Stop That Bleed! Implementing a Reversal Strategy for the Direct Oral Anticoagulants

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William Dager, Pharm.D., BCPS, FASHP, FCCM, FCCP, MCCM
Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
No conflicts of interest
Did work for Disney
Pre-Test Question

Which of one the following statements is correct?

A. The gastrointestinal tract is the most common site of anticoagulant related bleeding.
B. Intracerebral hemorrhage carries a low 30-day mortality rate ranging from 3.5% to 5.2% with most survivors expected to have full functional recovery.
C. Idarucizumab can be used to reverse rivaroxaban, apixaban, or edoxaban.
D. All of the above are correct.
Pre-Test Question

A 48 YO female taking Rivaroxaban 15mg twice daily (10 AM & 10PM) for DVT arrives unresponsive to your hospital at 12 Noon. Head CT which reveals intraventricular hemorrhage. What is the correct reversal agent and dose?

A. Vitamin K 10 mg subcutaneously
B. Andexanet bolus 400mg, then infusion 480 mg @ 4 mg/min
C. Andexanet bolus 800 mg, then infusion 960 mg @ 8 mg/min
D. Idarucizumab 2.5 grams IV push x 2 doses (total 5 grams)
An 83 y.o. female (70 kg) falls. Her dabigatran, for atrial fibrillation, is reversed prior to hip fracture surgery. She is now post-op day 2. Her dabigatran can safely be restarted:

A. Now  
B. In 7 days  
C. In 1 month  
D. In 3 months
Learning Objectives

• Given a patient case, evaluate current approaches and limitations to therapies used to reverse the effects of direct-acting oral anticoagulants.
• Given examples, describe the process of assessing, choosing, and implementing a reversal plan with follow-up and revisions.
• Develop a strategy for rapid reversal of a direct oral anticoagulant.
Outline

• Rates of bleeding associated with anticoagulant therapy
• Non-specific and specific reversal agents
• Professional guidelines and decision algorithms
• Patient selection
• Key takeaways
How Frequent is Bleeding?

Atrial fibrillation (AF):
• DOACs reduced intracranial hemorrhage by 52%.
• DOACs increased gastrointestinal (GI) bleeding by 25%.
• Major bleeding was reduced by 14% but was not statistically different.

Acute venous thromboembolism (VTE):
• DOACs reduced Intracranial hemorrhage by 63%.
• DOACs reduced GI bleeding by 22% but it was not statistically significant.
• DOACs reduced major bleeding by 39%.

Anticoagulant therapy:
• Incurs a significant risk of bleeding but events are infrequent.

## Non-Specific Reversal Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clotting Factors Replaced</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Factor-PCC</td>
<td>Factors II, VII, IX, X</td>
</tr>
<tr>
<td>3 Factor-PCC</td>
<td>Factors II, IX, X</td>
</tr>
<tr>
<td>aPCC</td>
<td>Factors II, VIIa, IX, X</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>FVIIa</td>
</tr>
</tbody>
</table>

*Only After D/C drug and Supportive Care (fluids / transfusions)*

<table>
<thead>
<tr>
<th></th>
<th>Idaracizumab</th>
<th>Andexanet alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternate names</td>
<td>aDabi-Fab, B1655075</td>
<td>PRT064445</td>
</tr>
<tr>
<td>Chemical structure</td>
<td>Humanized monoclonal antibody fragment</td>
<td>Recombinant truncated human factor Xa variant (decoy)</td>
</tr>
<tr>
<td>Binding</td>
<td>Noncompetitive binding to dabigatran</td>
<td>Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor-activated antithrombin</td>
</tr>
<tr>
<td>Target affinity</td>
<td>=350x greater affinity for dabigatran than factor IIa</td>
<td>Affinity for direct factor Xa inhibitors</td>
</tr>
<tr>
<td>Onset</td>
<td>&lt;5 min</td>
<td>2 min</td>
</tr>
<tr>
<td>Half-life</td>
<td>Initial: 47 min; Terminal 10.3 h</td>
<td>Terminal = 6 h</td>
</tr>
<tr>
<td>Elimination</td>
<td>Kidney (protein catabolism)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Anticoagulant(s) reversed</td>
<td>Dabigatran</td>
<td>Direct and Indirect factor Xa inhibitors</td>
</tr>
</tbody>
</table>
Group A: (n=301) Uncontrolled bleeding + dabigatran-treated

