STRATEGIES FOR ANTICOAGULATION REVERSAL FOR DIRECT ORAL ANTICOAGULANTS (DOAC)

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DISCLOSURES

• Received funding for research from Daiichi Sankyo
LEARNING OBJECTIVES

• Summarize clinical controversies surrounding the use of blood products for anticoagulation reversal.

• Explain the advantages and disadvantages associated with using blood products as the primary treatment approach for anticoagulation reversal.
STRATEGIES FOR ANTICOAGULATION REVERSAL FOR DOAC

OUTLINE

- DOAC: mechanism of action and pharmacokinetics
- Approved indications for the use of DOAC
- Anticoagulation reversal strategies
- Consensus guideline statements for the use of plasma products in DOAC reversal
- Review of clinical data on the use of prothrombin complex concentrates
- Case discussion
- Summary/rebuttal
DOAC: MECHANISM OF ACTION

DOAC: PHARMACOKINETICS

Adapted from Heidbuchel H et al. Europace 2013;15:625-651

**Dabigatran**
- Esterase-mediated hydrolysis
- Bio-availability 3–7%
- **P-gp** inhibitors (↑ exposure): ketoconazole, quinidine, amiodarone, verapamil.
- Inducers (↓ exposure): Rifampin

**Rivaroxaban**
- Bio-availability: 66% (without food) >80% (with food)
- $t_{1/2} = 5-9h$ (young) 11-13h (elderly)
- **P-gp** inhibitors (↑ exposure)
- Inducers (↓ exposure): Rifampin, St. John’s wort.

**Apixaban**
- Bio-availability 50%
- $t_{1/2} = 12h$
- **P-gp** inhibitors (↑ exposure): ketoconazole, clarithromycin, ritonavir.
- Inducers (↓ exposure): Rifampin

**Edoxaban**
- Bio-availability 62%
- $t_{1/2} = 9-11h$
- **CYP 3A4** inhibitors (↑ exposure): ketoconazole, clarithromycin, ritonavir.
- Inducers (↓ exposure): Rifampin, St. John’s wort.
Approved Indications for the Use of DOAC

- Primary thromboprophylaxis in knee/hip surgery: dabigatran, rivaroxaban, apixaban
- Primary thromboprophylaxis in hospitalized medically ill: betrixaban
- Non valvular atrial fibrillation: dabigatran, rivaroxaban, apixaban, edoxaban
- Venous thromboembolism treatment: dabigatran, rivaroxaban, apixaban, edoxaban
ANTICOAGULATION REVERSAL STRATEGIES FOR DOAC

- Specific antidotes:
  - Idarucizumab
  - Andexanet alfa

- Plasma and derived products
  - Fresh frozen plasma
  - Prothrombin complex concentrate (PCC)
    - FEIBA
    - 4-factor PCC

- Other hemostatic agents
  - Recombinant factor VII (rFVIIa)
  - Antifibrinolytics
Anti-inhibitor coagulant complex approved for the control and prevention of bleeding in hemophilia A/B patients with inhibitors: “bypassing” agent

- Intravenous use after reconstitution

- Human plasma-derived: non activated factors II, IX, X activated factor VII

- Recommended dose: 50-100 units per kg
ANTICOAGULATION REVERSAL STRATEGIES FOR DOAC: PCC

4 FACTOR-PROTHROMBIN COMPLEX CONCENTRATE

- Human prothrombin complex approved for the urgent reversal of acquired coagulation factor deficiency by vitamin K antagonist (warfarin) in the setting of major bleeding or urgent invasive procedure
- Intravenous use after reconstitution
- Human plasma-derived: factors II, VII, IX, X protein C and S antithrombin III albumin
- Recommended dose: 25-50 units per kg (of factor IX)
- Maximum single dose: 5,000 units
INTRACRANIAL BLEEDING AND DOAC

Anti-Xa inhibitors:

- “We suggest administering a 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure”

- “We suggest administering 4-factor PCC or activated PCC over rFVIIa because of the lower risk of adverse thrombotic events.

