Mechanism of Action and Reversal Strategies for Anticoagulant Medications

STN-EAST Concurrent Session
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Rochester, NY
Disclosures

I have nothing to disclose.
Overview

• Coumadin
  – Contemporary reversal strategies

• The new oral anticoagulants (NOAC)
  – Dabigatran, Rivaroxaban, Apixaban, Edoxaban
  – Review mechanism of action
  – Reversal strategies for these drugs

• Antiplatelet agents (if time)
Available Anti-coagulants

FDA approval history of anticoagulants

**NOACs**
- edoxaban 2015
- apixaban 2012
- rivaroxaban 2011
- dabigatran 2010
- argatroban & bivalirudin 2000
- enoxaparin & lepirudin 1998
- dalteparin fondaparinux 1999
- heparin 1939
- warfarin 1954
Coumadin

- Mainstay of oral anticoagulation
  - Approved for DVT/PE, A fib, mechanical valves

- **Advantages**
  - Lots of experience
  - Inexpensive
  - Has a Reversal agent

- **Disadvantages**
  - Narrow therapeutic index, difficult dosing
  - Requires intense monitoring
  - Numerous drug and food interactions
  - Must bridge with injectable anticoagulant first
Novel Oral Anticoagulants (NOAC)

- Target factors in coagulation cascade
- Approved for
  - A fib, some for VTE treatment/prevention
- Advantages
  - Equal or more effective than Coumadin
  - Possibly less bleeding and drug interactions
  - Do NOT require routine monitoring
  - Most do not require initiation with parenteral anticoagulant
- Disadvantages
  - More expensive
  - Less indications
  - No reversal agent for most
  - No reliable/clinically available lab test to determine levels
# Mechanisms of Action

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Vitamin K antagonist</td>
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<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Direct thrombin (factor IIa) inhibitor</td>
</tr>
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<td>Rivaroxaban (Xarelto)</td>
<td>Direct factor Xa inhibitor</td>
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<td>Apixaban (Eliquis)</td>
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<tr>
<td>Edoxaban (Savaysa)</td>
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The Coagulation Cascade
The Coagulation Cascade

Factor Xa inhibitors (ribovaxaban, apixaban, and edoxaban)

Factor Xa inhibitors (dabigatran)

Thrombin inhibitors (dabigatran)

Vitamin K antagonists (warfarin)

Synthetic pentasaccharide (fondaparinux)

Unfractionated heparin
Low-molecular-weight heparin

Venous thrombus

Nature Reviews | Disease Primers
The Coagulation Cascade

Nature Reviews | Disease Primers
Why Does This Matter?

Reversing them requires different agents!
Coumadin

Inhibits synthesis of vitamin K dependent clotting factors
Coumadin

Onset and Duration of Action

• Anticoagulation generally occurs within 24 hours after warfarin dose

• Peak effect may be delayed 72 to 96 hours

• Duration of action of a single dose is 2 to 5 days
Coumadin - Reversal

University of Rochester Medical Center
Emergent Warfarin Reversal Guideline for Adult Patients

**Major Bleeding**
- Acutely life-threatening hemorrhage OR
  - Hgb drop ≥ 2 g/dL
  - Requiring reversal in < 2 hours
- *Stop warfarin*
- *Give vitamin K 10 mg IV over 30 min AND*
- *Kcentra IV (Dose chart on page 2 and refer to Kcentra guideline)*
- *FFP 10-20 mL/kg*
- Recheck INR and aPTT 30 minutes after infusion of Kcentra or FFP
- If INR not at goal, consider:
  - FFP 10-20 mL/kg until INR at goal
  - Recheck INR 30 minutes after additional FFP
  - Do NOT redose Kcentra

**Not bleeding**
- Surgical or interventional procedure planned
- The attending service responsible for performing the procedure must determine whether reversal is necessary and its urgency, and must guide ordering of the appropriate method of reversal

**Emergent Procedure** (Immediate or within 2 hours):
- INR < 1.7:
  - *Stop warfarin*
  - *Give vitamin K 10 mg IV over 30 min*
  - *Consider one unit of FFP immediately prior to or intra-procedure*
- INR ≥ 1.7:
  - *Refer to major bleeding pathway*

**Urgent Procedure** (>2 to 24 hrs):
- *Stop warfarin*
- *Give vitamin K 5-10 mg IV q8h until INR ≤ 1.5 or at goal*
- ± FFP 10-20 mL/kg

Recheck INR in 4-8 hours
Not bleeding

Surgical or interventional procedure planned

The attending service responsible for performing the procedure must determine whether reversal is necessary and its urgency, and must guide ordering of the appropriate method of reversal

**Emergent Procedure** (Immediate or within 2 hours):
- **INR ≤ 1.7:**
  - Stop warfarin
  - Give vitamin K 10 mg IV over 30 min
  - Consider one unit of FFP immediately prior to or intra-procedure