Group B: (n=202) Emergency surgery or procedure + dabigatran-treated

5 grams idarucizumab (2 x 2.5 grams IV)

0–15 min     90 days follow-up

50
45
40
35
30
25
Baseline    Bet. Doses    30 min    1 Hr    2 Hr    4 Hr    12 Hr    24 Hr

Idarucizumab Dosing

Primary endpoint: Maximum reversal within 4 h based on dTT, ECT

### Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=301)</th>
<th>Group B (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>79 (24–96)</td>
<td>77 (21–96)</td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>172 (57.1)</td>
<td>102 (50.5)</td>
</tr>
<tr>
<td><strong>Creatinine clearance (mL/min)</strong></td>
<td>50.8 (6.1–216.9)</td>
<td>56.0 (7.9–198.7)</td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>117 (38.9)</td>
<td>65 (32.2)</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>73 (24.3)</td>
<td>36 (17.8)</td>
</tr>
<tr>
<td><strong>Dabigatran, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation indication</td>
<td>288 (95.7)</td>
<td>190 (94.1)</td>
</tr>
<tr>
<td>150 mg BID</td>
<td>94 (31.2)</td>
<td>57 (28.2)</td>
</tr>
<tr>
<td>110 mg BID</td>
<td>185 (61.5)</td>
<td>126 (62.4)</td>
</tr>
<tr>
<td>Patient-reported time since last dose (hrs)</td>
<td>14.6 (1.5, 90.4)</td>
<td>18.0 (2.6, 105.8)</td>
</tr>
<tr>
<td>Elevated dTT at baseline, n (%)</td>
<td>244 (81.1)</td>
<td>152 (75.2)</td>
</tr>
</tbody>
</table>

**Surgery Types (Group B, n=197)**

- Abdom: 31.7%
- Fx: 20.3%
- CV: 18.3%
- CNS: 8.4%
- Thor: 6.9%

**Bleed Types (Group A, n=301)**

- GI: 45.5%
- ICH: 32.6%
- Other: 21.9%


88% = Major and Life-threatening bleeding, 38% = Hemodynamic instability
Group A
• dTT normalized within 4 hours in 98.8% (241/244) patients.
• Study did not mandate repeat scanning of ICH events.
• Non-ICH bleeding assessed in 203 patients:
  • Time to Locally Reported Hemostasis (Bleeding Cessation) 2.5 (2.2 – 3.9) hours (median, 95% CI).

Group B
• 197 of 202 (97.5%) patients underwent surgery/procedures
• dTT normalized within 4 hours in 98.7% (150/152).
• Adequacy of hemostasis during surgery determined locally (below)


**Peri-Procedural Hemostasis in 197 Patients**

- Normal: 93.4%
- Mildly Abnormal: 5.1%
- Moderately Abnormal: 1.5%
- Severely Abnormal: 0.0%
Results

- At 72 hours, 22.9% of Group A and 66.8% of Group B had re-started anticoagulation or antiplatelet therapy.
- By 90 days antithrombotic therapy had been re-started in 72.8% of Group A and 90.1% of Group B patients.
- Patients restarted on dabigatran: 28.9% in Group A (median time 16 days), 61.4% in Group B (median time 6 days).

### Thrombotic events

<table>
<thead>
<tr>
<th>Events</th>
<th>Group A (n=301)</th>
<th>Group B (n=202)</th>
<th>Total (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>14 (4.6)</td>
<td>10 (5.0)</td>
<td>24 (4.8)</td>
</tr>
<tr>
<td>90 days</td>
<td>19 (6.3)</td>
<td>15 (7.4)</td>
<td>34 (6.8)</td>
</tr>
</tbody>
</table>

### Mortality

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=301)</th>
<th>Group B (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days</td>
<td>6.4%</td>
<td>7.9%</td>
</tr>
<tr>
<td>30 Days</td>
<td>13.5%</td>
<td>12.6%</td>
</tr>
<tr>
<td>90 days</td>
<td>18.8%</td>
<td>18.9%</td>
</tr>
</tbody>
</table>

- With 5 days of idarucizumab treatment 19 deaths occurred in Group A (6.3%) and 16 deaths had occurred in Group B 7.9%.)
RE-VECTO: Idarucizumab surveillance program

Methods:
• Patients ≥18 years of age treated with idarucizumab

Results:
• 359 patients (75%, >70 years of age) at 63 hospitals from 12 countries across Asia Pacific (14%), Europe (42%), and North America (44%).

