Management of Bleeding in Patients on Oral Anticoagulants: Factors (II, VII, IX, X) to Consider

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Pharmacy Grand Rounds
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Abbreviations

- ACC = American College of Cardiology
- anti-Xa = anti-factor Xa
- aPCC = activated prothrombin complex concentrate
- aPTT = activated partial thromboplastin time
- CAD = coronary artery disease
- DOAC = direct oral anticoagulant
- ECA = ecarin chromogenic assay
- ECT = ecarin clotting time
- FFP = fresh frozen plasma
- INR = International Normalized Ratio
- PCC = prothrombin complex concentrate
- PT = prothrombin time
- RBC = red blood cells
- TT = thrombin time
- VKA = vitamin K antagonist
Objectives

• Review 2017 ACC recommendations for management of bleeding in patients on oral anticoagulants

• Determine appropriate treatment for reversal of anticoagulation based on patient-specific factors

• Evaluate novel therapies for reversal of direct factor Xa inhibitors

ACC = American College of Cardiology
Anticoagulation

- Over 6 million patients in U.S. on oral anticoagulants
- DOAC use increasing for most common anticoagulation indications
  - Favorable risk-benefit profiles
  - Improved patient convenience and adherence
  - Emergence of reversal agents
- Bleeding-related mortality
  - Warfarin: 11%
  - DOACs: 7.6%


DOAC = direct oral anticoagulant
2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

ACC = American College of Cardiology
Definitions

- Major bleed
  - Hemodynamic compromise
    MAP < 65
  - Anatomically critical site
    Intracranial, spinal and thoracic, intra-abdominal, retroperitoneal, intraarticular, intramuscular
  - Hemoglobin decrease ≥ 2 g/dL
  - Transfusion of ≥ 2 units packed RBC

- Non-major bleed
  - All bleeds not classified as major

MAP = mean arterial pressure
RBC = red blood cells

Laboratory Measurement

- VKAs
  - INR or prothrombin time
- DOACs
  - Depends on specialized assay availability
  - Dilute thrombin time
  - Ecarin clotting time
  - Ecarin chromogenic assay
  - Anti-factor Xa
  - Activated partial thromboplastin time
  - Prothrombin time
## Laboratory Measurement of DOACs

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Preferred Test</th>
<th>Alternative Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Dilute TT, ECT, ECA</td>
<td>TT, aPTT</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Anti-Xa</td>
<td>PT</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Anti-Xa</td>
<td>PT</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-Xa</td>
<td>PT</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Anti-Xa</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Anit-Xa = anti-factor Xa  
aPTT = activated partial thromboplastin time  
DOAC = direct oral anticoagulant  
ECA = ecarin chromogenic assay  
ECT = ecarin clotting time  
PT = prothrombin time  
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Assessment Question #1

• Which of the following would constitute a major bleed according to the 2017 ACC Expert Consensus Decision Pathway?

a. Hemoglobin decrease of 1 g/dL from baseline
b. Mean arterial pressure of 68 mm Hg
c. Administration of 1 unit of packed red blood cells is required
d. Site of bleed is retroperitoneal
Assessment Question #1

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a. Hemoglobin decrease of 1 g/dL from baseline
b. Mean arterial pressure of 68 mm Hg
c. Administration of 1 unit of packed red blood cells is required
d. **Site of bleed is retroperitoneal**
Managing Non-Major Bleeds
General Recommendations

- Determine if oral anticoagulant and antiplatelet agents should be held
- Apply local measures to control bleeding
- Routine reversal of anticoagulation not recommended

Managing Major Bleeds
General Recommendations

- Hold anticoagulants and antiplatelet agents
- Obtain large-bore IV access
- Apply local measures to control bleeding
- Volume resuscitation
- Correct hypothermia and acidosis
- Reverse anticoagulation
- Consult appropriate service
Supportive Measures

• Transfusion when appropriate
  • RBC transfusions to maintain hemoglobin \( \geq 7 \text{ g/dL} \)
    • More liberal transfusion in underlying CAD
  • Platelets to maintain \( \geq 50 \times 10^9/\text{L} \)
  • Cryoprecipitate to maintain fibrinogen >100 mg/dL
  • \( \geq 3 \) units of packed RBCs within 1 hour
    • Massive transfusion protocol

CAD = coronary artery disease
RBC = red blood cells

Committee on Trauma of the American College of Surgeons. 2015.
Other Considerations

• Calcium if ionized calcium is abnormal
• Tranexamic acid within first 3 hours
• Severe renal dysfunction
  • Laboratory evaluation to detect residual anticoagulant activity
  • Risk for uremia-associated platelet dysfunction
    • Desmopressin
    • Cryoprecipitate
    • Hemodialysis