**INR ≥ 1.7:**
- Refer to major bleeding pathway

**Urgent Procedure** (>2 to 24 hrs):
- Stop warfarin
- Give vitamin K 5-10 mg IV over 30 minutes

Recheck INR in 4-8 hours

- May repeat Vitamin K 5-10 mg IV q8h until INR ≤ 1.5 or at goal
- ± FFP 10-20 mL/kg
Vitamin K (Phytonadione)

- Increases hepatic synthesis of all vitamin K dependent coagulation factors
- Indications:
  - Warfarin reversal
- Advantages
  - Inexpensive
  - Multiple routes of administration
- Disadvantages
  - Slow in onset
  - Can take up to 7 days to re-anticoagulated with warfarin
- Cost: PO $35 for 5mg, IV $25 for 10 mg
- Time to INR normalization:
  - PO: 24-28 hours
    - Onset of action 6-10 hours
  - IV 12-14 hours
    - Onset of action 1-2 hours
Fresh Frozen Plasma

- Indications:
  - Emergent warfarin reversal
- Advantages:
  - Contains all coagulation factors
  - Available in majority of hospitals
- Disadvantages:
  - Must be thawed before use, can take time
  - Infusion of large volumes in a short amount of time to correct INR
  - Reversal of coagulopathy is partial and inconsistent
- Onset: variable, 2-12 hours for INR normalizations
- Duration: variable, 8-12 hours for INR normalization
- Dose: is variable, 10-20 mL/kg IV, repeated as needed
- Cost: ~$135 per unit
Coumadin - Reversal

Major Bleeding

- Acutely life-threatening hemorrhage OR Hgb drop > 2 g/dL
- Requiring reversal in < 2 hours

- Stop warfarin
- Give vitamin K 10 mg IV over 30 min AND
- Kcentra IV (Dose chart on page 2 and refer to Kcentra guideline)
- FFP 10-20 mL/kg

Recheck INR and aPTT 30 minutes after infusion of Kcentra or FFP

If INR not at goal, consider:
- FFP 10-20 mL/kg until INR at goal
- Recheck INR 30 minutes after additional FFP
- Do NOT redose Kcentra

Kcentra

*(Prothrombin Complex Concentrate, Human)*

Contains factors II, VII, IX, X, Protein C and S
Kcentra

- A Four Factor Prothrombin Complex Concentrate
  - Replacement of vitamin K dependent coagulation factors
  - Contains Factors II, VII, IX and X

- Indications:
  - Emergent reversal of coagulation factor deficiency induced by warfarin therapy

- Contraindications:
  - Non-emergent reversal in patients with an elevated INR
  - Disseminated intravascular coagulation (DIC)
  - Known anaphylaxis to any components including antithrombin III and human albumin
Kcentra

- Advantages:
  - No need to thaw
  - No need for ABO matching
  - Relatively low volume (40-200 mL)
  - Faster INR reversal than FFP
    - ~15 minute INR normalization after infusion
    - Kcentra decreased INR to ≤ 1.3 within 30 minutes in most subjects (62%) in clinical trials
  - Long duration of action (> 24 hours)

- Disadvantages
  - More expensive (~$1.27/unit (average cost for 80kg patient = $3,800))
  - Not available in all hospitals
  - Risk of thrombotic events
Kcentra

- **Dose based on INR**
  - INR 2-<4 = 25 units/kg
  - INR 4-6 = 35 units/kg
  - INR >6 = 50 units/kg

- **Administration:**
  - Must be administered in a designated IV line at room temperature
  - Each 500 unit vial should be administered as a slow IV push over 3-5 minutes
  - Must give with vitamin K to maintain vitamin-k dependent clotting factors after the PCC effect is diminished

No Re-Dosing
Coumadin Reversal

Warfarin (Coumadin®)

Check INR

INR 1.4 - 3.9
Kcentra® 25 units/kg IV x 1
Max dose: 2500 units

INR 4 - 6
Kcentra® 35 units/kg IV x 1
Max dose: 3500 units

INR > 6
Kcentra® 50 units/kg IV x 1
Max dose: 5000 units

5-10 mg Vitamin K IV over 30 minutes x 1

Recheck INR 30 minutes after Kcentra® dose
Kcentra®=4-Factor PCC

Dose based on actual body weight up to 100 kg. Cannot redose Kcentra®
Available Anti-coagulants

FDA approval history of anticoagulants

- warfarin: 1954
- heparin: 1939
- dalteparin fondaparinux: 1999
- enoxaparin & lepirudin: 1998
- argatroban & bivalirudin: 2000
- rivaroxaban: 2011
- dabigatran: 2010
- apixaban: 2012
- edoxaban: 2015
Why New Anticoagulants?

- Rapid onset/shorter half-life
- Fewer drug and no food interactions
- No lab monitoring
- Equivalent to warfarin
  - Prevention of stroke, VTE
  - Bleeding rates
How do They Compare to Coumadin?