Indications:
• Bleeding (58%), Emergency surgery/procedure (36%), Planned surgery/procedure (3%).

Dosing:
• Patients received 5 g (2 vials, 95%)

Conclusions:
• No new side effects or toxicities reported.
• Off-label use and second-dose use were low.

Patients were not anticoagulated or received warfarin or a direct Xa inhibitor.

Agent causing Bleed
- Dabigatran 150mg: 48%
- Dabigatran 110mg: 33%
- Other: 18%

Types of Bleeding
- GI: 45%
- ICH: 39%
- Spontaneous: 62%
- Traumatic: 23%
- Post Procedural: 40%

ANNEXA-4 Study Design

Patient Screening

- Patient with acute major bleeding
- Within 18 hours of last dose of FXa inhibitor

Assessments:
- Change in anti-fXa activity
- Clinical hemostatic efficacy through 12 hours

Bleeding and Laboratory Assessment

- Andexanet
  - IV Bolus
  - 2-hour IV Infusion
  - After end of infusion

- Safety follow-up visit
- Day 1
- Day 3
- Day 30

Efficacy Outcomes

- Change in anti-fXa activity
- Clinical hemostatic efficacy through 12 hours

Safety Measurements

- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day mortality

ANNEXA-4 Dose Selection

Acute major bleeding ≤ 18 hours of last dose of apixaban, edoxaban, rivaroxaban, or enoxaparin

Andexanet IV bolus + 2 hour infusion

Apixaban or >7 h from last rivaroxaban dose
- Bolus 400 mg + Infusion 480 mg @ 4 mg/min

Enoxaparin, edoxaban or ≤7 h from last rivaroxaban dose
- Bolus 800 mg + Infusion 960 mg @ 8 mg/min

Rivaroxaban Patients (n=75)

Andexanet Dosing
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Population N=227</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr), mean ± SD</strong></td>
</tr>
<tr>
<td><strong>Time from presentation until Andexanet (hrs)</strong></td>
</tr>
<tr>
<td><strong>Estimated creatinine clearance &lt; 30 mL/min,</strong></td>
</tr>
<tr>
<td><strong>Indication for anticoagulation</strong></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Venous Thromboembolic Disease</td>
</tr>
<tr>
<td>Atrial fibrillation and VTE</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Heart Failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population N=227</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracranial Bleeding</strong></td>
</tr>
<tr>
<td>Intracerebral site</td>
</tr>
<tr>
<td>Sub-dural site</td>
</tr>
<tr>
<td>Subarachnoid site</td>
</tr>
<tr>
<td><strong>Gastrointestinal Bleeding</strong></td>
</tr>
<tr>
<td><strong>Other Bleeding site</strong></td>
</tr>
</tbody>
</table>
# Clinical Hemostatic Efficacy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Excellent or Good (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Efficacy Patients</strong></td>
<td>132</td>
<td>83 (76-89)</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>54</td>
<td>83 (73-93)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>68</td>
<td>82 (73-91)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>10</td>
<td>80 (55-100)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67</td>
<td>81 (71-90)</td>
</tr>
<tr>
<td>Female</td>
<td>65</td>
<td>85 (76-93)</td>
</tr>
<tr>
<td><strong>Site of bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>43</td>
<td>86 (76-96)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>74</td>
<td>81 (72-90)</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>80 (60-100)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>18</td>
<td>83 (66-100)</td>
</tr>
<tr>
<td>65-75 yr</td>
<td>38</td>
<td>87 (76-98)</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>76</td>
<td>80 (71-89)</td>
</tr>
<tr>
<td><strong>Andexanet dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>117</td>
<td>81 (74-88)</td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>93 (81-100)</td>
</tr>
</tbody>
</table>
Efficacy and Safety Assessment

- Thrombotic events occurred within 3 days of andexanet in 6 (2.6%) patients and by 30 days in 24 (11%)
- Anticoagulation re-started in 129 patients (57%) by 30 days
- Therapeutic anticoagulation was re-started in only 9 patients before a thrombotic event occurred
- 27 deaths occurred by 30 days (12%), of which 11 were cardiovascular