Department of Surgical Education. Antiplatelet Agent Reversal in Adults with Traumatic Intracranial Hemorrhage. 2017.
Other Considerations

- Hepatic dysfunction may be associated with coagulopathy
  - TEG may be of value
- Portal hypertension/esophageal varices
  - Use plasma cautiously
- Patients on antiplatelet agents
  - Several assays to evaluate platelet function
  - Limited evidence to support routine administration of platelets
Reversing Warfarin
Strategies for Reversal of Warfarin

- Vitamin K
- Prothrombin Complex Concentrate
- Plasma
Vitamin K

- Dose-dependent reduction
- Oral or IV administration
- Does not result in immediate correction of coagulopathy
- Must be accompanied by PCC or FFP for major bleeds

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>Oral</th>
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</thead>
<tbody>
<tr>
<td>Time to reduction of</td>
<td>4 to 6 hours</td>
<td>18 to 24 hours</td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FFP = fresh frozen plasma
INR = International Normalized Ratio
PCC = prothrombin complex concentrate

Prothrombin Complex Concentrates

- 3-factor PCC = Factors II, IX, X and Protein C, S
- 4-factor PCC = Factors II, VII, IX, X and Protein C, S
- Only 4-factor PCCs are licensed for rapid warfarin reversal
  - Do not require blood type testing
  - Can be stored at room temperature (as lyophilized powder)
  - Dosed based on INR and body weight
- Similar thromboembolic event rate as FFP
  - 4.2% vs. 4.8%

FFP = fresh frozen plasma
INR = International Normalized Ratio
PCC = prothrombin complex concentrate


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### 4-Factor PCC (Kcentra®)

<table>
<thead>
<tr>
<th>INR</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 4</td>
<td>25 units/kg</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35 units/kg</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50 units/kg</td>
</tr>
</tbody>
</table>

- **Maximum dose for warfarin reversal**
  - 5,000 units (capped at 100 kg body weight)
- **Administer with vitamin K 10 mg IV**
- **25 units/mL of vitamin K-dependent factors**

INR = International Normalized Ratio  
PCC = prothrombin complex concentrate

4-Factor PCC (Kcentra®)

- Low fixed-dosing
  - Option on ACC Expert Consensus Decision Pathway
  - 1,000 units for any major bleed
  - 1,500 units for intracranial hemorrhage
- Potential benefits
  - Less time to drug administration
  - Decreased cost per patient
  - Risk of thrombosis reduced
- Primarily retrospective studies
  - Variability in doses, products, endpoints, and patient population

Plasma

- Nonspecific reversal agent
- Contains 1 unit/mL of vitamin K-dependent clotting factors
- Requires ABO blood type matching
  - Increased time from order to transfusion
- Dose: 10-15 mL/kg
- DeltaINR after 1 FFP = $0.57 \times \text{PreINR} - 0.72$
- Adverse effects that are not typically seen with PCC

PCC = prothrombin complex concentrate

Assessment Question #2

- A patient who is on warfarin presents to the emergency department with an intracranial hemorrhage due to a fall (INR unknown). What low fixed-dose of 4-factor prothrombin complex concentrate is recommended by the ACC?

  a. 1000 units
  b. 1500 units
  c. 2000 units
  d. 5000 units

ACC = American College of Cardiology
INR = International Normalized Ratio
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a. 1000 units
b. **1500 units**
c. 2000 units
d. 5000 units

ACC = American College of Cardiology
INR = International Normalized Ratio
Reversing DOACs

DOAC = direct oral anticoagulant
Strategies for Reversal of DOACs

• Identify agent

• Evaluate extent of anticoagulation
  • Corresponding laboratory values
  • Time of ingestion
  • Renal function

• Agent-specific reversal agents

• PCC or aPCC

• Tranexamic acid

• Activated charcoal


aPCC = activated prothrombin complex concentrate
DOAC = direct oral anticoagulant
PCC = prothrombin complex concentrate
Dabigatran (Pradaxa®) Reversal

• Idarucizumab (Praxbind®)
  • Humanized monoclonal antibody fragment
  • Affinity is ~350x that of dabigatran for thrombin
  • Dose: 5 g IV (2 doses of 2.5 g ≤15 minutes apart)
  • Has not been studied outside of emergency reversal scenarios

Reversal of Dabigatran Anticoagulant Effect with Idarucizumab (RE-VERSE AD)

- Dabigatran-treated patients with anticoagulation emergencies
- Primary endpoint: maximum reversal of anticoagulant effect of dabigatran within 4 hours
- Secondary endpoints: restoration of hemostasis and safety measures
- Patients given two 2.5 g infusions