**Warfarin and Dabigatran**

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<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>CYP 1A2, 2C9, 3A4</td>
<td>P-glycoprotein (PGP)</td>
</tr>
<tr>
<td>Interactions</td>
<td>Many drugs, some foods</td>
<td>Drugs that affect its metabolism</td>
</tr>
<tr>
<td>Half-life</td>
<td>20-60 hours</td>
<td>12-17 hours</td>
</tr>
<tr>
<td>Onset and Duration of</td>
<td>Days/Several days</td>
<td>&lt;30 min/1-2 days</td>
</tr>
<tr>
<td>Anticoagulation Effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR</td>
<td>None routine</td>
</tr>
<tr>
<td>Pregnancy Category</td>
<td>X (use LMWH)</td>
<td>C</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Compatible</td>
<td>Effects unknown, use with caution</td>
</tr>
<tr>
<td>Dose Adjustment*</td>
<td>Based on INR</td>
<td>AF CrCl 15-30 ml/min: 75 mg BID</td>
</tr>
<tr>
<td>1 Month Cash Price</td>
<td>$5 (+ cost of monitoring)</td>
<td>$330</td>
</tr>
</tbody>
</table>

*Calculate CrCl for dosing NOACs based on ACTUAL body weight*
## How do They Compare to Coumadin?

### Oral Direct Factor Xa Inhibitors

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<tr>
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<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>PGP</th>
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<tbody>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP 3A4</td>
<td>CYP 3A4 and PGP</td>
<td>PGP</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Drugs that affect its metabolism, grapefruit juice</td>
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<td>Drugs that affect its metabolism</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>7-11 hours</td>
<td>9-14 hours</td>
<td>10-14 hours</td>
</tr>
<tr>
<td><strong>Onset and Duration of Anticoagulation Effect</strong></td>
<td>&lt;30 min/1-3 days</td>
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<td><strong>Monitoring</strong></td>
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</tr>
<tr>
<td><strong>Breastfeeding</strong></td>
<td>Effects unknown, not recommended</td>
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<tr>
<td><strong>Dose Adjustment</strong></td>
<td>AF CrCl 15-50 ml/min: 15 mg QD</td>
<td>AF 2.5 mg BID if SCr ≥ 1.5 mg/dl, and ≥ 80 years or body weight ≤ 60 kg</td>
<td>CrCl 15-50 ml/min: 30 mg QD (Avoid if CrCl &gt;95 ml/min)</td>
</tr>
<tr>
<td><strong>1 Month Cash Price</strong></td>
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Are Any Laboratory Studies Useful with NOACs?

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<tr>
<th></th>
<th>APTT</th>
<th>PT/INR</th>
<th>Anti-Xa</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>Dabigatran</td>
<td>Low sensitivity to low drug conc; nml lab excludes xs drug level</td>
<td>Low sensitivity</td>
<td></td>
<td>Normal TT excludes therapeutic drug level; Dilute TT, ECT can measure on therapy levels</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Low sensitivity</td>
<td>Low sensitivity to low drug conc; nml lab excludes xs drug level</td>
<td>Best measure of activity, need specific drug assay</td>
<td></td>
</tr>
<tr>
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Dabigatran
(Pradaxa)

Mechanism of Action
Dabigatran  
(Pradaxa)

• Pharmacokinetics:
  – Onset of action:
    • Immediate
    • Maximal anticoagulant effects between 2-3 hours

• Metabolism:
  – Hydrolyzed to dabigatran, the active moiety, and further metabolized through conjugation
  – No food and few drug interactions

• Half-life elimination: 12-17 hours
  – As renal function declines, the half-life of the drug is significantly increased
  – 85% excreted via the kidneys
Dabigatran  
(Pradaxa)

• Contra-Indications
  – A strong PGP inhibitor
    • Amiodarone, Dronedarone,
    • Clarithromycin, Cyclosporine, Ritonovir
    • Quinidine, Tacrolimus, Verapamil
  – CrCl < 50 ml/min
Dabigatran - Reversal
(Pradaxa)

Half Life
12-17 hours

Bleeding during dabigatran therapy

- Minor Bleeding
  - Delay next dose or discontinue as appropriate
- Moderate Bleeding
  - Routine supportive measures for the management of an acute bleed
  - Supportive blood product transfusion as indicated
  - Monitor laboratory tests as clinically indicated (if thrombin time (TT) and aPTT are normal – unlikely that dabigatran is significantly contributing to bleeding)
- Major Bleeding
  - Acutely life-threatening hemorrhage requiring reversal in < 2 hours
  - Implement measures for Moderate Bleeding
  - Idarucizumab (Praxbind): 5 g IV given as two 2.5 g boluses over 5 min each
  - aPTT may be used to evaluate efficacy, but does not correlate with hemostasis
  - Depending on severity of bleeding, more aggressive measures may be necessary to achieve hemostasis (e.g. surgery). This should occur in conjunction with administration of idarucizumab.

