Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation

Nicole Acquisto, PharmD, BCPS
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@ASHP_EMPharm
The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation: Warfarin

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Objective

- Discuss the literature related to the pharmacologic reversal of warfarin during life-threatening bleeding
Vitamin K Antagonists (Warfarin)

- Inhibits epoxide reductase → inhibits vitamin K dependent synthesis of active forms of clotting factors II, VII, IX, X, Protein C, and Protein S

- 30-50% reduction in factor activities leads to therapeutic effect

\[
INR = \left( \frac{PT_{pt}}{PT_{ref}} \right)^{ISI} = \text{International Sensitivity Index}
\]
Considerations for Reversal

- Symptomatic vs. asymptomatic
- Life-threatening vs. non life-threatening
- INR target (full or partial reversal)
- Last dose of warfarin
- Other anticoagulants (ex: LMWH)
Reversal of Vitamin K Antagonist Anticoagulation

Vitamin K Administration
• 5 – 10 mg IV or PO

Factor Replacement
• Plasma (FFP)
• Prothrombin complex concentrates
  • 3-F
  • 4-F
• rFVIIa
80 yo male with an LVAD
- Receiving warfarin, INR 4.3
- Presents with unresponsiveness (sudden onset)
- Diagnosed with an intracranial hemorrhage
Which reversal strategy should be implemented for this patient?

A. Don’t administer any reversal agents, too much risk for thrombosis
B. Vitamin K alone
C. Vitamin K and FFP
D. Vitamin K and 4-F PCC
## Plasma vs. PCC

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood typing required</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Thawing time</td>
<td>30-45 min</td>
<td>0</td>
</tr>
<tr>
<td>Infection risk</td>
<td>YES</td>
<td>YES*</td>
</tr>
<tr>
<td>Thrombosis risk</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>TRALI risk</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Clotting factor</td>
<td>LOW</td>
<td>HIGH</td>
</tr>
<tr>
<td>concentration</td>
<td>INFUSION VOLUME</td>
<td>10-20 mL/kg</td>
</tr>
<tr>
<td>Speed of INR correction</td>
<td>Slow</td>
<td>Quick</td>
</tr>
<tr>
<td>Duration of INR correction</td>
<td>6 hours</td>
<td>≥ 24 hours</td>
</tr>
<tr>
<td>Expense</td>
<td>Moderate</td>
<td>High</td>
</tr>
</tbody>
</table>

*Risk is greatly attenuated by heat treatment and nanofiltration (Kcentra)*
Phase IIIb multi-center, open label (Part 1)

- Acute life-threatening bleeding, warfarin, INR ≥ 2 (n = 202)
- Dose of study treatments (+ Vitamin K)

<table>
<thead>
<tr>
<th>Baseline INR</th>
<th>4F-PCC (units/kg)</th>
<th>Plasma (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt; 4</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>4-6</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>50</td>
<td>15</td>
</tr>
</tbody>
</table>

Max: 100 kg
Plasma rate: 1 unit/30-minute interval

Co-Primary Endpoints

- “Effective” hemostasis: 72.4% PCC vs. 65.4% FFP
- Rapid INR reduction: 62.2% PCC vs. 9.6% FFP
- Thromboembolic events: 7.8% PCC vs. 5.5% FFP
### Phase IIIb multi-center, open label (Part 2)

- Urgent surgical or invasive procedure within 24 hours, warfarin, INR ≥ 2 (n = 168)

<table>
<thead>
<tr>
<th></th>
<th>4F-PCC (n = 87)</th>
<th>Plasma (n = 81)</th>
<th>Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective hemostasis</td>
<td>89.7%</td>
<td>75.3%</td>
<td>14.3%</td>
<td>2.8-25.8</td>
</tr>
<tr>
<td>Rapid INR reduction</td>
<td>55.2%</td>
<td>9.9%</td>
<td>45.3%</td>
<td>31.9-56.4</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>8%</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- PCC 89% less volume than FFP
- Infusion time: 21 vs. 141 min

Fixed Dose PCC (1500 units)

- Retrospective, n = 39
- Median age = 70 years
- Mean weight = 79.5 kg (IQR 72.1-95.3)
- ICH = 71.8%
- Dose of 4F-PCC 1659 units (range, 1569-1710)
  - 20.4 (17.3-22.6) units/kg
- No thromboembolic events

9.3 Treatment of Anticoagulant-Related Bleeding

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma. (Grade 2C).

