63)</td>
<td>9 (69)</td>
<td>0.90</td>
</tr>
<tr>
<td>All cause mortality, n (%)</td>
<td>11 (69)</td>
<td>10 (77)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

No significant difference in the degree of hemostasis achieved and all cause mortality between groups

*Multivariable analysis adjusted for age, race, sex
Meet TY

TY is a 42 year old female with a past medical history of HF, unprovoked DVT one month prior, and HIT. She presents to the ED for altered mental status. CT positive for ICH.

Medication: Apixaban 5mg twice daily (last dose 6 hours ago)

Andexanet alfa is not on formulary
Meet TY

Which reversal option is most appropriate?

A. Fresh frozen plasma
B. Activated charcoal
C. 4F-PCC
D. aPCC
Meet SG

SG is a 62-year old female with PMH of atrial fibrillation (apixaban 5mg twice daily; last dose 10 hours ago), HTN, and DM. She presents to the ED complaining of multiple episodes of black tarry stool. Patient received 1 unit of packed red blood cells with good response (hemodynamically stable).

Labs: Hgb = 9.2 mg/dL (baseline 9.8), BP = 120/72 mmHg

Plan: Endoscopy in 8 hours
Team wants to reverse her anticoagulation, what do you recommend?

A. 4F-PCC
B. aPCC
C. Activated charcoal
D. No reversal
Summary Slide: Factor Xa reversal

• Reversal is indicated in patients with life-threatening bleeding

• Guidelines/expert opinion recommend andexanet alfa or 4F-PCC for factor Xa reversal

• Formulary addition of andexanet alfa has challenges

• On-going study to assess andexanet alfa compared to standard of care
Future Direction – Ciraparantag

- Synthetic molecule
- Binds anticoagulants through hydrogen bonds and charge interactions
  - Able to bind UFH, LMWH, fondaparinux, and DOACs
- Reversal measured with whole-blood clotting time (WBCT)
  - WBCT is a measure of the time it takes for blood to clot – clinically relevant physiologic outcome

<table>
<thead>
<tr>
<th>Ciraparantag</th>
<th>Anticoagulant reversal agent (potential for orphan drug designation)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>Regulatory Review</th>
<th>Approved/Marketed</th>
</tr>
</thead>
</table>

Future Direction – Ciraparantag

Mean Whole Blood Clotting Time (WBCT) by Timepoint

Individual Responder Analysis
(n=12 per dose)

*WBCT reversed to within 10% of baseline within 30 minutes and sustained for 24 hours
Summary

• Evaluate if anticoagulation reversal is indicated

• Warfarin reversal, vitamin K and 4F-PCC are recommended
  — The use of fixed dose 4F-PCC is guideline recommended

• Dabigatran reversal, idarucizumab is recommended

• Factor Xa Inhibitors reversal
  — Andexanet alfa – clinical data is limited, ongoing trial
  — 4F-PCC – clinical data is limited, fixed vs. variable dosing
Anticoagulation Reversal

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