Emergent Procedure or Acute Overdose
- Discontinue dabigatran immediately
- Idarucizumab (Praxbind): 5 g IV given as two 2.5 g boluses over 5 min each
  - aPTT may be used to evaluate efficacy, but does not correlate with hemostasis
- Acute Overdose:
  - Use oral activated charcoal if ingestion within 4 hours of presentation
Dabigatran - Reversal
(Pradaxa)

If your institution does not have Praxbind
Factor Xa Inhibitors

- Factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban)
- Thrombin inhibitors (dabigatran)
Available Factor Xa Inhibitors

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<td>Main CYP3A4; minor CYP1A2, 2C8, 2C9, 2C19, 2J2 to inactive metabolites</td>
<td>Minimal metabolism via hydrolysis, conjugation, or CYP3A4</td>
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<tr>
<td>Protein Binding</td>
<td>92-95%</td>
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<td>Half-life Elimination</td>
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Available Factor Xa Inhibitors

- Excretion
  - 2/3\textsuperscript{rd} renal
  - 1/3\textsuperscript{rd} liver
- Dose adjusted for reduced creatinine clearance
## Available Factor Xa Inhibitors

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  - 2/3\(^{rd}\) liver
  - 1/3\(^{rd}\) renal
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Savaysa

EAST

UR Medicine
Available Factor Xa Inhibitors

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Lack Specific Agents To Reverse Their Effect

Highly Protein Bound Not Easily Dialyzed
Factor Xa Reversal

**Bleeding during rivaroxaban/apixaban/edoxaban therapy**

- **Minor Bleeding**
  - Delay next dose or discontinue as appropriate
  - Monitor laboratory tests as clinically indicated

- **Moderate Bleeding**
  - Routine supportive measures for the management of an acute bleed
  - Supportive blood product transfusion as indicated

- **Major Bleeding**
  - (Acutely life-threatening hemorrhage)
  - Requiring reversal in < 2 hours
  - Hematology/Vascular medicine consult recommended, especially if factors are being considered

**Emergent Procedure or Acute Overdose**

- Discontinue rivaroxaban/apixaban/edoxaban immediately

**Consider:**

- **PCC (Kcentra):** 25 units/kg IV once
  - aPTT and PT may be used to evaluate efficacy, but does not correlate with hemorrhage

  OR

- **rFVIIa (NovoSeven):** 20 mcg/kg IV bolus over 10 minutes. A second dose may be repeated in 1 hour if hemostasis is not achieved
  - If patient $\leq 50,000/\mu\text{L}$, transfuse one five-pack of platelets while infusing rFVIIa
  - **NOTE:** aPTT and PT may be used to evaluate efficacy and lead to repeat rFVIIa, but does not correlate with hemorrhage

**Acute Overdose:**

- Use oral activated charcoal if ingestion within < 6 hours of presentation

**NOTE:** Protamine sulfate, FFP and vitamin K are NOT expected to affect the anticoagulant activity of rivaroxaban, apixaban, or edoxaban.

**Rivaroxaban, apixaban, and edoxaban are NOT dialyzable.**
Factor Xa Reversal

Bleeding during rivaroxaban/apixaban/edoxaban therapy

- **Minor Bleeding**
  - Delay next dose or discontinue as appropriate
  - Monitor laboratory tests as clinically indicated

- **Moderate Bleeding**
  - Routine supportive measures for the management of an acute bleed
  - Supportive blood product transfusion as indicated

- **Major Bleeding** (Acute life-threatening hemorrhage)
  - Reversal in < 2 hours
  - Hematology/Vascular medicine consult recommended, especially if factors are being considered
  - Implement measures for Moderate Bleeding

- **Emergent Procedure or Acute Overdose**
  - Discontinue rivaroxaban/apixaban/edoxaban immediately
  - Consider:
    - PCC (Kcentra): 25 units/kg IV once
      - aPTT and PT may be used to evaluate efficacy, but does not correlate with hemostasis
    - rFVIIa (NovoSeven): 20 mcg/kg IV bolus over 10 minutes. A second dose may be repeated in 1 hour if hemostasis is not achieved
      - if platelets < 50,000/mm³, transfuse one five-pack of platelets while infusing rFVIIa
      - NOTE: aPTT and PT may be used to evaluate efficacy and need to repeat rFVIIa, but does not correlate with hemostasis

- **Acute Overdose**
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**NOTE:** Protamine sulfate, FFP and vitamin K are NOT expected to affect the anticoagulant activity of rivaroxaban, apixaban, or edoxaban.

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**Factor Xa Reversal**

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- **Moderate Bleeding**
  - Routine supportive measures for the management of an acute bleed
  - Supportive blood product transfusion as indicated
  - Monitor laboratory tests as clinically indicated

- **Major Bleeding**
  - Acutely life-threatening hemorrhage
  - Requiring reversal in < 2 hours
  - Hematology/Vascular medicine consult recommended, especially if factors are being considered

- **Emergent Procedure or Acute Overdose**
  - Discontinue rivaroxaban/apixaban/edoxaban immediately

**Consider:**
- **PCC (Kycentra):** 25 units/kg IV once
  - aPTT and PT may be used to evaluate efficacy, but does not correlate with hemostasis
  - OR
  - **rFVIIa (NovoSeven):** 20 mcg/kg IV bolus over 10 minutes. A second dose may be repeated in 1 hour if hemostasis is not achieved
    - If patient is < 50,000/mm³, transfuse one five-pack of platelets while infusing rFVIIa
    - NOTE: aPTT and PT may be used to evaluate efficacy and need to repeat ifFVIIa, but does not correlate with hemostasis
    - OR
    - **SMH ONLY:** consider evaluating patient for enrollment in the ANNEXA-4 trial which is studying andexanet alf for the reversal of rivaroxaban, apixaban, and edoxaban.