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).
VKA should have their VKA withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K (Class I; Level of Evidence C). PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP (Class IIb; Level of Evidence C).
### Thromboembolic Events

- Retrospective, 18 months (n = 113), evaluated up to 60 days

<table>
<thead>
<tr>
<th>Categories</th>
<th>Thromboembolic event (%)</th>
<th>Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7 (6.1)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Indication for VKA reversal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH (n = 16)</td>
<td>2 (7.4)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>GI bleed (n = 27)</td>
<td>2 (9.5)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Other bleeds (n = 21)</td>
<td>3 (6.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Emergent procedure (n = 45)</td>
<td>0</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Elevated INR (n = 4)</td>
<td></td>
<td>1 (25)</td>
</tr>
<tr>
<td>Pre-PCC INR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 (n = 19)</td>
<td>1 (5.3)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>2-4 (n = 45)</td>
<td>2 (4.4)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>4-6 (n = 16)</td>
<td>0</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>&gt;6 (n = 33)</td>
<td>4 (12.1)</td>
<td>5 (15.2)</td>
</tr>
</tbody>
</table>

4F-PCC in Practice

- Treat each 4-PCC vial as 500 units (± 20%)
- Modified doses for high thromboembolic risk or INR < 2
- Empty bag and pump administration vs. IVP (each vial over 3-5 minutes)
- Automated dispensing cabinets vs. central pharmacy stock
- 80 yo male with an LVAD
- Receiving warfarin
- Presents with unresponsiveness (sudden onset)
- Diagnosed with an intracranial hemorrhage
Which reversal strategy should be implemented for this patient?

A. Don’t administer any reversal agents, too much risk for thrombosis
B. Vitamin K alone
C. Vitamin K and FFP
D. Vitamin K and 4-F PCC
Key Takeaways

- **Key Takeaway #1**
  - Several options for warfarin reversal
    - Vitamin K, FFP, 4F-PCC (modified dose)

- **Key Takeaway #2**
  - Not just about “fixing” the INR, need to think about overall anticoagulation and risk vs. benefit

- **Key Takeaway #3**
  - 4F-PCC are not without ADE, need to consider thromboembolic risk (reserve for life-threatening bleeding) or need for emergent life-saving intervention
Thank You!
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Bryan D. Hayes, PharmD, DABAT, FAACT
Clinical Pharmacist, EM & Toxicology, MGH
Assistant Professor of EM, Harvard Medical School

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- Intestinal Bleeding
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- Kidney Bleeding
- Uncontrolled Bleeding
- Or Even Death

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Call The Goldwater Law Firm Anytime, Day or Night
65 y/o m
74/52 mm Hg
122 bpm
“No regular blood tests means no disruption to your routine.”
(True or False) Commonly available lab tests are not helpful for estimating dabigatran activity.

A TRUE

B FALSE
(True or False) Commonly available lab tests are not helpful for estimating dabigatran activity.

A TRUE
B FALSE
<table>
<thead>
<tr>
<th></th>
<th>Sub-therapeutic</th>
<th>Low Therapeutic (trough)</th>
<th>High therapeutic (peak)</th>
<th>Supra-therapeutic</th>
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</thead>
<tbody>
<tr>
<td>PT</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>APTT</td>
<td>✗</td>
<td>✗/✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TT</td>
<td>✓</td>
<td>✓</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>ECT/ECA</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>dTT/DTI</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-Xa assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>dRVVT</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- ✗ Unaffected or normal result
- ✓ Measureable result
- ± Non-linear or unmeasureable result

