Simplifying DOAC Reversal

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Disclosure

I have nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.
Objectives

• Discuss currently available Direct Oral Anticoagulants (DOACs) and bleeding rates
• Discuss appropriate monitoring parameters for DOACs
• Evaluate non-urgent and emergency reversal options for DOACs
• Review reversal options
CURRENTLY AVAILABLE DOACS AND BLEEDING RATES
Anticoagulant Site of Action

**Intrinsic Pathway**
- XII → XIIa
- XI → IXa
- IX → X
- VIII → VIIIa
- Protein C + Thrombomodulin → Activated Protein C

**Extrinsic Pathway**
- VII → VIIa
- TF

**Warfarin** (also inhibits Factors II, VII, IX, X, Protein C, Protein S)

**Oral Xa Inhibitors**

**Direct Thrombin Inhibitors**

**Common Pathway**
- II → IIa
- Xa
- Ila → Ila
- XIII → Xllla → Fibrin Clot

**Legend**
- I = Fibrinogen
- II = Prothrombin, IIa = Thrombin
- TF = Tissue Factor
# DOAC – Review of Agents

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apixaban</th>
<th>Betrixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>FDA Approved Indications</strong></td>
<td>Novalvular AF, VTE (treatment, secondary prevention &amp; prophylaxis)</td>
<td>VTE (prophylaxis)</td>
<td>Novalvular AF, VTE (treatment, secondary prevention &amp; prophylaxis)</td>
<td>Nonvalvular AF, VTE (treatment)</td>
<td>Novalvular AF, VTE (treatment, secondary prevention &amp; prophylaxis), CAD &amp; PAD</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>12</td>
<td>20</td>
<td>8 – 15</td>
<td>10 – 14</td>
<td>7 – 11</td>
</tr>
<tr>
<td><strong>Renal Clearance (%)</strong></td>
<td>25</td>
<td>6 – 13</td>
<td>80</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

# Bleeding Rates

**TABLE 2** Distribution of Anatomic Sites Among DOAC and Warfarin-Associated Major Bleeding Events

<table>
<thead>
<tr>
<th>Event</th>
<th>DOAC (n = 460)</th>
<th>Warfarin (n = 1,542)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage (any), No. (%)</td>
<td>97 (21.1)</td>
<td>460 (29.8)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Epidural</td>
<td>0 (0.0)</td>
<td>≤ 5 (≤ 0.3)</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>23 (5.0)</td>
<td>125 (8.1)</td>
<td>.032</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>6 (1.3)</td>
<td>35 (2.3)</td>
<td>.260</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>34 (7.4)</td>
<td>93 (6.0)</td>
<td>.326</td>
</tr>
<tr>
<td>Subdural</td>
<td>61 (13.3)</td>
<td>293 (19.0)</td>
<td>.004</td>
</tr>
<tr>
<td>NOS</td>
<td>0 (0.0)</td>
<td>9 (0.6)</td>
<td>.129</td>
</tr>
<tr>
<td>GI (any), No. (%)</td>
<td>284 (61.7)</td>
<td>656 (42.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Upper GI</td>
<td>101 (22.0)</td>
<td>301 (19.5)</td>
<td>.260</td>
</tr>
<tr>
<td>Lower GI</td>
<td>143 (31.1)</td>
<td>266 (17.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>NOS</td>
<td>41 (8.9)</td>
<td>91 (5.9)</td>
<td>.025</td>
</tr>
<tr>
<td>Hematoma without compartment syndrome, No. (%)</td>
<td>8 (1.7)</td>
<td>82 (5.3)</td>
<td>.001</td>
</tr>
</tbody>
</table>

APPROPRIATE MONITORING PARAMETERS FOR DOACS
Monitoring - DABIGATRAN

- **aPTT & PT**: Significant variability based on reagent used
- **Thrombin Time**: Normal thrombin time indicates no or minimal dabigatran present
- **Dilute Thrombin Time (dTT)**: Shows linear, concentration dependent relationship
- **Ecarin Based Assays**: Shows linear, concentration dependent relationship

Monitoring - DABIGATRAN

Monitoring – APIXABAN/RIVAROXABAN

- aPTT & PT
  - Effects vary depending on reagent/drug
  - Poorly reflects the degree of anticoagulation
  - Can’t quantify drug plasma concentration

- Anti-factor Xa level
  - Need drug specific calibrator
  - Linear, concentration dependent relationship

Monitoring – APIXABAN/RIVAROXABAN

MANAGING DOAC BLEEDING
Is DOAC Present?