<table>
<thead>
<tr>
<th>Number of Major Bleeds Adjudicated</th>
<th>No. Patients who Achieved Excellent or Good Hemostasis</th>
<th>% of Patients who Achieved Excellent or Good Hemostasis</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>132</td>
<td>109</td>
<td>83%</td>
<td>76% - 89%</td>
</tr>
</tbody>
</table>

Number of Major Bleeds Adjudicated

<table>
<thead>
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<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>132</td>
<td>109</td>
<td>83%</td>
<td>76% - 89%</td>
</tr>
</tbody>
</table>
Anticoagulation Bleeding Algorithm

1. **Patient with active bleeding**
   - Compress bleeding sites mechanically
   - Assess hemodynamic status, blood pressure, basic coagulation parameters, blood count, kidney function
   - Obtain anticoagulation hx (last DOAC/VKA dose)

2. **VKA**
   - Delay VKA until INR <2
   - Add symptomatic treatment: Fluid replacement, Blood Transfusion, Treat bleeding cause (eg, gastroscopy)
   - Consider Vitamin K (1-10mg) IV
   - Consider PCC and FFP
   - Consider replacement of platelets where appropriate

3. **DOAC**
   - Delay DOAC for 1 dose or 1 day
   - Minor
     - Add symptomatic treatment: Fluid replacement, Blood Transfusion, Treat bleeding cause (eg, gastroscopy)
     - Consider Vitamin K (1-10mg) IV
   - Moderate
   - Severe or life-threatening
     - Add symptomatic treatment: Fluid replacement, Blood Transfusion, Treat bleeding cause (eg, gastroscopy)
     - Consider Vitamin K (1-10mg) IV
     - Consider specific antidote, or PCC if no antidote available
     - Consider replacement of platelets where appropriate


VKA = vitamin K antagonist
Building a DOAC Reversal Management Plan — What Do I Need to Know

William Dager, Pharm.D., BCPS-AQ Cardiology
A Physician wants to reverse the effects of a DOAC in a patient:

- **Intervention:** What is my role?
- **Assess the situation**
  - Medication History
  - Goals
- **What do I have available to me?**
- **Situation and Setting Dependent**
- **How fast can lab or imaging results be available?**
Assess the Situation and Potential Risks

- **Bleeding?**
  - Scan patient
  - Site: risk of a complication
- **Assess Urgency of Situation**
  - Eminent life threatening vs some time
- **Level of anticoagulation**
  - Organ failure may drive higher levels
  - Laboratory assay
  - Antiplatelet agents?
- **Keep in mind – need to restart anticoagulation**
History of Present Illness:
• 81yo M (112kg) s/p fall from standing at approximately 3 PM today.
• Rivaroxaban 20mg QAM for AF this AM.
• Head strike on a wooden cabinet, denies LOC, laid on the ground for 5 hours
• Taken to an OSH, where CTH showed R SAH and C5-6 jumped facets.
• Transferred for further care.
• He denies headache, nausea, emesis, or lethargy.
• His RUE is subjectively weak.

Physical Examination:
Temperature: 97.2 °F
Heart Rate: 69 [68-69]
Respiratory Rate: 18
BP: 116/56(108-139)/(56-67)
O2 Sat: 96 % [92 % - 96 %]
General - NAD. Oriented x 3.

Plan:
Orthopedic Surgery plans to take him emergently to OR for C5-6 facets for incomplete spinal cord injury.
Audience Response Questions

• Is WB a candidate for anticoagulation reversal?

  1. Yes
  2. No
ICH: Types

- Skull
- Epidural Hemorrhage
- Subarachnoid Hemorrhage
- Dura
- Intracerebral Hemorrhage
- Subdural Hemorrhage
- Intraventricular Hemorrhage

W Dager: Anticoagulation Therapy 2018
Audience Response Questions

• It is now 11 PM.
• Is laboratory assessment warranted?