Direct thrombin inhibitors:

- We suggest administering aPCC (50 units/kg) or 4-factor PCC (50 units/kg) to patients with intracranial hemorrhage associated with direct thrombin inhibitors if idarucizumab is not available”
MAJOR BLEEDING AND DOAC

- “In patients with dabigatran-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with idarucizumab 5 g IV. If idarucizumab is not available, we suggest treatment with APCC 50 units/kg IV”

- “In patients with rivaroxaban-associated or apixaban-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with andexanet alfa dosed according to the US FDA label. If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units”

- “In patients with edoxaban-associated or betrixaban-associated major bleeding in whom a reversal agent is warranted, we suggest off-label treatment with either high dose andexanet alfa (800 mg bolus given at 30 mg/min followed by a continuous infusion of 8 mg/min for up to 120 min) or four-factor PCC 2000 units”

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Clinical scenario</th>
<th>DOAC</th>
<th>Hemostatic agent</th>
<th>Laboratory parameter</th>
<th>Impact on laboratory parameter</th>
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</thead>
<tbody>
<tr>
<td>Pernod et al., 2012</td>
<td>10</td>
<td>Healthy volunteers</td>
<td>Dabigatran 150 mg Rivaroxaban 20 mg</td>
<td>Novoseven 120 ug/kg aPCC (80 U/kg) 4-PCC (25 U/kg)</td>
<td>Thrombin generation (CAT)</td>
<td>Partial correction</td>
<td>Not assessed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* 2 hours after DOAC ingestion</td>
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</tr>
<tr>
<td>Dunkley et al., 2012</td>
<td>8</td>
<td>Healthy volunteers</td>
<td>Dabigatran</td>
<td>aPCC (50, 75, 100 U/kg)</td>
<td>Thrombin generation (CAT)</td>
<td>At 50 U/kg - restoration</td>
<td>Not assessed</td>
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<tr>
<td>Dager et al., 2019</td>
<td>64</td>
<td>Retrospective DOAC-bleeding (28/64 ICH)</td>
<td>Rivaroxaban (28) Apixaban (20) Dabigatran (16)</td>
<td>aPCC (20-50 U/kg) * 2 ICH received a second dose</td>
<td>Ecarin clotting assay Anti-Xa</td>
<td>Partial correction Heterogeneous report</td>
<td>VTE / Mortality * At 30 days</td>
</tr>
<tr>
<td>Mao et al., 2016</td>
<td>11</td>
<td>Retrospective DOAC-bleeding</td>
<td>Rivaroxaban (8) Apixaban (3)</td>
<td>aPCC (20 U/kg) (within 48 hours from DOAC or unknown time of last dose AND prolonged PTT)</td>
<td>INR/aPTT (12 hours post-aPCC)</td>
<td>INR &lt; 1.5 (5/6) aPTT &lt; 35&quot; (4/4)</td>
<td>VTE/Bleeding expansion/ Mortality * At 30 days</td>
</tr>
<tr>
<td>Frontera et al., 2015</td>
<td>5</td>
<td>Prospective AF-ICH</td>
<td>Rivaroxaban (3) Apixaban (1) Dabigatran (1)</td>
<td>aPCC (50 U/kg) within 48 hours from DOAC (median time: 13 h)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Bleeding expansion (at 6h) Rankin Scale (3 months)</td>
</tr>
<tr>
<td>Schulman et al., 2017</td>
<td>32</td>
<td>Prospective nested cohort of major bleeding events in AF/VTE trials</td>
<td>Dabigatran</td>
<td>aPCC (50 U/kg) with a repeat dose after 1 hour as needed (median time: 14h) * 4 patients required a second dose aPCC</td>
<td>aPTT Thrombin time</td>
<td>Not reported</td>
<td>Clinical hemostasis/VTE/ Mortality * At 30 days</td>
</tr>
</tbody>
</table>
**Good clinical hemostasis**