Dabigatran

- TT normal
  - Excluded

- APTT, dRVVT normal
  - Probably Excluded

Apixaban / Rivaroxaban

- Anti-Xa normal
  - Excluded

- PT, dRVVT normal
  - Probably Excluded

Basic Test Panel: PT, APTT, TT

All normal

Exclude significant rivaroxaban/dabigatran

Rivaroxaban*

Dabigatran*

Anti-Xa dRVVT

If negative, significant TSOAC activity excluded

* Suggestive; requires confirmation

STEP 1: D/C DRUG
STEP 2: ANTIDOTE

STEP 1: D/C DRUG
ANTIDOTE
A randomized study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran


110 healthy male pts (age 18-45)

Increasing doses over 5 or 60 min

$T_{1/2} \sim 45$ min

No effect on coagulation

AE rare

Tier 3, B, Outstanding
Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial


47 healthy male pts (age 18-45)

4 days dabigatran

5 or 60 min infusion

~100% immediate reversal (ECT, aPTT, TT)

Tier 2, B, Outstanding
Idarucizumab for Dabigatran Reversal


Group A: uncontrolled bleeding (51)

Group B: emergent surgery (39)

5 gm dose
Good \quad \text{versus} \quad \text{Bad}
STEP 1: D/C DRUG

STEP 2: ANTIDOTE

STEP 3: FACTORS
FACTORS
FFP
<table>
<thead>
<tr>
<th></th>
<th>Recombinant Factor VIIa</th>
<th>3-Factor PCC</th>
<th>4-Factor PCC *</th>
<th>FEIBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>✓ (activated)</td>
<td></td>
<td>✓</td>
<td>✓ (activated)</td>
</tr>
<tr>
<td>IX</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* Also contains Protein C, Protein S, ATIII, and heparin
Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects


12 healthy volunteers

Dabigatran 150 mg BID X 2 days

PCC 50 U/kg

No reversal of aPTT, ECT, or TT

Tier 2, B, Outstanding
Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers


10 healthy volunteers

Dabigatran 150 mg X 1

PCC, rFVIIa, or FEIBA
Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers


PCC, rFVIIa, and FEIBA corrected thrombin generation

Only rFVIIa and FEIBA corrected altered lag time
Coagulation Factor Concentrates Fail to Restore Alterations in Fibrin Formation Caused by Rivaroxaban or Dabigatran in Studies With Flowing Blood From Treated Healthy Volunteers


10 healthy volunteers

Dabigatran 150 mg BID X 5 days

PCC, rFVIIa, or FEIBA
Coagulation Factor Concentrates Fail to Restore Alterations in Fibrin Formation Caused by Rivaroxaban or Dabigatran in Studies With Flowing Blood From Treated Healthy Volunteers


PCC had no effect on aPTT

rFVIIa and FEIBA

Partially improved all parameters
Which of the following factor replacements is probably not effective in reversing dabigatran?

A. aPCC (FEIBA)
B. 4-factor PCC
C. rFVIIa
D. FFP
Which of the following factor replacements is probably not effective in reversing dabigatran?

A. aPCC (FEIBA)
B. 4-factor PCC
C. rFVIIa
D. FFP
Dabigatran

High clotting risk

FEIBA NF®
50 units/kg
(max 5000)

FEIBA NF®
30 units/kg

Do not repeat
STEP 1: D/C DRUG

STEP 2: ANTIDOTET

STEP 3: FACTORS

STEP 4: ADJUNCT
RRT
65 y/o m

74/52 mm Hg

122 bpm
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt</td>
<td>106</td>
</tr>
<tr>
<td>PT</td>
<td>23.4</td>
</tr>
<tr>
<td>INR</td>
<td>2.0</td>
</tr>
<tr>
<td>PTT</td>
<td>74</td>
</tr>
<tr>
<td>TT</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Summary</td>
</tr>
<tr>
<td>---</td>
<td>---------</td>
</tr>
<tr>
<td>1</td>
<td>Routine coags can help</td>
</tr>
<tr>
<td>2</td>
<td>Idarucizumab role TBD</td>
</tr>
<tr>
<td>3</td>
<td>Factor replacement: aPCC or rFVIIa</td>
</tr>
<tr>
<td>4</td>
<td>Adjuncts: FFP, charcoal, RRT</td>
</tr>
</tbody>
</table>
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Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation

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Associate Clinical Professor
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@ZEDPharm
80 year old woman
AMS 40 min PTA

BP: 194/83
HR: 88
O2: 92%

CODE STROKE!
80 year old woman
AMS 40 min PTA

BP: 194/83
HR: 88
O2: 92

CODE STROKE!
PMH:
DVTs, PE, IVC
STEMI, PCI

Med List:
Rivaroxaban
Aspirin
Metoprolol
Rosuvastatin
Metformin
SCr = 1.20
Plt = 273
aPTT = 32
PT = 13.8
INR = 1.1
What Do You Do Regarding Reversal?

