Managing Bleeding in the Patient on DOACs

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Conflicts of Interest

Boehringer Ingelheim
Scientific Ad Boards/Consultant

Pfizer/Bristol Meyer Squibb
Independent Review Committee

St Jude’s (Thoratec)
Consultant
Agenda

• First steps
• Specific reversal agents
• Current status, future needs
Despite:

- Multitude of pharmacologic advantages and ease of use
- Similar or improved overall efficacy compared to warfarin
  - “non-inferior”
- Composite lower rates of major bleeding, ICH, fatal bleeding, and all-cause mortality—*without specific antidotes available*

Both patients and providers have had significant anxiety for use due to lack of antidotes
## Comparative Properties

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran Etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6-7%</td>
<td>~80%</td>
<td>~66%</td>
<td>~60%</td>
</tr>
<tr>
<td><strong>T (max) 2-3 hours</strong></td>
<td>2 h</td>
<td>2-4 h</td>
<td>3 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td><strong>Half-life 10-12 hours</strong></td>
<td>12-14 h</td>
<td>7-13 h</td>
<td>8-13 h</td>
<td>9-11 h</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>35%</td>
<td>90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice (or once) daily</td>
<td>Once (or twice) daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% renal</td>
<td>67% renal (1/2 active) 33% fecal</td>
<td>25% renal 75% fecal</td>
<td>35% renal 65% fecal</td>
</tr>
<tr>
<td><strong>Potential Drug Interactions</strong></td>
<td>Potent P-gp inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
<td>CYP 3A4 (&lt;4%) and P-gp inhibitors</td>
</tr>
</tbody>
</table>
DOAC Related Bleeding

The basics:

– Stop anticoagulant
– Assess severity
– Baseline coag tests, CBC, creatinine
– When was the last dose of drug--short half life

– Standard supportive measures
  • IV fluid, RBC, platelets, fibrinogen, antifibrinolytics
    – Massive hemorrhage or trauma protocols
  • Localization and management of specific site
DOAC Related Bleeding

- **Assess severity**
  - Minor
  - Life threatening
    - Intracranial hemorrhage, critical organ, massive hemorrhage, hemodynamic instability
    - Requires emergent major surgery
  - Moderate to severe

- **Need for immediate reversal of anticoagulation?**
  - Can you support patient or delay surgery until anticoagulant effects wear off?
  - Risk of bleeding versus restoring to baseline pro-thrombotic state
## Coagulation Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Scenario</th>
</tr>
</thead>
</table>
|               | Exclude Relevant Anticoagulant Effect  | Detect Over-Anticoagulation  
|               |                                        | Monitor Drug Activity |
| Dabigatran    | TT, aPTT                               | aPTT, TT, ECA, ECT  
|               |                                        | Dilute TT, ECA, ECT  
| Rivaroxaban   | anti-Xa<sup>1</sup>                     | PT<sup>4</sup>, anti-Xa<sup>2</sup>  
|               |                                        | anti-Xa<sup>2</sup>  
| Apixaban      | anti-Xa<sup>1</sup>                     | anti-Xa<sup>2</sup>  
|               |                                        | anti-Xa<sup>2</sup>  
| Edoxaban      | anti-Xa<sup>1</sup>                     | anti-Xa<sup>2</sup>  
|               |                                        | anti-Xa<sup>2</sup>  

<sup>1</sup> Anti-Xa assays with LMWH standards can be used to exclude the presence of drug, but not to quantify drug level  
<sup>2</sup> Drug-specific anti-Xa  
<sup>3</sup> Includes HEMOCLOT assay  
<sup>4</sup> If calibrated in laboratory using rivaroxaban standard
DOAC Antidotes

• Trial Design:

• Unethical to randomize bleeding patients with no alternative reversal agents

• Unethical to use in anticoagulated patients who are not bleeding—thrombosis risk
Idarucizumab

- PRAXBIND = idarucizumab
  - 350 x higher affinity for dabigatran than dabigatran has for thrombin

- FDA approved Oct 16, 2015
  - EMA approval Nov 2016
  - 283 healthy volunteers participated in 3 early studies
  - RE-VERSE AD: phase III study
RE-VERSE AD

**Group A:** Uncontrolled bleeding + dabigatran-treated

**Group B:** Emergency surgery or procedure + dabigatran-treated

5 g idarucizumab (two separate infusions of 2.5 g)

