All Bleeding Stops! Update on Emergent Reversal of Anticoagulation

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I have nothing to disclose
Objectives

- Discuss the mechanism of action and indication of oral anticoagulants
- Explain the indications for emergent anticoagulation reversal
- Identify the appropriate reversal agents for anticoagulants
- Create a plan for the emergent reversal of anticoagulants
Out with the old, in with the new!

- Warfarin has been used for > 60 years
- Direct oral anticoagulants approval
  - Dabigatran 2010
  - Rivaroxaban 2011
  - Apixaban 2012
  - Edoxaban 2015
- Why use the Direct Oral Anticoagulants (DOACs)
  - AKA:
    - TSOAC: Target Specific Anticoagulants
    - Non–vitamin K oral antagonists
# Guideline Recommendations

<table>
<thead>
<tr>
<th>Atrial Fibrillation Guidelines</th>
<th>VTE Guidelines</th>
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<tr>
<td>AHA/ACC/HRS</td>
<td>ACCP</td>
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<tr>
<td>ACCP</td>
<td>ESC</td>
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<td>ESC</td>
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<td>ESC</td>
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<tr>
<td>General Recs</td>
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<tr>
<td>VKA (1A) or DOAC (1B)</td>
<td>OAC (1A)</td>
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<tr>
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<tr>
<td>OAC (1A)</td>
<td>AC (1B) DOAC (2B) VKA (2C)</td>
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<tr>
<td>Parenteral AC 1C) or OAC (1B)</td>
<td></td>
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<tr>
<td>Drug Preference</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>DOAC (2B)</td>
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<tr>
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<td>DOAC (2B)</td>
</tr>
<tr>
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<td>N/A</td>
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</tbody>
</table>

*VKA (1A) or DOAC (1B):**

**OAC (1A):**

**DOAC (2B):**

**N/A:**

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Cicci.CCSAP.2017
DOAC Risk of Bleeding

- Meta-analysis of 12 RCT comparing DOACs with VKAs with target INR 2–3:
  - Statistically significant reduction in:
    - Major bleeding:
      - RR: 0.72, NNT: 156
    - Fatal bleeding
      - RR: 0.53, NNT: 454
    - Intracranial bleeding
      - RR: 0.43, NNT: 185
    - Clinically relevant non major bleeding:
      - RR: 0.78; NNT: 99
    - Total bleeding:
      - RR: 0.76; NNT: 18
    - Major GI Bleeding
      - No significant reductions overall
DOAC Mortality Data

- Systematic Review and Meta-analysis 13 RCT comparing DOACs vs warfarin
  - Case fatality rate of major bleeding:
    - DOAC: 7.57%
    - Warfarin: 11.04%
  - Rate of fatal bleeding:
    - DOAC: 0.16 per 100 patient-years
    - Warfarin: 0.32 per 100 patient-years
  - Statistically significant reduction DOACs vs warfarin
    - Fatal bleeding
    - Cardiovascular death Afib
    - All Cause Mortality

Anticoagulation Reversal

- Emergent reversal
- Urgent reversal (1–24 hours)
- Non-urgent reversal (>24 hours)
Is the Patient on an Oral Anticoagulation

Yes

Is the Patient Bleeding

Yes

Is Emergent Reversal Needed

Yes

Emergent Reversal < 1 hr

No

No

Exit Algorithm

No

Does Patient Need Invasive Procedure

Yes

Urgent (< 1 Hr)

No

No

Does Patient Need Invasive Procedure

Yes

Urgent (< 1 Hr)

No

No

Gulseth. AJHP.2016.
Is the Patient on an Oral Anticoagulation

Yes

Is the Patient Bleeding

Yes

Is Emergent Reversal Needed

Yes

Emergent Reversal < 1 hr

No

No

No

Exit Algorithm

Does Patient Need Invasive Procedure

Yes

Urgent (< 1 Hr)

No

No

Other Considerations

Does Patient Need Invasive Procedure

Gulseth. AJHP.2016.
Is the Patient Bleeding?

- Indication for reversal
- What anticoagulant
- Indication for anticoagulation
- Level of anticoagulation
- Pharmacokinetics
  - Half-life
  - Renal function
- Patient’s wishes
Is the Patient on an Oral Anticoagulation

Yes → Is the Patient Bleeding

No → Exit Algorithm

Yes

Is the Patient Bleeding

No

Yes

Does Patient Need Invasive Procedure

No

Yes

Urgent (< 1 Hr)

Other Considerations

Yes

Emergent Reversal Needed

No

Emergent Reversal < 1 hr

Gulseth. AJHP.2016.
Urgent (< 1 hr) Reversal

- Hold anticoagulant
- Indication for anticoagulation
- Risk of thromboembolic events
- Need for bridge anticoagulant therapy
- Bleeding risk/thrombosis risk for procedure
- Laboratory tests
Emergent Reversal

- Hold anticoagulation and use mechanical interventions
- Full or partial reversal
- Short and long term risks for thrombosis and bleeding
- Laboratory tests
- Reversal agents
  - Fresh frozen plasma (FFP)
  - Prothrombin complex concentrate (PCC)
  - Antidotes
  - Vitamin K
  - Lady Luck!!