**Acute Overdose:**
- Use oral activated charcoal if ingestion within < 6 hours of presentation
Factor Xa Reversal

Bleeding during rivaroxaban/apixaban/edoxaban therapy

- Minor Bleeding
  - Delay next dose or discontinue as appropriate
  - Monitor laboratory tests as clinically indicated

- Moderate Bleeding
  - Routine supportive measures for the management of an acute bleed
  - Supportive blood product transfusion as indicated

- Major Bleeding
  - Acutely life-threatening hemorrhage
  - Requiring reversal in < 2 hours
  - Hematology/Vascular medicine consultation recommended, especially if factors are being considered

- Emergent Procedure or Acute Overdose
  - Discontinue rivaroxaban/apixaban/edoxaban immediately

Implement measures for Moderate Bleeding

Consider:
- PCC (Kcentra): 25 units/kg IV once
  - INR and PT may be used to evaluate efficacy, but does not correlate with hemostasis
  - OR

- rFVIIa (NovoSeven): 20 mcg/kg IV bolus over 10 minutes. A second dose may be repeated in 1 hour if hemostasis is not achieved
  - OR
  - PTT and PT may be used to evaluate efficacy and need to repeat rFVIIa, but does not correlate with hemostasis

NOTE: Protamine sulfate, FFP and vitamin K are NOT expected to affect the anticoagulant activity of rivaroxaban, apixaban, or edoxaban.

Rivaroxaban, apixaban, and edoxaban are NOT dialyzable

Acute Overdose
- Use oral activated charcoal if ingestion within < 6 hours of presentation
The Coagulation Cascade
Recombinant Factor VIIa
(NovoSeven)

- Contains Factor VIIa
- Indicated for hemophilia
  - Off label use for emergent warfarin reversal
- Exclusion Criteria:
  - Hypersensitivity to mouse, hamster, or bovine products
  - Lactate greater than 15mg/dL, Arterial pH<7
  - Ongoing cardiopulmonary arrest resuscitation (CPR)
  - If platelet count <50,000 /mm, transfuse one 5-pack of platelets during rFVIIa infusion
  - If fibrinogen < 80 mg/dL, transfuse cryoprecipitate during rFVIIa infusion
Kcentra

- A Four Factor Prothrombin Complex Concentrate
  - Replacement of vitamin K dependent coagulation factors
  - Contains Factors II, VII, IX and X
Factor Xa Reversal

**Bleeding during rivaroxaban/apixaban/edoxaban therapy**

- **Minor Bleeding**
  - Delay next dose or discontinue as appropriate
  - Monitor laboratory tests as clinically indicated

- **Moderate Bleeding**
  - Routine supportive measures for the management of an acute bleed
  - Supportive blood product transfusion as indicated
  - Consider:
    - **PCC (Kcentra):** 25 units/kg IV once
      - aPTT and PT may be used to evaluate efficacy, but does not correlate with hemorrhage
    - **rFVIIa (NovoSeven):** 20 mcg/kg IV bolus over 10 minutes. A second dose may be repeated in 1 hour if hemorrhage is not achieved
      - For patients < 50,000/mm³, transfuse one five-pack of platelets while infusing rFVIIa
    - **OR**
    - SMH ONLY: consider evaluating patient for enrollment in the ANNEXA-4 trial which is studying andexanet alf for the reversal of rivaroxaban, apixaban, and edoxaban

- **Major Bleeding**
  - Acutely life-threatening hemorrhage
  - Requiring reversal in < 2 hours
  - Hematology/Vascular medicine consult recommended, especially if factors are being considered
  - Implement measures for Moderate Bleeding

- **Emergent Procedure or Acute Overdose**
  - Discontinue rivaroxaban/apixaban/edoxaban immediately

**NOTE:** Protamine sulfate, FFP and vitamin K are NOT expected to affect the anticoagulant activity of rivaroxaban, apixaban, or edoxaban.