**VTE**

**Overall mortality**

**Bleeding-related death**

**VTE-related death**

**ICH expansion**

**Mortality in ICH**

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**Dager et al., 2019**

**Frontera et al., 2015**

**Mao et al., 2016**

**Schulman et al., 2017**
## Clinical Studies Using 4 Factor-Prothrombin Complex Concentrate in DOAC Reversal

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<tbody>
<tr>
<td>Eerenberg et al., 2011</td>
<td>12</td>
<td>Healthy volunteers</td>
<td>Rivaroxaban 20 mg BID Dabigatran 150 mg BID</td>
<td>4-PCC (50 U/kg) (after 2 ½ days of DOAC)</td>
<td>PT (Rivaroxaban) Thrombin generation (ETP) aPTT (dabigatran) Ecarin clotting time Thrombin time</td>
<td>PT normalization ETP restored (rivaroxaban) Unchanged aPTT Thrombin time remain unmeasurable Ecarin clotting time unchanged</td>
<td>Minor bleeding (6/12)</td>
</tr>
<tr>
<td>Levi et al., 2014</td>
<td>35</td>
<td>Healthy volunteers</td>
<td>Rivaroxaban 20 mg BID</td>
<td>4-PCC versus 3-PCC versus control (4 hours after 5 days of DOAC)</td>
<td>PT aPTT Thrombin generation Calibrated anti-Xa</td>
<td>PT decrease within 30’ (4-PCC) Unchanged aPTT Thrombin generation restored after 2-4h (AUC) by 4- and 3-PCC Unchanged anti-Xa</td>
<td>Bleeding events (3/35) VTE (0/35)</td>
</tr>
<tr>
<td>Barco et al., 2015</td>
<td>6</td>
<td>Healthy volunteers</td>
<td>Rivaroxaban 15 mg BID</td>
<td>4-PCC 37.5 U/kg versus 25 U/kg versus placebo (3 hours after 2 days of DOAC)</td>
<td>Thrombin generation (ETP) PT Calibrated anti-Xa</td>
<td>Modest increment in ETP PT decreased within 15’ Unchanged anti-Xa * Effects of PCC 37.5 U/kg sustained at 24 hours</td>
<td>Minor bleeding (3/6)</td>
</tr>
<tr>
<td>Levy et al., 2017</td>
<td>145</td>
<td>Healthy volunteers</td>
<td>Rivaroxaban 20 mg BID</td>
<td>4-PCC (50 U/kg) versus tranexamic acid (1 gr IV-10’) versus placebo (after 4 days of DOAC)</td>
<td>PT Thrombin generation</td>
<td>Partial PT correction with 4-PCC Thrombin generation restored * Observed only with PCC</td>
<td>Unchanged bleeding volume and duration after punch biopsy thigh (before DOAC and after PCC)</td>
</tr>
<tr>
<td>Cheung et al., 2015</td>
<td>6</td>
<td>Healthy volunteers</td>
<td>Apixaban 10 mg BID</td>
<td>4-PCC 37.5 U/kg versus 25 U/kg versus placebo (3 hours after 3 days of DOAC)</td>
<td>Thrombin generation (ETP) PT</td>
<td>Modest increment in ETP PT correction within 15’ * Effects of PCC 37.5 U/kg sustained at 24 hours</td>
<td>Bleeding events (1/6)</td>
</tr>
<tr>
<td>Kraft et al., 2016</td>
<td>12</td>
<td>Healthy volunteers</td>
<td>Apixaban 5 mg BID</td>
<td>4-PCC (25 U/kg) (3 hours after 5 doses of DOAC)</td>
<td>Thrombin generation PT aPTT anti-Xa</td>
<td>Increment in peak thrombin and endogenous generation PT normalization aPTT and anti-Xa unchanged</td>
<td>Not reported</td>
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<td>Quintana et al., 2013</td>
<td>5</td>
<td>Retrospective acute GI bleeding</td>
<td>Dabigatran 110 mg BID</td>
<td>4-PCC</td>
<td>aPTT</td>
<td>Unchanged</td>
<td>Bleeding cessation</td>
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<tr>
<td>* All treated for AF</td>
<td></td>
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<tr>
<td>Sheikh-Taha et al., 2018</td>
<td>29</td>
<td>Retrospective DOAC-major bleeding (21/29 ICH)</td>
<td>* 23/29 AF</td>
<td>4-PCC (50 U/kg)</td>
<td>PT</td>
<td>Not reported</td>
<td>Clinical hemostasis Mortality</td>
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<td>(21/29 ICH)</td>
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<td>Smith et al., 2019</td>
<td>31</td>
<td>Retrospective DOAC-major bleeding (18/31 ICH)</td>
<td>Apixaban (17) Rivaroxaban (14)</td>
<td>4-PCC (25-50 U/kg) (median time: 2 h post admission)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Clinical hemostasis Mortality Thrombotic events Cost * During hospital stay [4-10] days</td>
</tr>
<tr>
<td>Tao et al., 2019</td>
<td>43</td>
<td>Retrospective cases emergent DOAC-reversal (16/43 ICH)</td>
<td>Apixaban (22) Rivaroxaban (21) * AF (30/43)</td>
<td>4-PCC (25-50 U/kg)</td>
<td>PT aPTT</td>
<td>PT normalization (6/10)</td>
<td>Thrombotic events * Within 14 days post PCC</td>
</tr>
<tr>
<td>Arachchillage at al., 2019</td>
<td>80</td>
<td>Retrospective DOAC-major bleeding (46/80 ICH)</td>
<td>Apixaban (40) Rivaroxaban (40) * AF (65/80)</td>
<td>4-PCC (20-50 U/kg)</td>
<td>PT aPTT Calibrated anti-Xa</td>
<td>Not reported</td>
<td>Clinical hemostasis Thrombotic events Mortality * At 30 days post PCC</td>
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STRATEGIES FOR ANTICOAGULATION REVERSAL FOR DOAC