Gulseth. AJHP.2016.
Warfarin Reversal
Vitamin K antagonist:
  ◦ Decreases factors II, VII, IV, X, protein C and protein S in the liver

Dose: Patient specific

Onset: 24–72 Hours

Full Effect: 5–14 days

Monitoring: PT/INR, CBC

Adverse effects

Dager.AJHP.2015
Micromedex.Warfarin.2017
Emergent Warfarin Reversal Agents

- Vitamin K
- Fresh Frozen Plasma (FFP)
- Prothrombin Complex Concentrate (PCC)
  - 3 Factor (Profilnine)
  - 4 Factor (Kcentra)
Vitamin K for Warfarin Reversal

- Promotes formation of activated clotting factors II, VII, IX, X
- Dose: 5–10 mg IV or PO
- Must use with FFP or PCC
Fresh Frozen Plasma

- Clotting factors: II, VII, XI, X
- Dose: 10–20 ml/kg
- Must be thawed
- Must get type and crossmatch
- Risk of transfusion reactions, fluid overload, infection transmission

Nutescu. AJHP. 2013
FFP. Medscape. 2017
4–Factor PCC (Kcentra)

- Factors II, VII, IX, X, Protein C, Protein S, Heparin
- Must give with vitamin K
- Do not use if heparin allergy or history of HIT
- Reversal in 30 minutes

<table>
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<tr>
<th>INR</th>
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<tr>
<td>2–3.9</td>
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<tr>
<td>4–5.9</td>
<td>35 units/kg (Max 3500 units)</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>50 units/kg (Max 5000 units)</td>
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Onset and Duration of Effect

- Phytonadione i.v.
- Phytonadione p.o.
- FFP
- PCC
- rFVIIa

INR

Time

2–4 hr

-6 hr

-24–48 hr

Gulseth.AJHP.2016.
Effective Hemostasis at 24 hours achieved in 72.4% of 4F–PCC vs 65.4% in FFP

Superior INR reduction ≤ 1.3 at 30 minutes after infusion completion
  ◦ 62.2% in 4F–PCC vs 9.6% FFP

Safety profile similar between groups
4F–PCC for Warfarin Reversal and Urgent Surgery/Interventions

- Effective hemostasis achieved in:
  - 4F–PCC: 90%
  - FFP: 75%

- Rapid INR reduction:
  - 4F–PCC: 55%
  - FFP: 0%

- INR $\leq 1.3$ at 60 min ($p < 0.001$)
  - 4F–PCC: 54%
  - FFP: 0%

- Similar rate of any adverse events
Safety of 4F–PCC vs FFP

- Adverse Effects:
  - 4F–PCC: 60.2% vs FFP: 62.9%

- SAE:
  - 4F–PCC: 28.3% vs FFP: 24.9%

- Deaths:
  - 4F–PCC: 6.8% vs FFP: 6.6%

- Fluid Overload:
  - 4F–PCC: 4.7% vs FFP: 12.7%
Emergent Warfarin Reversal

Major/Life Threatening Bleeding

- Stop Warfarin!
- Hemodynamic support, blood, fluids
- 4F–PCC + Vitamin K 5–10 mg IV

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- Alternative options:
  - 3F–PCC + FFP 10–15 ml/kg + Vitamin K IV
  - FFP 10–15 ml/kg + Vitamin K IV
DOACs

- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)
Dabigatran

- MOA: Direct thrombin inhibitor
- Half-life: 12–17 hr
- Lab Monitoring:
  - Thrombin Time, Diluted thrombin time, ecarin clotting time, aPTT
Dabigatran Reversal

- Idarucizumab (Praxbind)
  - Humanized monoclonal antibody fragment
RE–VERSE AD Trial

- Ongoing multicenter, prospective cohort study
- 2 patient groups
  - Serious bleeding (51 patients)
  - Urgent surgery (39 patients)
- Study Drug:
  - 2.5 g IV bolus x 2 doses
- Primary end point:
  - Max percentage reversal of dabigatran anticoagulant effect within 4 hours of the second 2.5 mg dose

Smythe M. AJHP. 2016
Maximum percentage anticoagulation reversal of 100% in both groups
Clotting times normalized
Dabigatran levels decreased to $< 20$ ng/ml
Normal intraoperative hemostasis achieved 92% of emergent procedure patients
Overall all mortality rate of 20%
Dabigatran Emergent/Urgent Reversal

