## Update on Reversal Agents for Oral Anticoagulants

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### Patient Characteristic

<table>
<thead>
<tr>
<th>DOAC (n=460)</th>
<th>Warfarin (n=1,542)</th>
<th>Standardized Diff/ P=Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (yr)</td>
<td>81.19</td>
<td>87.4</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>4.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>15.2</td>
<td>26.6</td>
</tr>
<tr>
<td>Concurrent antithrombotic agent (%)</td>
<td>26.7</td>
<td>39.5</td>
</tr>
<tr>
<td>ASA</td>
<td>9.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Other NSAID</td>
<td>25.2</td>
<td>26.6</td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>6.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Anatomic site of major bleeding (%)</td>
<td>72.9</td>
<td>77.8</td>
</tr>
<tr>
<td>Intracranial (any)</td>
<td>81.21</td>
<td>81.21</td>
</tr>
<tr>
<td>GI (any)</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Hematoma w/o compartment syndrome</td>
<td>26.6</td>
<td>26.6</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>9.1</td>
<td>9.1</td>
</tr>
</tbody>
</table>

### Reversal Agent

<table>
<thead>
<tr>
<th>DOAC (n=460)</th>
<th>Warfarin (n=1,542)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K (%)</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Tranexamic acid (%)</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Any blood product (%)</td>
<td>52.0</td>
<td>52.0</td>
</tr>
<tr>
<td>FFP (%)</td>
<td>12.4</td>
<td>12.4</td>
</tr>
<tr>
<td>pRBC (%)</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Prothrombin complex concentrate (PCC, %)</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>aPCC (%)</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>rFVIIa (%)</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Platelets (%)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
</tr>
</tbody>
</table>

### Treatment of Vitamin K Antagonist-Associated Bleeding

**Clinically Relevant Non-Major Bleeding**

- **General Measures**
  - VKA withdrawal
  - Local hemostasis
  - Volume replacement

- Vitamin K 1-2 mg slow IV

**Major Bleeding**

- **General Measures and Transfusion as needed**
  - Vitamin K 5-10 mg slow IV
  - 4-Factor PCC Administration
    - INR 2 - 4 25 U/kg
    - INR 4 - 6 50 U/kg
  - PCC (IU) 5,000 (2-4)
  - FFP 1-2 units

<table>
<thead>
<tr>
<th>Cost</th>
<th>4-Factor PCC (45-100) $</th>
<th>Plasma (5-10) $</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 kg patient</td>
<td>$2200-$4400</td>
<td>$1600/patient</td>
</tr>
</tbody>
</table>

**References**

- Xu, Chest 2017
- Yates, J Thromb Haemost 2015
- Shander, Vox Sang 2016
- Sarode, Circulation 2013
Direct Thrombin Inhibitors and Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Non-valve atrial fibrillation</td>
<td>Valve thrombosis in TAVR/TSK</td>
<td>Non-valve atrial fibrillation</td>
<td>Valve thrombosis in TAVR/TSK</td>
<td>Non-valve atrial fibrillation</td>
</tr>
<tr>
<td>Peak effect (hrs)</td>
<td>1-3</td>
<td>2-4</td>
<td>3-4</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>7-17</td>
<td>5-9</td>
<td>8-15</td>
<td>10-14</td>
<td>19-27</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80% excreted in urine</td>
<td>33%</td>
<td>25%</td>
<td>50%</td>
<td>13%</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>3.11%/yr</td>
<td>3.6%/yr</td>
<td>2.13%/yr</td>
<td>2.75%/yr</td>
<td>0.67%/yr (passive)</td>
</tr>
</tbody>
</table>

Reversal Agents for DOACs

**Idarucizumab**
- Structure/mechanism: Monoclonal antibody Fab fragment against dabigatran
- FDA indications: For patients treated with dabigatran when reversal is needed for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding
- Dosing:
  - Initial IV Bolus: 5 g
  - Follow-On IV Infusion: 5 g
- Precaution: Thromboembolic risk, re-elevation of coagulation parameters, hypersensitivity
- Cost: AWP = $3600-$3800 per dose

- Anti-Xa activity 89%
- 67 pts (avg 77 yr) with acute major bleeding (only 6% enoxaparin)
  - GI bleed 49%
  - ICH 42%
  - Other 9%
  - Good/excellent hemostasis (after 12 hrs) in 79%
  - Death 15%
  - Thromboembolism 18%


**Andexanet alfa**
- Structure/mechanism: Recombinant truncated decoy human F Xa variant
- FDA indications: For patients treated with rivaroxaban and apixaban, when reversal is needed due to life-threatening or uncontrolled bleeding
- Dosing:
  - Low Dose: 300 mg at 30 mg/min
  - High Dose: 600 mg at 60 mg/min
- Precaution: Rebound FXa activity after infusion completed (reversible binding to FXa inhibitor)


**Reversal Agents for DOACs**

- **Andexanet alfa**
  - FDA indications: For patients treated with marina and apixaban, when reversal is needed due to life-threatening or uncontrolled bleeding
  - Dosing:
    - Low Dose: 400 mg at 30 mg/min
    - High Dose: 800 mg at 60 mg/min
  - Cost: AWP = $3300 per 100 mg vial
  - Low Dose Bolus + Infusion: $28,800
  - CMS additional payment $14K - $15K

Andexanet alfa

**Structure/mechanism**
Recombinant truncated decoy human F Xa variant

**FDA indications**
For patients treated with rivaroxaban and apixaban, when reversal is needed due to life-threatening or uncontrolled bleeding

**Dosing**
- **Low Dose**
  - Initial IV Bolus: 400 mg at 30 mg/min
  - Follow-On IV Infusion: 4 mg/min for up to 120 min
- **High Dose**
  - Initial IV Bolus: 800 mg at 30 mg/min
  - Follow-On IV Infusion: 8 mg/min for up to 120 min

**Half-life (hrs)**
5-7 hrs

**Cost**
- AWP = $3300 per 100 mg vial
  - Low Dose Bolus + Infusion: $26,400
  - High Dose Bolus + Infusion: $59,400
  - CMS additional payment $14K - $15k

**Precaution**
Rebound FXa activity after infusion completed (reversible binding to FXa inhibitor)

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Management of patients with active bleeding on oral anticoagulants (DOAC and VKA)

**Antithrombotic Therapy for Atrial Fibrillation**

- Minor bleeding
  - NOAC: Delay 1 dose or 1 day
  - VKA: Delay until INR ≤2.5

- Moderate bleeding
  - Delay or discontinuie NOAC or VKA
  - Mechanical compression/intervention to establish hemostasis
  - Transfusion: PLTs, FFP (as plasma required, platelets as necessary)
  - Consider adding vitamin K (1-10 mg/day)

- Severe or life-threatening bleeding
  - NOAC: Consider absorption-activated charcoal if last dose 2-4 h
  - VKA: Consider activated charcoal if last dose 2-4 h

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Management of patients with active bleeding on oral anticoagulants (DOAC and VKA)

Lip, Chest 2018