1. Yes
2. No
Laboratory Assessments

• Timing/Priority
• Reflect the situation
• Correct Assay
  – Anticoagulant Specificity
  – Limitations
  – Bleeding Assessment
• Value ≠ Clinical presentation → Repeat test
### Assessing intensity of Oral anticoagulation effects

<table>
<thead>
<tr>
<th>Drug Present</th>
<th>Dabigatran</th>
<th>Rivaroxaban/Apixaban/Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin Time</td>
<td>? Chromogenic anti-Factor Xa (Calibrated to the drug versus UFH or LMWH)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantitative Test</th>
<th>? Dilute thrombin time (dTT) or Chromogenic ECT</th>
<th>Chromogenic anti-factor Xa</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sensitivity: PT vs aPTT (Reagent Dependent)</th>
<th>aPTT &gt; PT (Point-of-Care INR &gt; Central Lab)</th>
<th>PT &gt; aPTT</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No/Limited effect</th>
<th>anti-factor Xa activity</th>
<th>ECT, TT</th>
</tr>
</thead>
</table>

---

Potential INR response with higher DOAC serum concentrations
Direct Oral Anticoagulants (DOACs)

- Complete Testing Range for Measurement in Plasma, when Needed
- Excellent correlation with reference method

[Diagram showing interactions of Thrombin, Xa, Inhibitors, and Fibrinogen and Clot]
Audience Response Questions

Which coagulation test would you recommend?
1. PT
2. INR
3. aPTT
4. Anti-Xa activity
5. All of the above
<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Units</th>
<th>Test</th>
<th>Reference Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM</td>
<td>136 - 145 mmol/L</td>
<td>140</td>
<td>WBC</td>
<td>4.00 - 10.00 K/uL</td>
<td>12.56 (H)</td>
</tr>
<tr>
<td>POTASSIUM</td>
<td>3.4 - 5.0 mmol/L</td>
<td>4.1</td>
<td>RBC</td>
<td>4.50 - 6.40 M/uL</td>
<td>4.62</td>
</tr>
<tr>
<td>CHLORIDE</td>
<td>98 - 107 mmol/L</td>
<td>100</td>
<td>HGB</td>
<td>13.5 - 18.0 g/dL</td>
<td>14.0</td>
</tr>
<tr>
<td>CO2</td>
<td>22 - 31 mmol/L</td>
<td>23</td>
<td>HCT</td>
<td>40.0 - 54.0 %</td>
<td>40.4</td>
</tr>
<tr>
<td>BUN</td>
<td>6 - 23 mg/dL</td>
<td>27 (H)</td>
<td>PLT</td>
<td>150 - 450 K/uL</td>
<td>170</td>
</tr>
<tr>
<td>CREATININE</td>
<td>0.50 - 1.20 mg/dL</td>
<td>1.09</td>
<td>MCV</td>
<td>80.0 - 95.0 fL</td>
<td>87.4</td>
</tr>
<tr>
<td>GLUCOSE</td>
<td>70 - 100 mg/dL</td>
<td>199 (H)</td>
<td>MCH</td>
<td>27.0 - 32.0 pg</td>
<td>30.3</td>
</tr>
<tr>
<td>ALBUMIN</td>
<td>3.5 - 5.2 g/dL</td>
<td>4.0</td>
<td>MCHC</td>
<td>32.0 - 36.0 g/dL</td>
<td>34.7</td>
</tr>
<tr>
<td>CALCIUM</td>
<td>8.8 - 10.7 mg/dL</td>
<td>9.6</td>
<td>RDW</td>
<td>11.5 - 14.5 %</td>
<td>14.6 (H)</td>
</tr>
<tr>
<td>ALK Phos</td>
<td>35 - 130 U/L</td>
<td>44</td>
<td>MPV</td>
<td>8.4 - 12.0 fl</td>
<td>9.9</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;59 mL/min/1.73m2</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>11.5 - 14.5 sec</td>
<td>17.1 (H)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>0.9 - 1.1</td>
<td>1.4 (H)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Audience Response Questions

• Is laboratory testing warranted after surgery?

  1. Yes
  2. No
Hospital Course

1 AM
- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 400 mg Intravenous-Once @ 160 mL/hour over 15 minutes.
- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 480 mg Intravenous-Once @ 24 mL/hour over 120 Minutes.

2 AM-Taken to the OR and underwent general endotracheal anesthesia.
- C5-6 laminectomy and C3-T2 fusion
- The patient was extubated and transferred in stable condition to the surgical ICU at 6AM.