- Urgent and Emergent:
  - Hold dabigatran
  - 50 g activated charcoal (last dose < 2 hours)
  - Prolonged HD (> 2 hr)

- Emergent reversal
  - Idarucizumab 5 g IV
  - Hemodynamic support, blood products, FFP
Direct FXa–Inhibitors

### Pharmacokinetics of Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
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<tbody>
<tr>
<td>$T_{\text{max}}$(hr)</td>
<td>2–3</td>
<td>3–4</td>
<td>2–3.5</td>
</tr>
<tr>
<td>$T_{1/2}$(hr)</td>
<td>6–9</td>
<td>8–15</td>
<td>9–10</td>
</tr>
<tr>
<td>Renal Elimination (%)</td>
<td>36</td>
<td>25–29</td>
<td>35</td>
</tr>
</tbody>
</table>

- **Lab monitoring:**
  - Anti–Xa assays
  - PT
Direct Factor Xa Inhibitor Reversal Agents

- No FDA approved specific reversal agent
- Consider:
  - Fresh frozen plasma
  - 4F-PCC (Kcentra)
  - 3F-PCC (Profilnine)
  - Activated factor VII
  - aPCC (FEIBA)
- Antidotes in studies
  - Andexanet alfa
  - Ciraparantag
4 small studies in young, healthy subjects with no bleeding
  ◦ Rivaroxaban: 2 Studies
  ◦ Apixaban: 1 study
  ◦ Edoxaban: 1 study

4F–PCC dose:
  ◦ 50 IU/kg
    • PT and endogenous thrombin potential (ETP) normalized
    • Whole blood clotting time reversed
  ◦ Dose ≤ 37.5 IU/kg not effective
Urgent and Emergent Reversal of Factor Xa Inhibitors

- **Urgent and Emergent**
  - Stop drug
  - Activated Charcoal (Last dose < 2 hours) and repeat 6 hours later
  - Hemodynamic support, fluids, FFP

- **Emergent:**
  - 4F–PCC: 50 IU/kg x 1, MAX dose 5000 units IV x 1
  - Hemodynamic support with fluids, blood products, FFP
Factor Xa-Inhibitor
Antidotes
Andexanet Alfa
Ciraparantag
Factor Xa Inhibitor Reversal

- Andexanet alfa
  - Recombinant, modified human factor Xa decoy protein
ANNEXA–A and ANNEXA–R

- Parallel, randomized, double-blind, placebo-controlled studies
- Healthy volunteers 50–75 years \((N = 145)\)
- Part 1: study bolus dose of andexanet alfa
- Part 2: study bolus dose plus 2 hour infusion

Siegel. *NEJM.* 2015
Antifactor–Xa activity decreased by > 90%  
Thrombin generation restored  
Significant decrease in apixaban and rivaroxaban concentrations after andexanet alfa  
Rebound in ETP levels with peak at 3 hours post dose  
No serious or severe adverse events
ANNEXA-4

- Multicenter, prospective, open-label, single group study of patients with acute major bleeding
- 2 dosing regimens
- Primary outcomes:
  - Percent change in anti-factor Xa activity
  - Rate of excellent or good hemostatic efficacy 12 hours after infusion

Connolly. *NEJM*. 2015
ANNEXA-4 Results

- Significant decrease in anti-FXa activity from baseline to end of bolus
- Anti-FXa activity was still > 30% below baseline 4 hours after infusion
- 79% of patients with excellent to good hemostasis 12 hours after end of infusion
- 12 patients (18%) with thrombotic events
Andexanet alfa Concerns

- Appropriate dose and duration for each factor–Xa inhibitor to be determined
- Patients on chronic therapy that are bleeding will have different body loads and renal function
- Relationship of timing of last dose of factor Xa inhibitor and andexanet dose
- Laboratory test to determine degree of anticoagulation
- When to restart anticoagulation
Ciraparantag or PER977
Small studies with escalating doses of ciraparantag
- Edoxaban 60 mg dose
- Whole blood clotting time decreased after administration of ciraparantag dose > 100 mg
- Immediate reversal that last ~24 hours
Ciraparantag Concerns

- Ideal characteristics for anticoagulation reversal
- Whole blood clotting time as biomarker for anticoagulant effect and reversal
- Utility during procedures
- 24 hour duration of reversal
- Phase 3 studies to be completed
  - Effectiveness in bleeding patients
- Restarting anticoagulation
Final Remarks

- Use 4F–PCC and idarucizumab for warfarin and dabigatran reversal
- Reversal agents halt or blunt medication effect on anticoagulation
- Reversal of anticoagulation is not without risk
- Limited data on anticoagulation reversal with cessation of bleeding
- No perfect reversal agent
Questions


References


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