• When was last dose?

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (h)</td>
<td>12</td>
<td>8 – 15</td>
<td>7 – 11</td>
</tr>
<tr>
<td>Renal Clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
</tr>
</tbody>
</table>

• What are labs?
  – Dabigatran: normal TT = no drug
  – Dabigatran: prolonged TT = clinically relevant OR trivial levels
  – Dabigatran: normal aPTT = excludes above ‘on-therapy’ levels
  – Rivaroxaban: prolonged PT = may indicate ‘on-therapy’ or above ‘on-therapy’ levels
  – Apixaban: prolonged PT = suggests above ‘on-therapy’ levels
  – FXa: undetectable heparin anti Xa = no drug

Managing Bleeding

Supportive Measures
- IV fluids
- Blood products

Local hemostasis
- Mechanical compression
- Referral for definitive procedures & surgical intervention

Adjunct Treatments
- Activated charcoal
- Antifibrinolytics
- Desmopressin

Reversal agents
- Idarucizumab
- Andexanet alfa
- Prothrombin complex concentrates (PCCs)
SCC of the ISTH: To Reverse or Not to Reverse??

Consider reversal
- Life threatening bleeding
- Bleeding in a closed space or critical organ
- Persistent major bleeding despite local hemostatic measures
- Need for urgent intervention
- Emergency surgery

Avoid reversal
- Elective surgery
- GI bleeds responding to supportive measures
- High drug levels without associated bleeding
- Need for intervention that can be delayed long enough to allow for drug clearance

American College of Cardiology: To Reverse or Not to Reverse??

Does ≥ 1 of the Factors Apply?
- Bleeding at critical site?
- Hemodynamic instability
- Bleeding with Hgb decrease ≥ 2g/dL or administration of ≥ 2 units RBCs

Major Bleed
Is the bleed at a critical site or life threatening?

- Yes
  - Stop DOAC
  - Control bleeding
  - Consider reversal agent

- No
  - Stop DOAC
  - Control bleeding

Nonmajor Bleed
REVERSAL AGENTS FOR DOACS
# Prothrombin Complex Concentrate (PCC4)

<table>
<thead>
<tr>
<th>FDA approved indication</th>
<th>Indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (warfarin) therapy in adult patients with acute major bleeding or need for an urgent surgery/invasive procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Blood coagulation factor replacement product; contains the Vitamin K dependent coagulation Factors II, VII, IX, and X, together known as the Prothrombin Complex, and the antithrombotic Protein C and Protein S</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Within 10 minutes</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>6 – 8 hours</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>~ $3,000 per 2000 IU</td>
</tr>
</tbody>
</table>
# Idarucizumab

<table>
<thead>
<tr>
<th>FDA approved indication</th>
<th>Indicated for patients treated with dabigatran when reversal is needed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its metabolites with higher affinity than that of dabigatran to thrombin, neutralizing their anticoagulant effect</td>
</tr>
<tr>
<td>Target affinity</td>
<td>Affinity for dabigatran &amp; its metabolites (no effect on Xa inhibitors)</td>
</tr>
<tr>
<td>Onset</td>
<td>Within minutes</td>
</tr>
<tr>
<td>Half-life</td>
<td>10.3 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine</td>
</tr>
<tr>
<td>Cost</td>
<td>$3,500 per treatment course</td>
</tr>
</tbody>
</table>
# Andexanet alfa