A. FFP
B. 4-factor PCC
C. FEIBA
D. Do nothing
Anti Xa-reversal

- When to give?
- What to give?
- And then what?
Non-valve Afib (CHA$_2$DS$_2$VASc ≥2)

- Warfarin
  - I, A
- Dabigatran
- Rivaroxaban
- Apixaban
  - I, B

AHA/ACC/HRS Afib Guidelines
Circulation. 2014 Dec 2;130(23):2071-104.
# Post Marketing Data

### Table 3. Dispensed oral anticoagulant prescriptions 2014 Q4*

<table>
<thead>
<tr>
<th></th>
<th>Prescriptions</th>
<th>Person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>1,758,016</td>
<td>505,560</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>560,887</td>
<td>252,780</td>
</tr>
<tr>
<td>Apixaban</td>
<td>609,301</td>
<td>231,618</td>
</tr>
<tr>
<td>Warfarin</td>
<td>80,266,745</td>
<td>3,944,233</td>
</tr>
</tbody>
</table>

Data from IMS Health National Prescription Audit

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Incidence of Warfarin, %</th>
<th>Incidence of NOACs, %</th>
<th>RR (95% CI)</th>
<th>I² Heterogeneity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent DVT</td>
<td>2.7</td>
<td>2.5</td>
<td>0.9 (0.8–1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>1.7</td>
<td>1.5</td>
<td>0.9 (0.75–1.1)</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>0.1</td>
<td>0.3</td>
<td>2.6 (1.1–5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.8</td>
<td>1.1</td>
<td>0.6 (0.5–0.8)</td>
<td>44</td>
</tr>
</tbody>
</table>

NOAC, New oral anticoagulant; RR, relative risk; CI, confidence interval; DVT, deep venous thrombosis; MI, myocardial infarction.

Institute for Safe Medication Practices
## Post Marketing Data

### Table 5. Domestic, serious reports for 3 anticoagulant drugs, 2014

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total</th>
<th>Direct to FDA Number, %</th>
<th>Death outcome Number, %</th>
<th>Embolic-thrombotic* Number, %</th>
<th>Hemorrhage* Number, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>3,331</td>
<td>525 (15.8%)</td>
<td>379 (11.4%)</td>
<td>1129 (33.9%)</td>
<td>1,647 (49.4%)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>3,592</td>
<td>188 (5.2%)</td>
<td>752 (20.9%)</td>
<td>721 (20.1%)</td>
<td>2,709 (75.4%)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1,014</td>
<td>95 (9.4%)</td>
<td>108 (10.7%)</td>
<td>224 (22.1%)</td>
<td>492 (48.5%)</td>
</tr>
</tbody>
</table>

*Standardized MedDRA queries (SMQ), broad scope
<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>HL</th>
<th>PT/INR</th>
<th>aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Xa</td>
<td>~10h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Xa</td>
<td>~12h</td>
<td></td>
<td>“May be prolonged”</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Xa</td>
<td>~12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>DTI</td>
<td>~12h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


ECT – Ecarin Clotting Time
TT – Thrombin Time
<table>
<thead>
<tr>
<th>Patients</th>
<th>Ingestion</th>
<th>Measurements</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 PCC / 9 states</td>
<td>Apixaban (11%)</td>
<td>Normal INR: 80%</td>
<td>Kids do OK</td>
</tr>
<tr>
<td>203 adults</td>
<td>Rivaroxaban (89%)</td>
<td>PT: 87%</td>
<td>All bleeds on chronic therapy:</td>
</tr>
<tr>
<td>20 kids</td>
<td>211 therapy errors</td>
<td>PTT: 91%</td>
<td>8 GI bleeds</td>
</tr>
<tr>
<td></td>
<td>12 suicide attempts</td>
<td></td>
<td>3 mouth/gums</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50% suicide attempts had</td>
<td>1 bruise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>normal coags</td>
<td>1 urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 subdural (fall)</td>
</tr>
</tbody>
</table>