Rivaroxaban, apixaban, and edoxaban are NOT dialyzable

**Acute Overdose:**
- Use oral activated charcoal if ingestion within < 6 hours of presentation
Anti-Platelet Agents

- Permanently inactivate platelets
- Can take 7 days from last dose for platelet function to return
Anti-Platelet Agent Reversal

Aspirin
Clopidogrel (Plavix)
Prasugrel (Effient)
Ticagrelor (Brilinta)
Ticlopidine (Ticlid)
Cilostazol (Pletal)

1 apheresis platelet pack over 15 min
Consider additional platelets if bleeding persists
Consider desmopressin (DDAVP)
0.3mcg/kg IV over 15min in NS 50ml
Summary
Available Anti-coagulants

FDA approval history of anticoagulants

Warfarin 1954
Heparin 1939
Dalteparin fondaparinux 1999
Enoxaparin & lepirudin 1998
Argatroban & bivalirudin 2000
Dabigatran 2010
Rivaroxaban 2011
Apixaban 2012
Edoxaban 2015

NOACs
# Coumadin - Reversal

## Clinical Pearls of Reversal Agents

<table>
<thead>
<tr>
<th></th>
<th>Vitamin K</th>
<th>PCC</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Replenishment of key factor in the production of Vitamin K dependent clotting factors</td>
<td>Direct administration of high-concentration of vitamin-K dependent clotting factors</td>
<td>Direct administration of vitamin-K dependent clotting factors</td>
</tr>
<tr>
<td><strong>Time to INR target</strong></td>
<td>8-12hrs</td>
<td>&lt;30 minutes</td>
<td>2-4 hours</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Indefinite</td>
<td>24 hours</td>
<td>4-6 hours</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>IV: diluted in 50mL</td>
<td>40-200 mL</td>
<td>250mL per unit (500-1,000mL per adequate dose)</td>
</tr>
<tr>
<td><strong>Hospital Cost</strong></td>
<td>PO: $56.03 for 5mg tab</td>
<td>$1.34 per unit (~$1,340 - $5,000 per dose)</td>
<td>$45 per unit ($90-$180 per dose)*</td>
</tr>
<tr>
<td><strong>PO: $11.50 for 10mg vial, $3.45 for 1mg syringe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adverse events**

- TE in non-anticoagulated patient
- Possible increased risk in thrombotic events
- TE in non-anticoagulated patient
- TRALI/TACO

*does not include transfusion-related costs

TE = thromboembolic events; TRALI = Transfusion-related acute lung injury; TACO = Transfusion-associated circulatory overload
NOAC Reversal

Novel Oral Anticoagulants (NOAC)

Rivaroxaban (Xarelto®) or Apixaban (Eliquis®)

- Check INR and PTT (Be aware these may not reflect level of coagulopathy)
  - INR < 1.4 AND NOAC within 24 hrs:
    - Kcentra® 25 units/kg IV x 1
    - Max dose: 2500 units
  - INR 1.4-3.9
    - Kcentra® 25 units/kg IV x 1
    - Max dose: 2500 units
  - INR > 4
    - Kcentra® 50 units/kg IV x 1
    - Max dose: 5000 units

Kcentra® = 4-Factor PCC
- If signs/symptoms of allergic reaction to infusion – stop infusion.
- Avoid Kcentra® in patients with history of HIT or allergy to albumin.

Dabigatran (Pradaxa®)

- Check INR and PTT (Be aware these may not reflect level of coagulopathy)
  - Dabigatran taken within 24 hrs:
    - Praxbind® 5 grams IV x 1
  - Dabigatran taken 24-48 hrs ago AND INR/PTT elevated:
    - Praxbind® 5 grams IV x 1

May consider an additional 5 gram dose if:
- Re-bleeding and INR/PTT are elevated
- 2nd emergent surgery is needed and INR/PTT are elevated

Praxbind® = Idarucizumab
- Given as 2 consecutive 2.5 gram infusions
- Praxbind contains 4 grams sorbitol. Consider this if calculating total daily amount of sorbitol/fructose in patients with hereditary fructose intolerance.
Anti-Platelet Agent Reversal

Aspirin
Clopidogrel (Plavix)
Prasugrel (Effient)
Ticagrelor (Brilinta)
Ticlopidine (Ticlid)
Cilostazol (Pletal)

1 apheresis platelet pack over 15 min
Consider additional platelets if bleeding persists
Consider desmopressin (DDAVP)
0.3mcg/kg IV over 15min in NS 50ml
Conclusion

- What situation are you in?
  - Major/Moderate/No Bleeding Risk?
  - Urgent intervention needed?
  - When was the last dose taken?
Conclusion

• What agent are you trying to reverse?
Reversal of Anti-platelet and/or Target-Specific Oral Anticoagulants in Trauma Patients

A. Britton Christmas, M.D., FACS
Vice Chief of Trauma and Associate Medical Director
The F.H. “Sammy” Ross, Jr. Trauma Center
Carolinas Medical Center
Charlotte, NC
Objectives

1) To discuss the utility and significance of anticoagulation studies.
2) To understand the mechanism of action of various anticoagulants.
3) To discuss potential reversal strategies for anticoagulants in trauma patients.
Successful Completion

- To successfully complete this course, participants must attend the entire event and complete/submit the evaluation at the end of the session.
- Society of Trauma Nurses is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
A. Britton Christmas, MD, FACS

“Utility and interpretation of anticoagulation studies”

Nicole Stassen, MD, FACS

“Mechanism of action and reversal strategies for anticoagulant medications”
Utility and Interpretation of Anticoagulation Studies

A. Britton Christmas, M.D., FACS
Vice Chief of Trauma and Associate Medical Director
The F.H. “Sammy” Ross, Jr. Trauma Center
Carolinias Medical Center
Charlotte, NC
Disclosures

• Nothing to disclose
Background

• As the geriatric population continues to rise, trauma centers are experiencing increasing difficulties surrounding the management of anticoagulant medications.