Uncontrolled Bleeding (A)  
N=301

Urgent Surgery (B)  
N=202
RE-VERSE AD Results

• Primary endpoint
  • Maximum reversal within 4 hours achieved in 100% of patients (95% CI, 100-100)
  • Reversal of anticoagulant effect happens within minutes
    • Does not necessarily correlate with hemostasis restoration

ECT = ecarin clotting time
TT = thrombin time

RE-VERSE AD Results

• Secondary Endpoints

<table>
<thead>
<tr>
<th>Group</th>
<th>Cessation of Bleeding within 24 hours</th>
<th>Median time to hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>134 patients (68%)</td>
<td>2.5 hours (95% CI, 2.2-3.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal Hemostasis</th>
<th>Mild/Moderate Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B</td>
<td>184 patients (93%)</td>
<td>13 patients (7%)</td>
</tr>
</tbody>
</table>

• Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>Thrombotic Event</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

ECT = ecarin clotting time
TT = thrombin time

Alternatives to Idarucizumab

- 4-factor PCC or aPCC
  - 50 units/kg IV
- Hemodialysis
  - Particularly in patients with impaired renal function
- Activated charcoal
  - 50 g PO
  - Ingestion within last 2 to 4 hours


aPCC = activated prothrombin complex concentrate
PCC = prothrombin complex concentrate
Apixaban/Betrixaban/Edoxaban/Rivaroxaban Reversal

• Specific antidote recently approved
• 4-factor PCC and aPCC are nonspecific reversal strategies
  • 50 units/kg IV
• Activated charcoal
  • 50 g PO
  • Ingestion within last 2 to 4 hours

aPCC = activated prothrombin complex concentrate
PCC = prothrombin complex concentrate

Andexanet Alfa (AndexXa®)

- Specific reversal agent for factor Xa inhibitors
  - FDA-approved for abixaban and rivaroxaban reversal
- Recombinant protein with similar structure to endogenous factor Xa
- FDA approval: May 3, 2018

DOAC = direct oral anticoagulant

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors (ANNEXA-4)

- Multicenter, prospective, open-label, single-group study
- 227 patients with acute major bleeding
  - Within 18 hours of factor Xa inhibitor
  - Outcomes evaluated in 227 (safety) and 132 (efficacy) patients

<table>
<thead>
<tr>
<th>apixaban or rivaroxaban &gt;7 hours prior</th>
<th>rivaroxaban, edoxaban, or enoxaparin within 7 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg IV bolus</td>
<td>800 mg IV bolus</td>
</tr>
<tr>
<td>480 mg infusion</td>
<td>960 mg infusion</td>
</tr>
<tr>
<td>(4 mg/min x 2 hrs)</td>
<td>(8 mg/min x 2 hrs)</td>
</tr>
</tbody>
</table>

ANNEXA-4

• Primary endpoints
  • Change in anti-Xa activity
  • Clinical hemostasis at 12 hours

• Secondary Endpoints
  • Thrombotic events
  • 30-day all-cause mortality

ANNEXA-4 Results

• Efficacy outcomes
  • Excellent/good hemostasis
    109 of 137 (83%) patients (95% CI, 76-89)
  • Reduction in median anti-Xa activity: 92%

• Safety outcomes
  • Thrombotic events
    • 24 of 227 (11%) patients (95% CI, 7-16)
  • 30-day mortality
    • 27 of 227 (12%) patients

Anti-Xa = anti-factor Xa

Ciraparantag (PER977)

- Reversal agent for DOACs and heparin
- Non-covalent binding
- Still in early stages of development

DOAC = direct oral anticoagulant


https://www.medkoo.com/products/6719
Assessment Question #3

• When reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, andexanet alfa is FDA-approved for reversal of which factor Xa inhibitors?

a. edoxaban and rivaroxaban  
b. apixaban and edoxaban  
c. apixaban and rivaroxaban  
d. enoxaparin and rivaroxaban
Assessment Question #3

• When reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, andexanet alfa is FDA-approved for reversal of which factor Xa inhibitors?

a. edoxaban and rivaroxaban
b. apixaban and edoxaban
c. **apixaban and rivaroxaban**
d. enoxaparin and rivaroxaban
Summary

- Numerous risks and benefits to consider when reversing anticoagulation
- 2017 decision pathways published by ACC helps simplify management
- 4-factor PCC and vitamin K are preferred for warfarin
- Idarucizumab recommended for dabigatran
- Andexanet alfa recently approved
  - 4-factor PCC has been agent of choice for factor Xa inhibitors
References


References


10. Hall ST, Molina KC. Fixed-dose 4-factor prothrombin complex concentrate: we don’t know where we’re going if we don’t know how to get there. *J Thromb Thrombolysis.* 2018; doi: 10.1007/s11239-018-1653-y. [Epub ahead of print].


References


Questions and Discussion