Reversing the Irreversible: Updates on the Management of Oral Anticoagulant Related Bleeding

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April 1st 2014

No conflicts of interest to report

Parts of this presentation discuss off-label use of reversal agents. Clinical judgment and evaluation of each agent in the context of the specific patient scenario is warranted.

Objectives

Evaluate how target-specific anticoagulants compare to traditional oral anticoagulation with warfarin

Compare and contrast the clinical evidence supporting the use of various reversal strategies for patients receiving oral anticoagulants

Recommend reversal options for a patient receiving oral anticoagulants that develops bleeding complications

Bleeding Risk on Warfarin

15 – 20% = incidence per year of warfarin-related bleeding of any kind

1-3 % = incidence per year of warfarin-related life-threatening bleeding

2 % = patients suffering an intracerebral hemorrhage or subdural hematoma during therapy (79% mortality rate)

Factors associated with bleeding events

- Intensity and quality of anticoagulant therapy
- New initiation to anticoagulant therapy
- Patient-specific factors
  - History of previous bleeding (especially GI)
  - Advanced age
  - Cancer
  - Renal or liver impairment
  - Prior stroke
  - Alcohol abuse
  - Concomitant therapy with medications known to increase bleeding or anticoagulation
  - Procedures

Overview of Clinical Trials in Afib

<table>
<thead>
<tr>
<th>Drug</th>
<th>RELY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>AVERROES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Dose</td>
<td>Not studied</td>
<td>CCl 30 – 49</td>
<td>15 mg daily</td>
<td>2.5 mg BID</td>
</tr>
<tr>
<td>Renal Dose</td>
<td>150mg &amp; 110mg BID</td>
<td>20mg daily</td>
<td>5mg BID</td>
<td></td>
</tr>
<tr>
<td>5mg BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>Randomized open label</td>
<td>Randomized double blind</td>
<td>Randomized double blind</td>
<td>Randomized double blind</td>
</tr>
<tr>
<td>Previous Stroke/TIA</td>
<td>20%</td>
<td>55%</td>
<td>19%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Warfarin Naive</td>
<td>50.4%</td>
<td>37.5%</td>
<td>43%</td>
<td>60.5%</td>
</tr>
<tr>
<td>Mean CHADS2</td>
<td>2</td>
<td>3.5</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Comparator</td>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Aspirin</td>
</tr>
<tr>
<td>TTR: 67%</td>
<td>TTR: 57.6%</td>
<td>TTR: 66%</td>
<td>81 – 324mg</td>
<td></td>
</tr>
</tbody>
</table>
**Novels Pharmacokinetic Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>BID</td>
<td>Daily or BID</td>
<td>BID</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>~7%</td>
<td>~40%</td>
<td>~20%</td>
</tr>
<tr>
<td>Time of Onset</td>
<td>1-2 hours</td>
<td>2-4 hours</td>
<td>2-6 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-27 hours</td>
<td>9-13 hours</td>
<td>8-15 hours</td>
</tr>
<tr>
<td>Elimination</td>
<td>85% renal</td>
<td>80% renal</td>
<td>90% renal</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Conjugation – No CYP involvement</td>
<td>Primarily CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Substrates</td>
<td>All are substrates for P-glycoprotein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein Binding</td>
<td>~35%</td>
<td>~95%</td>
<td>~87%</td>
</tr>
<tr>
<td>Routine Lab Monitoring</td>
<td>No routine monitoring required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**What We Can Reverse**

Warfarin
**When Should the INR Be Reversed**

<table>
<thead>
<tr>
<th>INR</th>
<th>Hold</th>
<th>Vitamin K</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.5</td>
<td>Yes</td>
<td>No</td>
<td>• Hold dose, consider dose reduction, monitor INR</td>
</tr>
<tr>
<td>No bleeding</td>
<td></td>
<td></td>
<td>• INRs ≤ 0.5 from goal may not require dose reductions</td>
</tr>
<tr>
<td>4.5 – 10</td>
<td>Yes</td>
<td>No</td>
<td>• Hold 1-2 doses, monitor INR</td>
</tr>
<tr>
<td>No bleeding</td>
<td></td>
<td></td>
<td>• Evaluate need for dose reduction</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>Yes</td>
<td>Yes</td>
<td>• Hold warfarin until INR in range</td>
</tr>
<tr>
<td>No bleeding</td>
<td></td>
<td></td>
<td>• Give Vitamin K PO 2.5-5mg</td>
</tr>
<tr>
<td>Bleeding regardless of INR</td>
<td>Yes</td>
<td>Yes</td>
<td>• Give Vitamin K IV 5-10 mg by slow infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Consider factor replacement for major bleeding</td>
</tr>
</tbody>
</table>

**Review Question**

Which of the following patients would require their INR to be reversed pharmacologically?