8 AM
- Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>11.5 - 14.5 sec</td>
<td>17.1 (H)</td>
</tr>
<tr>
<td>INR</td>
<td>0.9 - 1.1</td>
<td>1.4 (H)</td>
</tr>
<tr>
<td>APTT</td>
<td>23.8 - 36.6 sec</td>
<td>31.0</td>
</tr>
</tbody>
</table>

Follow-up
- SICU course was uncomplicated, never requiring intubation.
- Rivaroxban held.
- Enoxaparin 30 mg BID for VTE prophylaxis.
Anticoagulant “Reversal” Strategy

• Depends on:
  – Setting (ED, OR, ICU, Cardiac Cath Lab)
  – Urgency
• Hold Anticoagulation
• Mechanical Intervention (Surgery)
• Pharmacological intervention
  • Topical Agents
  • Neutralize the drug – Need to last the duration necessary
  • Reverse the effects of the drug independently
• Replace losses
• Optimize management of co-morbid situations
DOAC – Agent Unclear

Bleeding or need for Urgent Reversal

Assessment
- Amount of Drug (↑ INR/PT etc)
  - Thrombin Time/Anti-Xa
  - Bleeding Risk
  - Charcoal if ingestion recent
  - Med Rec: Dosing QD/BID

Thrombin Time High
Anti-Xa Low
? ↑ aPTT > PT (assay dependent)

Dabigatran

Administer Antidote
Consider Adding Hemostatic Agent if urgent – life threatening bleed

Semi Urgent

Consider Antidote Hemostatic Agent if clinically necessary (low dose titrate to effect)

Bleeding

Supportive Management
- Underlying Condition
- Transfuse
- Need for invasive procedure

Rivaroxaban
Apixaban
Edoxaban

Thrombin Time Low
Anti-Xa High
? ↑ PT > aPTT (assay dependent)

Non-Urgent

Watch

Urgent

Underlying Condition
Transfuse
Need for invasive procedure

Supportive Management
- Transfuse
- Need for invasive procedure

Consider Antidote Hemostatic Agent if clinically necessary (low dose titrate to effect)
Concentrated clotting factor may depend on what is available – Reassess 5-10 min post administration - If time available, start with lower doses and repeat if necessary

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban/Apixaban/Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No rush, Minor bleeding</strong></td>
<td>• Monitor – re-check labs</td>
<td>• Monitor – re-check labs</td>
</tr>
</tbody>
</table>
| **Expedited (1-24 hr), Major bleeding** | • Idarucizumab 5gm  
• Consider PCC4 (25 units/kg) or low dose factor VIII inhibitor bypassing activity (aPCC) | • Andexanet  
• Evaluate if PCC needed.  
• Consider PCC4 or PCC3 if clinically necessary  
• Option: low dose aPCC (8-12 units/kg) |
| **Emergent (< 1 hr), Major bleeding** | • Idarucizumab 5gm  
• Option - Add: aPCC 10-25 units/kg, have next dose ready; (or PCC4 25-50 units/kg) or TXA (bolus + Infusion) | • Andexanet  
• aPCC 12 - 50 units/kg or  
• PCC4 or PCC3 25-50 units/kg |

CASE-Unidentified Male

History of Present Illness:
• 67yo M (101 kg) with unknown medical history, transferred from OSH for ICH.
• Last seen at 9 AM on park bench
• Medical bracelet staes “Blood thinner”.
• OSH’s CT showed ICH.
• Given Kcentra 1500 units, Mannitol, Vitamin K 10 mg SC before transfer.
• Patient arrives here minimally responsive hypertensive and not verbally answering questions.

Physical Examination:
Temperature: 99.0 °F
Heart Rate: 69 [68-69]
Respiratory Rate: 30
BP: 158/92(108-139)/(56-67)
O2 Sat: 96 % [92 %-96 %].

Repeat Imaging:
Large left intraparenchymal hemorrhage involving the left MCA territory. There is associated severe mass effect with subfalcine and uncal herniation with mild coning in the foramen magnum.
Audience Response Questions

• Is the unknown male a candidate for anticoagulation reversal?