• Specific challenges arise when patients incur traumatic brain injuries or significant hemorrhage necessitating reversal of these agents.
Tests of Platelet Phase

Bleeding time

- Vasoconstriction → Platelet plug → Clot matrix
- Normal 7 - 9 minutes
- Purpura, spontaneous bruising, mucosal hemorrhage
- Thrombocytopenia or platelet dysfunction
- ASA, NSAIDS, von Willebrand’s
Test of Coagulation Cascade

- Activated Partial Thromboplastin Time (aPTT)
- Prothrombin Time (PT)
- Thrombin Time
**Activated Partial Thromboplastin Time (aPTT)**

- Time to generate fibrin from intrinsic pathway
- Factors V, VIII, IX, X, XI, XII, prothrombin and fibrinogen
- Prolonged if < 30% normal activity
- Hemophilia A and B, Vit K deficiency, liver dysfunction
- DIC and massive transfusion
Prothrombin time (PT)

- Time to generate fibrin after activation of factor VII
- Measures extrinsic and common pathways
- Factors V, VII, X, prothrombin, fibrinogen
- Warfarin
- Liver disease, severe bleeding, massive transfusion
**Thrombin time**

- Time for fibrinogen $\rightarrow$ fibrin in presence of thrombin
- Deficient fibrinogen ($<100$ mg/dL) or abnormal
- Heparin or fibrin degradation products
Coagulation Cascade

Intrinsic Pathway
- PTT
- HMWK, FII, F XII
- F XI, F Xa, Kallikrein
- F IX, F IXa
- F VIII, F VIIIa
- F VII

Extrinsic Pathway
- PT
- Tissue Factor (TF)
- F VIIa, F VII
- F V, F Va
- F X, F Xa
- F VIIIa
- Antithrombin
- Thrombin (F IIa)
- Fibrinogen
- Fibrin monomer
- Cross-linked fibrin
- Fibrin multimer
- Factor XIII
- Factor Xlla

Thromboelastography (TEG)
What is a TEG?

Whole picture of coagulation cascade

- Clot Initiation
- Clot Kinetics
- Clot Strength
- Clot lysis
**Normal TEG Tracing**

![Normal TEG Tracing](image)

<table>
<thead>
<tr>
<th>R (min)</th>
<th>K (min)</th>
<th>Angle (deg)</th>
<th>MA (mm)</th>
<th>PMA</th>
<th>G</th>
<th>EPL (%)</th>
<th>A</th>
<th>CI (%)</th>
<th>LY30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>1.3</td>
<td>72.0</td>
<td>64.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 — 6</td>
<td>1 — 4</td>
<td>47 — 74</td>
<td>55 — 73</td>
<td></td>
<td></td>
<td>8.9K</td>
<td>0.0</td>
<td>2.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Time**

---

Carolina HealthCare System
Uncompromising Excellence. Commitment to Care.
Clot time (R)

- Time from start of sample until 2 mm of clot amplitude formed.
- Reaction time, surrogate for assessing activation of clotting cascade.
- A look at the thrombin burst (Thrombin Critical Mass) required to start clotting.
- Normally 4-8 minutes.
Clot Time Irregularities

Long Clot Time (R) > 8min
- Possible etiologies:
  - Factor deficiency/dysfunction
  - Residual heparin
- Common treatments:
  - FFP
  - Protamine

Short Clot Time (R) < 4min
- Possible etiologies:
  - Enzymatic hypercoagulability
- Common treatments:
  - Anticoagulant
**Clot Kinetics**

- **Clot formation time (K)**
  - Time from 2mm to 20mm clot to form.

- **Alpha Angle (α)**: Value used most often
  - Angle of line tangent to curve from 2mm to 20mm.
  - Surrogate to assess rate and efficacy of clotting system to generate thrombin and conversion of fibrinogen to fibrin.
Clot Kinetic Irregularities

Prolonged Kinetics
K>4min; \( \alpha < 47^\circ \)

Possible etiologies:
- Low fibrinogen levels or function
- Insufficient rate/amount of thrombin generation
- Platelet deficiency/dysfunction

Common treatments:
- FFP
- Cryoprecipitate

Shortened Kinetics
K<1min; \( \alpha > 74^\circ \)

Possible etiologies:
- Platelet hypercoagulability
- Fast rate of thrombin generation

Common treatments:
- None
Clot Strength

Max Amplitude (MA)
- Max amplitude of pin oscillation.
- Clot strength = 80% platelets + 20% fibrinogen

Clot Viscosity (G)
- Calculated from MA, $G = \frac{8000 \times A}{100 - A}$
Clot Strength Irregularities

**High MA**

Possible etiologies:
- Platelet hypercoagulability

Common treatments:
- Antiplatelet agents

**Low MA**

Possible etiologies:
- Poor platelet function
- Low platelet count
- Low fibrinogen levels or function

Common treatments:
- Platelet transfusion
Clot Lysis

LY30

*Percent decrease* in the amplitude of pin oscillation (i.e. clot strength) 30 minutes after MA is attained.