A. INR of 4.5 presenting to the ED with controlled epistaxis
B. INR of 2 requiring elective surgery in 3 days with goal INR <1.3
C. INR of 10.5 without signs/symptoms of bleeding
D. Both B & C

**When Should the INR Be Reversed**

*Warfarin-related Major Bleeding*

- Prothrombin Complex Concentrates (PCC) recommended over Fresh Frozen Plasma (FFP) (Grade 2C)
- Vitamin K IV 5 -10 mg by slow IV infusion should be used in combination with factor replacement rather than using factors alone (Grade 2C)

**Review Question**

A 50 year-old female with a mechanical mitral valve presents to the ED with minor epistaxis that resolves spontaneously. She is otherwise stable but is worried about what her INR is given a previous bleeding event. Her INR test results back 12.5.

What would be the appropriate course of action for this patient’s elevated INR?

A. Give Vitamin K IV 5-10 mg x 1 and admit for monitoring of INR
B. Give Vitamin K PO 2.5 mg x 1 and recheck the INR in 24 hours
C. Give Vitamin K PO 5 mg x 1 and recheck the INR in 24 hours
D. Patient should be considered for a novel anticoagulant because of her bleeding history and better bleeding outcomes with novels

**Vitamin K Effect vs. Time**

- **Phenytoin (I.V.)**
- **Phenytoin p.o.**
- **Vitamin K IV**
- **PCC**
- **FFP**
- **fVIIa**

**Fresh Frozen Plasma (FFP)**

Inactivated factors II, VII, IX, X in a diluted form

- **Dosing**
  - 10-20 mL/kg IV infusion
  - 1 unit of FFP is ~200 - 250 mL

- **Advantages**
  - Provides more rapid short-term reversal
  - No excess risk of thrombosis
  - Low cost

- **Disadvantages**
  - Frozen – takes time for thaw (~30 minutes)
  - Substantial volume limits rapid infusion and decreases tolerance
  - Transfusion reactions
  - Risk of disease transmission (low)
PCC Products Available in the U.S.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>3-Factor PCC</th>
<th>4-Factor PCC</th>
<th>Activated 4-Factor PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profiltine SD®</td>
<td>Bebulin VH®</td>
<td>Prothromplex HT®</td>
<td>FEIBA®</td>
</tr>
<tr>
<td>Factors Included</td>
<td>II, IX, X</td>
<td>II, VII, IX, X</td>
<td>II, VIIa, IX, X</td>
</tr>
<tr>
<td>Approved for Warfarin Reversal</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>All agents are dosed based on the number of units/mL of Factor IX which varies from lot to lot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


4-Factor PCC vs. Warfarin

4-Factor PCC (Kcentra) vs. FFP for Warfarin-Related Major Bleeding

| Population | 103 PCC/109 FFP with major bleeding on warfarin with INR ≥ 2 |
| Dosing | PCC 25, 35, or 50 Factor IX units/kg |
| Outcomes | Effective hemostasis through 24 hours |


4-Factor PCC vs. Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Results</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective hemostasis</td>
<td>PCC 72.4%</td>
<td>FFP 65.4%</td>
</tr>
<tr>
<td>Reduction of INR ≤ 1.3 in 30 minutes</td>
<td>PCC 62.2%</td>
<td>FFP 9.6%</td>
</tr>
</tbody>
</table>

Other Advantages
- Less volume required for complete reversal of warfarin (105 mL vs. 365 mL)
- Faster infusion time with PCC than plasma (24 min vs. 169 min)
- Thromboembolic events (TEE) were low and no difference was found between plasma and PCC
- Greatest risk of TEE occurred in patients with a previous history of thrombosis


Overview of Therapies for Warfarin Reversal

<table>
<thead>
<tr>
<th>Product</th>
<th>Time to Effect</th>
<th>Duration of Effect</th>
<th>Evidence for Use</th>
<th>Risk of Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K PO</td>
<td>24 hours</td>
<td>Days</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin K IV</td>
<td>8-12 hours</td>
<td>Days</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>FFP</td>
<td>Immediate</td>
<td>12-24 hours</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>PCC</td>
<td>Immediate</td>
<td>12-24 hours</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Immediate</td>
<td>2-6 hours</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Adapted from Garcia DA, Crowther MA. Circulation. 2012;125:2944-2947.