1. Yes
2. No
<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Units</th>
<th>Reference Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>136 - 145 mmol/L</td>
<td>136</td>
<td>WBC</td>
<td>4.00 - 10.00 K/uL</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.4 - 5.0 mmol/L</td>
<td>4.1</td>
<td>RBC</td>
<td>4.50 - 6.40 M/uL</td>
</tr>
<tr>
<td>Chloride</td>
<td>98 - 107 mmol/L</td>
<td>93</td>
<td>HGB</td>
<td>13.5 - 18.0 g/dL</td>
</tr>
<tr>
<td>CO2</td>
<td>22 - 31 mmol/L</td>
<td>31</td>
<td>HCT</td>
<td>40.0 - 54.0 %</td>
</tr>
<tr>
<td>BUN</td>
<td>6 - 23 mg/dL</td>
<td>13</td>
<td>PLT</td>
<td>150 - 450 K/uL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.50 - 1.20 mg/dL</td>
<td>1.09</td>
<td>MCV</td>
<td>80.0 - 95.0 fL</td>
</tr>
<tr>
<td>Glucose</td>
<td>70 - 100 mg/dL</td>
<td>197 (H)</td>
<td>MCH</td>
<td>27.0 - 32.0 pg</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5 - 5.2 g/dL</td>
<td>3.5</td>
<td>MCHC</td>
<td>32.0 - 36.0 g/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.8 - 10.7 mg/dL</td>
<td>8.6</td>
<td>RDW</td>
<td>11.5 - 14.5 %</td>
</tr>
<tr>
<td>ALK Phos</td>
<td>35 - 130 U/L</td>
<td>75</td>
<td>MPV</td>
<td>8.4 - 12.0 fl</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;59 mL/min/1.73m2</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>11.5 - 14.5 sec</td>
<td>19.0 (H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>0.9 - 1.1</td>
<td>1.6 (H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aPTT</td>
<td>23.9-36.6 sec</td>
<td>38.3 (H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>undetectable</td>
<td>2.94 (H)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3 PM
- In the ED patient has acute worsening of mental status, requiring emergent intubation.
- Arterial line was placed for blood pressure monitoring, boluses of labetalol were given with reduction in blood pressure, and a nicardipine IV started for blood pressure optimization.
- Discussions with Neurology and Hematology ensue.
- Hematology's recommendation to administer andexanet for immediate anticoagulation reversal (last dose greater than 12 hour ago). Order written by Neurology resident.

4 PM
- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 400 mg Intravenous-Once @ 160 mL/hour over 15 minutes.
- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 480 mg Intravenous-Once @ 24 mL/hour over 120 Minutes.

9 PM
- Labs
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<td>INR</td>
<td>0.9 - 1.1</td>
</tr>
<tr>
<td>APTT</td>
<td>23.8 - 36.6 sec</td>
</tr>
</tbody>
</table>

Follow-up
- Admitted to the MICU.
- Enoxaparin 30 mg BID for VTE prophylaxis.
- Nicardipine for blood pressure control
- Propofol for sedation.
Idarcuizumab – Dabigatran Reversal

Humanized Fab fragment specific to dabigatran

- Affinity: Dabigatran 350 times > Thrombin
- No evidence of prothrombotic effect
- Rapid onset and dose dependent effect
  - Sustained > 24 hours with dose > 2 gm
  - 2.5gm Vial – 2 vials = 5gm dose
- aPTT, TT and ECT normalized

Van Ryn J Circulation 2012;126; Schele F et al. Blood 2013;121:3554-62; Clinical Trials.gov
Antibody Maximal Effect

Antibody > Target Agent

Drug Neutralized

Target Agent > Antibody

Drug Effects Persist

Idarucizumab and excessive Dabigatran levels

2 cases – high dabigatran levels (1480ng/ml and 2260 ng/ml)
- Both had AKI (Scr increased baseline to 1.98 and 2.08)
- INR values were > 13
- 5gm Idarucizumab reversed ~ 700 - 800ng/ml Dabigatran
- FEIBA ~20 units/kg given both cases
- One pt had CRRT initiated – unclear if CRRT removed the bound up Dabigatran as their was no means to measure this.

Ref: Steele AP, Lee JA, Dager WE: Clin Tox 2018;56:216-18
A: Figure A depicts short term hemodialysis of Dabigatran with tissue rebound into plasma occurring.

