DOAC’s and their Reversal: “The Slippery Slope”

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# Direct Oral Anticoagulants (DOACs)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target for activity</strong></td>
<td>Thrombin (II)</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-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% (&gt; 80% capsule opened)</td>
<td>&gt; 80%</td>
<td>&gt; 50%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Time to peak Cp</strong></td>
<td>2 hr (Delayed by food)</td>
<td>3 hr (Delayed by food)</td>
<td>3 hr</td>
<td>1.5 hr</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 hr</td>
<td>5-9 hr (Elderly 11-13hr)</td>
<td>9-14 hr</td>
<td>8-10 hr</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>Once or twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>80%</td>
<td>36%</td>
<td>25%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>P-gp inhibitors or inducers, PPI</td>
<td>CYP 3A4</td>
<td>CYP 3A4; P-gp modifiers</td>
<td>P-gp modifiers</td>
</tr>
</tbody>
</table>

CYP - cytochrome P450; P-gp - P glycoprotein; PPI - proton pump inhibitors; hr – hours; Cp = peak plasma concentration

Assess the Situation

- **Bleeding?**
  - Scan patient
  - Site: risk of a complication

- **Assess Urgency of Situation**
  - Eminent life threatening vs some time

- **Level of anticoagulation**
  - Laboratory assay
  - Antiplatelet agents?

- **Keep in mind – need to restart anticoagulation**
Look at the Big Picture – What path will we take?
Is the situation CLEAR
Anticoagulant “Reversal” Strategy

- Depends on setting (ED, OR, ICU, Cardiac Cath Lab) and urgency
- Hold Anticoagulation
- Bleeding?
  - Site and severity – may influence outcomes
- Mechanical Intervention (Surgery)
- Pharmacological intervention
  - Topical Agents
  - Neutralize the drug
  - Reverse the effects of the drug independently
- Replace losses
- Optimize management of co-morbid situations
Prior to procedure: Anticoagulant “Lowering Intensity or Reversal” Strategy

- **Bleeding Risk Assessment**
  - Site and severity – may influence outcomes

- Create a plan and request necessary follow up
  - **Stop or slow it to locate and treat**

- Pre-Operative
- Intra-Operative: Mechanical Intervention (Surgery)
- Post-Operative
Assessing intensity of Oral anticoagulation effects

<table>
<thead>
<tr>
<th>Drug Present</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban/Apixaban/Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR/PT Clotting Factor (II and X)</td>
<td>Thrombin Time</td>
<td>? Chromogenic anti-Factor Xa (Calibrated to the drug?)</td>
<td>? Anti-factor Xa (calibrated to UFH or LMWH)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantitative Test</th>
<th>INR/PT Clotting Factor (II and X)</th>
<th>? Dilute thrombin time (dTT) or Chromogenic ECT</th>
<th>Chromogenic anti-factor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT vs aPTT</td>
<td>aPTT &gt; PT (Point-of-Care INR &gt; Central Lab)</td>
<td>PT &gt; aPTT</td>
<td></td>
</tr>
</tbody>
</table>

| No/Limited effect | aPTT, anti-factor Xa activity | anti-factor Xa activity | ECT, TT |

Effects of Dabigatran on PT, aPTT and Thrombin Time

Dager W et al Ann Pharmacotherapy 2012
Potential INR response with higher DOAC serum concentrations
Determining a Course

CLARITY
Reversing Newer Oral Anticoagulants: Bleeding Patients

- Activated charcoal if recent ingestion
- 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

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<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) | • 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) | • aPCC 25 - 50 units/kg or  
  • PCC4 or PCC3 25-50 units/kg |

# Concentrated Blood Factor Products in USA

<table>
<thead>
<tr>
<th></th>
<th>rFVIIa</th>
<th>3-Factor PCC (PCC3)</th>
<th>4-Factor PCC (PCC4)</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Names</strong></td>
<td>Novo-Seven®</td>
<td>Bebulin VH® Profilnine SD®</td>
<td>Kcentra®</td>
<td>FEIBA®</td>
</tr>
<tr>
<td><strong>Factors Provided</strong></td>
<td>VII</td>
<td>II, IX, X (Some VII)</td>
<td>II, VII, IX, X</td>
<td>II, VII, IX, X</td>
</tr>
<tr>
<td><strong>Activated?</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
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</table>