Estimated percent lysis value (EPL)

*Estimates the rate of change in amplitude* after MA is reached; assessment of the rate of overall clot breakdown.

Coagulation Index (CI)

*Calculated factor from MA, R, K, and α angle to describe global hemostatic index.*
Fibrinolysis

Primary Fibrinolysis
LY30 >7.5% (or EPL >15%) with CI ≤1.0.

- Possible etiologies:
  - High levels of tPA
- Common treatments:
  - Antifibrinolytic agent

Secondary Fibrinolysis
LY30 >7.5% (or EPL >15%) with CI >3.0.

- Possible etiologies:
  - Microvascular hypercoagulability (i.e. DIC)
- Common treatments:
  - Anticoagulant

<table>
<thead>
<tr>
<th>Index</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native Whole Blood</td>
<td>CI = -0.2454R - 0.0184K + 0.1655MA - 0.0241te - 5.0220</td>
</tr>
<tr>
<td>Cellite-activated WB</td>
<td>CI = -0.6516R - 0.3772K, + 0.1224MA, + 0.0759te - 7.7922</td>
</tr>
<tr>
<td>Combined</td>
<td>CI = -0.112R - 0.222K + 0.040MA - 0.042te - 0.578R, + 0.370K, + 0.111MA, + 0.087te - 8.397</td>
</tr>
</tbody>
</table>
# Quick Review

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting Time</td>
<td>R</td>
<td>Time from start to 2mm of clot amplitude (initial fibrin formation).</td>
</tr>
<tr>
<td>Clot Kinetics</td>
<td>K</td>
<td>Speed to reach 20mm clot amplitude (clot kinetics)</td>
</tr>
<tr>
<td></td>
<td>α Angle</td>
<td>Measure of rapidity of fibrin build up and cross linking (fibrinogen level)</td>
</tr>
<tr>
<td>Clot Strength</td>
<td>MA</td>
<td>Direct function of max dynamic properties of fibrin and platelet bonding.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Max platelet function)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>Conversion of MA to dynes/cm²</td>
</tr>
<tr>
<td>Coagulation Index</td>
<td>CI</td>
<td>Global hemostatic index</td>
</tr>
<tr>
<td>Clot Stability</td>
<td>LY30</td>
<td>Rate of amplitude reduction 30 min after MA</td>
</tr>
<tr>
<td></td>
<td>EPL</td>
<td>Estimates % lysis on amplitude reduction after MA</td>
</tr>
</tbody>
</table>
Example 1

<table>
<thead>
<tr>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>4 – 9 min</td>
</tr>
<tr>
<td>K</td>
<td>1 – 4 min</td>
</tr>
<tr>
<td>α angle</td>
<td>47° – 74°</td>
</tr>
<tr>
<td>MA</td>
<td>55 – 73 mm</td>
</tr>
<tr>
<td>G</td>
<td>6.0K – 13.2K</td>
</tr>
<tr>
<td>EPL</td>
<td>0 – 15</td>
</tr>
<tr>
<td>LY30</td>
<td>0 – 8%</td>
</tr>
</tbody>
</table>

Delayed clot formation, suspect heparin or factor deficiency

R=13
K=4
MA= 55
Angle= 54.5
Example 2

<table>
<thead>
<tr>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>4 – 9 min</td>
</tr>
<tr>
<td>K</td>
<td>1 – 4 min</td>
</tr>
<tr>
<td>α angle</td>
<td>47° – 74°</td>
</tr>
<tr>
<td>MA</td>
<td>55 – 73 mm</td>
</tr>
<tr>
<td>G</td>
<td>6.0K – 13.2K</td>
</tr>
<tr>
<td>EPL</td>
<td>0 – 15</td>
</tr>
<tr>
<td>LY30</td>
<td>0 – 8%</td>
</tr>
</tbody>
</table>

R = 8.5
K = 2
\textbf{MA = 79.5} Hypercoagulable state
Angle = 78
Example 3

<table>
<thead>
<tr>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>4 – 9 min</td>
</tr>
<tr>
<td>K</td>
<td>1 – 4 min</td>
</tr>
<tr>
<td>α angle</td>
<td>47° – 74°</td>
</tr>
<tr>
<td>MA</td>
<td>55 – 73 mm</td>
</tr>
<tr>
<td>G</td>
<td>6.0K – 13.2K</td>
</tr>
<tr>
<td>EPL</td>
<td>0 – 15</td>
</tr>
<tr>
<td>LY30</td>
<td>0 – 8%</td>
</tr>
</tbody>
</table>

R=4.8  
K=25.5  
MA=55  
Angle=34.8

Weak clot formation. Suspect platelet dysfunction, thrombocytopenia.
More Examples

Normal
R; K; MA; Angel: normal

[Diagram showing various examples with shapes and text labels]
Final Algorithm
Thank You!