B: Figure B depicts prolonged hemodialysis and reduced tissue rebound and greater removal of Dabigatran from the plasma over the time period.
## Reversing oral anti-Xa Anticoagulants

<table>
<thead>
<tr>
<th>Plasmapheresis</th>
<th>Limited information, with apixaban being removed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidote</td>
<td>Andexanet Alfa</td>
</tr>
</tbody>
</table>
| Concentrated clotting factors | The agent and dose to reverse the effects of oral anti-Xa agents: Not established.  
  - Minor bleeding: monitor and recheck laboratory results.  
  - Major bleeding: PCC or aPCC.  
  - Unclear if any differences between nonactivated and activated PCC.  
  - **Less urgent bleeding** → treatment can begin with a low-dose (8-12 U/kg IV strategy).  
  - **Semi-urgent bleeding**: PCC/aPCC up to 25 U/kg IV. If time allows, treatment can begin with a lower dose approach, with additional doses based on clinical assessment.  
  - **Emergent life-threatening bleed**: PCC/aPCC 25-50 IV U/kg. |

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial IV Bolus</th>
<th>Follow-On IV Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Dose</strong></td>
<td>400 mg at a target rate of 30 mg/min</td>
<td>4 mg/min for up to 120 minutes</td>
</tr>
<tr>
<td><strong>High Dose</strong></td>
<td>800 mg at a target rate of 30 mg/min</td>
<td>8 mg/min for up to 120 minutes</td>
</tr>
</tbody>
</table>
Andexanet: Reversing Oral Anti-Xa agents

Potential challenges with DOAC antidotes

- Tissue rebound of either the anticoagulant or antidote
- Need for emergent hemostasis – when is a hemostatic agent necessary, which agent and what dose
- Rapid availability to patient; adaptable order sets
- Ability to measure/assess when the antidote can be stopped
- Prolonged infusion until bleeding stops as anticoagulant effects may be sustained for days
- Neutralization of other anticoagulants that may be necessary for emergent therapy (e.g. ECLS or cardiopulmonary bypass)
- Availability, especially if the cost is high; Storage
Use of PCC or aPCC with DOACS: Bleeding

- No randomized comparisons to Antidote’s
- Doses variable (8 – 100 units/kg)
- Single doses and low doses in GI Bleeds have worked
  - Rare need to repeat doses; Onset seems to be rapid.
- Any advantage with aPCC over PCC with Anti-Factor Xa agents unclear
- Thrombosis has been reported - ? If incidence higher
- Mortality Rates Vary
- Neurocritical Care Society Guidelines: Rec 50 units/kg PCC or aPCC in ICH
  - Dabigatran: If no Idarucizumab given
  - Some success in case reports

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANEXXA-4 (Safety Population) (n=67)</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>Majeed et al (n=84) – 4 Factor PCC</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Schulman et al (n=66) – 4 Factor PCC</td>
<td>14%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Key Considerations

• Being in the know: Assessing Urgency once on your radar
  – Bleeding Severity
  – Other management modalities
  – Who are the players
  – What is my role – and seeing it through

• Operating Room

• Labs ordered (baseline and follow-up assessments)

• Seeing it through – (Bedside assessments)

• Duration of reversal effect understood
  – Therapy in place
  – Avoid interruption with short acting agents
Getting Drug to the patient

1. Patient Arrives
2. Situation assessed, Medication History, Labs
3. Decision to treat
4. Medications Ordered
5. Pharmacy Processes Order
6. Ordered Medications sent to patient
7. Medication Infused

- Labs
- Orders
- Antidote
- PCC/aPCC
- Dialysis
- Blood
- Surgery
Restarting Anticoagulation

Assessment of Thrombosis vs Bleeding

↑ Thrombosis Risk: Surgery, PCC, Acutely Ill

ICH: (Pts on warfarin)

• Higher long term survival and lower incidence of thrombosis with minimal risk of recurrent bleeding events

• Potential Exceptions (CNS bleeds):
  • Cerebral amyloid angiopathy (lobar)
  • Microvascular risk
  • Microbleeds on gradient-echo MRI
  • Indication: Primary prevention; Atrial fibrillation, low CHADS2 < 4 or CHA2DS2-VASc < 5; Anticipated difficulty managing anticoagulation

Be Prepared

- Pre thought out process in place --- Avoid Delays
- Order set(s) developed
- Key services on board (Medical, Lab, Nursing)
- Who is involved in each step
  - Initial Presentation → Process Completed
- Key services on board (Medical, Lab, Nursing)

- Follow up for long term considerations
  - VTE Prophylaxis
  - Re-establishing Anticoagulation
1) **KEY TAKEAWAY**
   Reversal agents for direct acting oral anticoagulants are available for use.

2) **KEY TAKEAWAY**
   Careful patient assessment and goals of treatment are key.

3) **KEY TAKEAWAY**
   Reversal agents have unique characteristics and may require support with blood products or dialysis.