<table>
<thead>
<tr>
<th>FDA approved indication</th>
<th>Indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Recombinant truncated human factor Xa variant (decoy) that temporarily shuts down the activity of factor Xa (does not remove it)</td>
</tr>
<tr>
<td><strong>Binding</strong></td>
<td>Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor-activated antithrombin</td>
</tr>
<tr>
<td><strong>Target affinity</strong></td>
<td>Affinity for direct factor Xa inhibitors (no effect on dabigatran)</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>2 minutes</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5 – 7 hours</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$22,000 - $50,000+</td>
</tr>
</tbody>
</table>
Andexanet Alfa

INDICATIONS AND USAGE

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo) is a recombinant modified human factor Xa (FXa) protein indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. (1)

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies that demonstrate an improvement in hemostasis in patients. (1, 14)

Limitations of Use
ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban. (1)
# Andexanet Alfa vs PCC4

<table>
<thead>
<tr>
<th></th>
<th>ANNEXA-4 (n=67)</th>
<th>Majeed et al (n=84)</th>
<th>Schulman et al (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>77.1 ± 10</td>
<td>75 ±10.9</td>
<td>76.9 ± 10.4</td>
</tr>
<tr>
<td><strong>Primary bleed site</strong></td>
<td>ICH, n=28 (42%)</td>
<td>ICH, n=59 (70%)</td>
<td>ICH, n=36 (55%)</td>
</tr>
<tr>
<td></td>
<td>GI, n=33 (49%)</td>
<td>GI, n=13 (16%)</td>
<td>GI, n=16 (24%)</td>
</tr>
<tr>
<td><strong>Time since last DOAC dose (hr)</strong></td>
<td>R 12.8 ± 4.2</td>
<td>12.5 (9-16)</td>
<td>16.9 (12-21)</td>
</tr>
<tr>
<td></td>
<td>A 12.1 ± 4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Effectiveness for CNS bleeds excellent or good</strong></td>
<td>160 (80%)</td>
<td>43 (73%)</td>
<td>25 (76%)</td>
</tr>
<tr>
<td><strong>Thrombotic events</strong></td>
<td>12 (18%)</td>
<td>3 (5%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>10 (15%)</td>
<td>27 (32%)</td>
<td>9 (14%)</td>
</tr>
</tbody>
</table>

Andexanet Alfa vs PCC4

“The similar effectiveness results in our study and in ANNEXA-4 could, if true, be because both methods are effective or, alternatively, because reversal has minimal or no effect on the outcome. The latter could, in turn, be due to too late administration (intracranial hemorrhage – the damage is already done) or that the anticoagulation effect is rapidly vanishing with the short half-life of the Xa inhibitors.”

Universal reversal agent – Coming soon....

• **Ciraparantag**
  – Synthetic molecule that binds to direct thrombin inhibitors and factor Xa inhibitors
  – Currently in Phase II trials, currently recruiting
Summary

• Degree of anticoagulation can be estimated based on the specific agent, dose, interval since last dose, renal & hepatic function, & laboratory evaluation
  – Use caution when interpreting labs!
• Reversal agent should only be considered if bleeding is life-threatening, into a critical organ, supportive measures have failed, and there is belief that patient has clinically relevant plasma DOAC levels
• Use of reversal agents for DOACs have not demonstrated improved outcomes
• Andexanet alfa dosed according to FDA labeling appears as effective as fixed dose PCC
Question

Which of the following options depicts DOACs that are appropriately matched to the labs that are useful in providing some level of monitoring? (select all that are appropriate)

a) Rivaroxaban: INR
b) Dabigatran: thrombin time
c) Apixaban: correlated anti-factor Xa level
d) Dabigatran: correlated anti-factor Xa level
Question

A patient is brought to ED by EMS for unresponsiveness & immediately intubated. Family states patient is on an anticoagulant for Afib, but does not know which one or if the patient is compliant. Which labs should be obtained? (select all that are appropriate)

a) INR  
b) TT  
c) aPTT  
d) PT  
e) Anti Xa level
Question

Which of the following agents would be appropriate to emergently reverse the effects of apixaban or rivaroxaban? (select all that are appropriate).

a) PCC4
b) Idarucizumab
c) Andexanet alfa
d) Ciraparantag