CLINICAL STUDIES USING 4 FACTOR-PROTHROMBIN COMPLEX CONCENTRATE IN DOAC BLEEDING

CLINICAL OUTCOMES

<table>
<thead>
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<th>Outcome</th>
<th>Rate (%)</th>
</tr>
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<tr>
<td>Good clinical hemostasis</td>
<td></td>
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<tr>
<td>VTE</td>
<td></td>
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<td>Overall mortality</td>
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*Quintana et al., 2013
Sheikh-Taha et al., 2018
Smith et al., 2019
Tao et al., 2019
Arachchillage at al., 2019*
PRACTICAL CONSIDERATIONS FOR PREVENTION OF BLEEDING DURING DOAC THERAPY

- Renal insufficiency
  Avoid use if Cr Cl < 30 ml/min

- Liver dysfunction
  Avoid in significant liver dysfunction (i.e.: advanced cirrhosis)
  Avoid if transaminases > 2 ULN

- Absorption and drug interactions

- Not recommended if upper GI malignancy, malabsorption, intractable nausea.

- Dose adjustment/avoid if concurrent modulators of CYP 3A4

- Dose adjustment if other concurrent P-glycoprotein substrates
PRACTICAL CONSIDERATIONS FOR PREVENTION OF BLEEDING DURING DOAC THERAPY

- Severe myelosuppression and thrombocytopenia
  Not recommended if platelet count < 100K/uL
  Avoid if anticipated severe cytopenias, myeloablation

- High risk of bleeding patients
  Untreated brain metastases (renal cell/melanoma)
  Active GI / GU malignancies
STRATEGIES FOR ANTICOAGULATION REVERSAL FOR DOAC: CASE DISCUSSION

PRACTICAL CONSIDERATIONS FOR MANAGEMENT OF BLEEDING DURING DOAC THERAPY

Risk Stratification

Minor

1. Local hemostasis.
2. Consider anticoagulant withdrawal.

Moderate

1. Local measures.
2. Anticoagulant withdrawal.
4. Blood product transfusion

Severe

Volume resuscitation
Blood product transfusion
Local measures
Anticoagulant withdrawal

Reversal agent
Idarucizumab (dabigatran)
Andexanet (anti-Xa)

Reversal agent not available:
Activated charcoal (< 2 hours since ingestion)
Consider aPCC (80 U/kg) or 4 factor-PCC (50U/kg)
Hemodialysis if CrCl < 30 mL/min (dabigatran)

Adapted from Siegal et al., BLOOD, 2014
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<th>Characteristic</th>
<th>PCC</th>
<th>Andexanet alfa</th>
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<tr>
<td>Availability</td>
<td>Readily available at most hospitals</td>
<td>Limited availability</td>
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<td>Rate of Effective Management of Major Bleeding (95% CI)</td>
<td>75% (53% to 97%)</td>
<td>83% (75% to 89%)</td>
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<td>Rate of Thromboembolic Complications (95% CI)</td>
<td>5% (1% to 9%)</td>
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<td>Cost</td>
<td>$1.27 per unit (USD) For 2000 units 4F-PCC $2,540</td>
<td>$3,300 per vial of 100 mg Low dose (9 vials) $29,700, high dose (18 vials) $59,400</td>
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LEARNING ASSESSMENT QUESTION #1

• The following are associated with the incidence of bleeding complications during direct oral anticoagulant therapy, except:
  a) Upper gastrointestinal diseases, such as peptic ulcer disease and malignancy
  b) Concurrent use of p-glycoprotein inhibitors
  c) Concurrent use of cytochrome CYP3A4 inhibitors
  d) Lack of routine anticoagulant effect monitoring
LEARNING ASSESSMENT QUESTION #1

• The following are associated with the incidence of bleeding complications during direct oral anticoagulant therapy, except:
  a) Upper gastrointestinal diseases, such as peptic ulcer disease and malignancy
  b) Concurrent use of p-glycoprotein inhibitors
  c) Concurrent use of cytochrome CYP3A4 inhibitors
  d) **Lack of routine anticoagulant effect monitoring**
LEARNING ASSESSMENT QUESTION #2

• The use of coagulopathy reversal strategies is desirable in all bleeding scenarios during the use of direct oral anticoagulants
  a) True
  b) False
• The use of coagulopathy reversal strategies is desirable in all bleeding scenarios during the use of direct oral anticoagulants
  a) True
  b) False
THANKS FOR YOUR ATTENTION
## STRATEGIES FOR ANTICOAGULATION REVERSAL FOR DOAC: SUMMARY/REBUTTAL

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