Some PCC’s (Kcentra) contain Heparin
Concentrated Clotting Factors with non-Vitamin K related oral anticoagulants

- In-Vitro Data and Ex Vivo observations vary and depends on parameter measured - Results inconsistent
- Independently drives hemostasis – does not remove anticoagulant
- 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.
  - Some failures
- Unclear need to repeat dose if anticoagulant effects persist
- Bleeding patients limited to case reports/series

Dager WE et al AJHP in press
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

- rFVIIa
- PCC 3or 4
- aPCC
Idarcuizumab – Dabigatran Reversal

- Humanized Fab fragment specific to dabigatran
  - No evidence of prothrombotic effect
  - Rapid onset and dose dependent effect (aPTT, TT and ECT normalized)

Interim Phase III Analysis - RE-VERSE AD
- Prospective – 5gm dose

<table>
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<tr>
<th>A (n=51) Serious Bleeding</th>
<th>B (n=39) Urgent Procedure</th>
</tr>
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<tbody>
<tr>
<td>Mean Dabigatran Cp = 132ng/ml</td>
<td>Mean Dabigatran Cp = 114ng/ml</td>
</tr>
<tr>
<td>Reversed (Cp &lt; 20ng/ml) in minutes</td>
<td>Reversed (Cp &lt; 20 ng/ml) in minutes</td>
</tr>
<tr>
<td>Hemostatic effect at 11.4 hr (median)</td>
<td>Acceptable procedure hemostasis</td>
</tr>
</tbody>
</table>

Most remained reversed at 24 hours

Pollack CV et al. NEJM 2015;373:511-20
Idarucizumab: Duration of Dabigatran reversal


Bleeding Patient

Surgical Patient
Andexanet
Factor Xa inhibitor Antidote PRT4445

Recombinant Protein structurally similar to Factor Xa

- Acts as “decoy”, binding to Factor Xa inhibitors, thus limiting the effect of a Factor Xa inhibitor (Direct and Indirect)
- Does not cleave prothrombin to thrombin
- Ex-Vivo – Dose dependent inhibition, corrects clotting times

Andexanet: Reversing Apixaban and Rivaroxaban Activity

Siegal et al. NEJM 2015
Ciraparantag
“Universal” Factor Xa and IIa inhibitor Antidote: PER977

- Synthetic small molecule directly binds and reverses heparins, direct factor Xa- and IIa-inhibitors. Does not bind to blood coagulation factors/other blood proteins.
- Reverses anticoagulant activity as soon as 10-30 minutes after IV dose.
- Effects last at least 24 hours in most cases.
- Dose dependent complete reversal of rivaroxaban and apixaban anti-Xa activity ex vivo in human plasma. May reverse Enoxaparin and Fondaparinux.
- No evidence of prothrombotic effects.

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 a emergent therapy (e.g. ECLS or cardiopulmonary bypass)
- Availability, especially if the cost is high; Storage
Restarting Anticoagulation
Very Slippery and we may Slide

Assessment of Thrombosis vs Bleeding

↑Thrombosis Risk: Surgery, PCC, Acutely Ill
Will their be a change in the anticoagulant?

- GIB and 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

Overall Mortality

Adjusted HR= 0.67, 95% CI 0.56-0.81

Time of restarting

Am J Card 2014;113:662-68
Intracranial Hemorrhage

Figure 5. Kaplan-Meier Survival Rates of Patients With Atrial Fibrillation With and Without OAC Resumption

- OAC resumption
- No OAC resumption

Log-rank $P < .001$
Breslow $P < .001$
Tarone-Ware $P < .001$

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>OAC resumption</th>
<th>No OAC resumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>108</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>108</td>
<td>146</td>
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<tr>
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<td>99</td>
<td>106</td>
</tr>
</tbody>
</table>

Time Since Index ICH, wk
0 4 8 12 16 20 24 32 36 40 44 48 52

The ability to managing anticoagulant bleeding