How to Reverse Xa Inhibitors?
Historically

- FFP
- FIIa
- 3-Factor PCCs
- 4-Factor PCCs

**In-vitro**

**Animal models**

**Healthy volunteers**

**Prothrombogenicity**

**BLACK BOX:**
Premature discontinuation of [NOACs] increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if [NOACs] are discontinued for a reason other than pathological bleeding or completion of a course of therapy.
Andexanet alfa

- Factor Xa decoy protein
- Recombinant, modified, human Xa
- No anticoagulant activity
- Potential reversal for
  - Apixaban
  - Rivaroxaban
  - Edoxaban
  - Enoxaparin
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Completed</td>
<td>A Study in Older Subject to Evaluate the Safety and Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Biological: Andexanet; Other: Placebo</td>
</tr>
<tr>
<td>2</td>
<td>Completed</td>
<td>A Study in Older Subjects to Evaluate the Safety and Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Apixaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Biological: Andexanet; Other: Placebo</td>
</tr>
<tr>
<td>3</td>
<td>Recruiting</td>
<td>A Study in Patients With Acute Major Bleeding to Evaluate the Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Direct and Indirect Oral Anticoagulants</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Condition:</strong> Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Intervention:</strong> Biological: Andexanet</td>
</tr>
</tbody>
</table>
# Andexanet alfa

<table>
<thead>
<tr>
<th>Patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>145 healthy volunteers</td>
<td>A: apixaban, or R: rivaroxaban X4 days + Andexanet bolus +/- infusion x2 hours</td>
<td>A: apixaban, or R: rivaroxaban X4 days + Placebo</td>
<td>Anti-Xa decrease 92-97% Effect NOT sustained U-shape drop &amp; bounce</td>
</tr>
<tr>
<td>50 – 75 y.o</td>
<td>n=101</td>
<td>n=44</td>
<td></td>
</tr>
</tbody>
</table>

NCT02329327 recruiting Hemostasis

<table>
<thead>
<tr>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 super sick patients</td>
</tr>
<tr>
<td>Acute major bleeding w/in 18 hours</td>
</tr>
<tr>
<td>GI: 49%</td>
</tr>
<tr>
<td>ICH: 42%</td>
</tr>
<tr>
<td>Other: 9%</td>
</tr>
<tr>
<td>~77 y.o</td>
</tr>
</tbody>
</table>

Anti-Xa Activity

Bolus  2-hr  4-hr
<table>
<thead>
<tr>
<th>Patients</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 super sick patients</td>
<td><strong>Andexanet bolus</strong> + 2-hour infusion</td>
<td>1. <strong>PD Outcome</strong></td>
</tr>
</tbody>
</table>
| Acute major bleeding w/in 18 hours | **Riva**: 26 pts  
**Apix**: 20 pts  
**Enox**: 1 pt  
**Edox**: 0 pt | a) Anti-factor Xa activity: U-shape drop & bounce |
| GI: 49%                        |                                     |                                       |
| ICH: 42%                      |                                     |                                       |
| Other: 9%                     |                                     |                                       |
| ~77 y.o                       |                                     |                                       |

Andexanet alfa

• Bolus (15-30 minutes) + 2-hour infusion
  400 mg bolus + 480 mg infusion
  800 mg bolus + 960 mg infusion

• Clotting?
• Deaths?
• Safety 47 -> 162
• Efficacy 67 -> 230
Key Takeaways

- NOAC use is increasing
- Rising concern with NOAC post-marketing data
- No universally accepted agent for reversal of anti-Xa inhibitors
- Andexanet alfa FDA approval pending more data
Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation

Bryan D. Hayes, PharmD, DABAT, FAACT
Nicole Acquisto, PharmD, BCPS
Zlatan Coralic, PharmD, BCPS

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