Reverses up to the 99th percentile of dabigatran levels measured in RE-LY

0–15 minutes

90 days follow-up

0–24 hours

Hospital arrival

Pre-1st vial

Pre-2nd vial

~20 min 1 h 2 h 4 h 12 h 24 h 30 d 90 d

Blood samples

N=300

Interim analysis of 90 patients reported in NEJM August 2015
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>n=51</td>
<td>n=39</td>
<td>N = 90</td>
</tr>
<tr>
<td>Indication for dabigatran stroke prevention in A Fib</td>
<td>47/51</td>
<td>39/39</td>
<td>86/90</td>
</tr>
<tr>
<td>Age median, range (years)</td>
<td>77 (48–93)</td>
<td>76 (56–93)</td>
<td>76.5 (48–93)</td>
</tr>
<tr>
<td>Creatinine clearance median, range (mL/min)</td>
<td>51.5 (15.8–186.8)</td>
<td>60.1 (11.5–171)</td>
<td>57.6 (11.5–186.8)</td>
</tr>
<tr>
<td>Patient-reported time since last dose, median (hours)</td>
<td>15.2</td>
<td>16.6</td>
<td>15.4</td>
</tr>
<tr>
<td>Elevated dTT at baseline</td>
<td>40/51</td>
<td>28/39</td>
<td>68/90</td>
</tr>
<tr>
<td>Elevated ECT at baseline</td>
<td>47/51</td>
<td>34/39</td>
<td>81/90</td>
</tr>
<tr>
<td>Elevated dTT or ECT at baseline</td>
<td>47/51</td>
<td>34/39</td>
<td>81/90</td>
</tr>
</tbody>
</table>
RESULTS: Primary endpoint in Group A
Reversal of dabigatran with idarucizumab
**Primary endpoint:** maximal reversal of dabigatran within 4 hours based on lab tests:
median maximal reversal 100%

**Secondary endpoints and safety:**

- “Normal” hemostasis in >90% undergoing surgery
- Hemostasis achieved by 11 hours in bleeding patients
- 18 deaths, half > 96 hours after idarucizumab, due to underlying conditions
- 5 thrombotic events, 1 within 72 hrs
- On presentation:
  - 24% normal dTT  10% normal ECT
Annexa = andexanet alpha

- “decoy” recombinant \textbf{FXa} molecule with mutation in catalytic site, lacks Gla domain
- “universal” Fxai antidote
- Studies to date in healthy volunteers
ANNEXA Studies

Healthy older volunteers age 50-75 years

**Annexa-A:** apixaban 5 mg bid x 3.5 days

- **n=48** andexanet 400 mg bolus + 480 mg ci
- **n=17** placebo

**Annexa-R:** rivaroxaban 20 mg qd x 4 days

- **n=53** andexanet 800 mg bolus + 960 mg ci
- **n=27** placebo
• Andexanet rapidly reversed anticoagulant effects of factor Xa inhibitors within 2-5 minutes.
  – 80% or greater reversal of anti-Xa activity
  – Decreased plasma concentrations of fXai
  – Restored thrombin generation

• No AE, no thrombotic events— healthy volunteers

• Antibodies in 17%
  – Non-neutralizing
  – None to native X or Xa

• ANNEXA-4: phase 3b/4 “real world” study
  – In progress, for Xai and enoxaparin
  – Bleeding patients only, not for surgery within 12 hours
Antidote: ciraparantag

- Reversal agent for ALL anticoagulants:
  - DTI, Xai, LMWH, fondaparinux

- PER977: aripazine 500 Da cationic molecule binds through non-covalent bonds to active site

- Ciraparantag

- Dose dependent decrease in whole blood clotting time following edoxaban in healthy volunteers

NEJM Nov 2014
## Non-specific Reversal Approaches

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral charcoal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemoperfusion with charcoal</td>
<td>Possible</td>
<td>Possible</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>FFP</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Activated rFVIIa</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>4 factor PCC</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Activated PCC</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Use of Antidotes

How should targeted reversal agents be used?

Life-threatening bleeding
Emergency Surgery
Anticipated delayed clearance and bleeding

Not for use in:
Elective surgery or surgery that can be delayed
Elevated coag tests but no bleeding
Bleeding managed with routine supportive care
SUMMARY

• For any bleeding patient:

  Initial assessment and stabilization

Anticoagulation reversal—yes or no?
  • Dabigatran—idarucizumab and supportive care
  • Xai—4PCC with aggressive supportive care

Requires continued assessment
  • Giving the first dose of a specific reversal agent is easy
  • Continued monitoring, serial evaluation, supportive and adjunctive care are necessary
SUMMARY

• Specific reversal agents are here. They work.
• How best to use them requires ongoing optimization:
  • Dosing
  • Monitoring
  • Efficacy and safety data
  • Oversight
## Criteria for use: Recommendations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Critical life-threatening bleeding</th>
<th>Less severe bleeding</th>
<th>Emergency surgery/procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>For critical life-threatening bleeding defined as bleeding that causes hemodynamic compromise, threatens a vital organ (e.g., central nervous system, ocular, spinal cord, intrapulmonary, retroperitoneal, or intramuscular with compartment syndrome) or may result in disability, that does not respond to conventional measures</td>
<td>For less severe bleeding</td>
<td>Emergency surgery or urgent procedures that cannot be delayed for at least 8 hours and for which immediate hemostasis is required</td>
</tr>
<tr>
<td><strong>Notification</strong></td>
<td>The designated hospital service at your institution (e.g., Hematology, Blood Bank, Cardiovascular Medicine, Hemostatic and Antithrombotic Stewardship, etc.), must be notified when idarucizumab is requested</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time since last dose of dabigatran</strong></td>
<td>Known drug ingestion</td>
<td>i. CrCl 50 ml/min or higher: less than 24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii. CrCl less than 50 ml/min: less than 48 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline laboratory tests</strong></td>
<td>Order PTT and TT in all patients</td>
<td>One of the following is significantly elevated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>i. PTT [in trial median baseline PTT ~50s]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii. TT [in trial median baseline TT ~60s]</td>
<td></td>
</tr>
<tr>
<td><strong>Idarucizumab</strong></td>
<td>Administer immediately</td>
<td>Consult with designated service at your institution regarding use</td>
<td></td>
</tr>
</tbody>
</table>
Rapid reversal in the bleeding patient is logical but whether it will translate into improved outcomes is uncertain.
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