Can We Reverse These Agents?

Data is mixed – largely based on coagulation markers not hard outcomes

Most human data is in healthy volunteers – limits extrapolation to bleeding patients

Data on reversal in bleeding limited to animal models and case reports

Reversal Options

Target-Specific Anticoagulants
Renal Function Matters

<table>
<thead>
<tr>
<th>Dabigatran Half-Life Stratified by Renal Function</th>
<th>CrCl Estimated Half-Life in Hours mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>13 (11-22)</td>
</tr>
<tr>
<td>&gt;50 to ≤ 80</td>
<td>15 (12-34)</td>
</tr>
<tr>
<td>&gt;30 to ≤ 50</td>
<td>18 (13-23)</td>
</tr>
<tr>
<td>≤ 30</td>
<td>27 (22-35)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rivaroxaban Half-Life Stratified by Renal Function</th>
<th>CrCl (mL/min)</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>50-79</td>
<td>8.3</td>
</tr>
<tr>
<td>50-79</td>
<td>35-49</td>
<td>8.7</td>
</tr>
<tr>
<td>≤ 30</td>
<td>&lt;30</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.5</td>
</tr>
</tbody>
</table>

Review Question

Which of the following laboratory assays may be most useful for determining whether dabigatran is present during an acute bleeding event?
A. INR or PT
B. aPTT
C. Thrombin time (TT)
D. Lack of data for any test

Results for Dabigatran
- 4PCC had NO EFFECT seen ANY coagulation parameter measured

Results for Rivaroxaban
- Complete normalization of the PT 15 minutes after infusion of PCC (p<0.001)
- ETP normalized 15 minutes after infusion (p<0.001)
- Effects sustained for 24 hours

Ex Vivo Reversal of Dabigatran and Rivaroxaban

- Dabigatran: aPTT, ETP lag time, ECT, TT
- Rivaroxaban: PT, ETP

Monitoring

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>PT</th>
<th>aPTT</th>
<th>TT</th>
<th>ECT</th>
<th>Anti-Xa activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↑</td>
<td>↑</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Apixaban</td>
<td>↑</td>
<td>↑</td>
<td>NE</td>
<td>NE</td>
<td>↑</td>
</tr>
</tbody>
</table>

NC = no change; ↑ = increase; NE = no effect
PT = prothrombin time; aPTT = activated partial thromboplastin time; TT = thrombin time; ECT = ecarin clotting time

Ex Vivo Reversal of Dabigatran and Rivaroxaban

Results for aPCC (FEIBA)
- Consistent effect on thrombin generation of rivaroxaban
- Less consistent effect for dabigatran

Results for 4PCC and FVIIa
- Inconsistent impact on thrombin production

Advantage for aPCC?
- Possibly due to combining actions of FVIIa and 4PCC


Case Report

CASE
67 y/o M on dabigatran
150mg BID for Afib
Cardiac ablation (last dose 7 hours prior)
Heparin 5000 unit bolus and drip at 200 units/hr
Trans-septal perforation

OUTCOME
Pericardiocentesis of 4.5 L
2 units FFP + protamine 100mg
6 units RBCs
Epinephrine drip
Last Resort: FEIBA 26 units/kg
Visual cessation of bleeding
No effect on TT or ECT;
aPTT and INR normalized


Potential Reversal Agents

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Factor PCC</td>
<td>Lack of data</td>
<td>Limited Data</td>
</tr>
<tr>
<td>4 Factor PCC</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>aPCC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FVIIa</td>
<td>Lack of data</td>
<td>Lack of data</td>
</tr>
<tr>
<td>FFP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Activated Charcoal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>Lack of data</td>
<td>Lack of data</td>
</tr>
</tbody>
</table>

Considerations

Is goal to stop bleeding or prevent bleeding?
Assess pharmacokinetic and dynamic aspects of the anticoagulant
What patient specific factors are involved that may alter the plan

Review Question

PATIENT CASE
85 y/o M presents to ED with a severe GI bleed
He takes dabigatran 150 mg BID for afib (last dose 8 hours ago)
Also has HTN, HF, CKD III
CrCl = 38 mL/min
Noted to have decreased Hgb and Hct, hypotension, signs of multi-system organ failure

QUESTION
The team has elected to attempt to reverse dabigatran, which options are most appropriate in addition to supportive care?
A. 3 Factor PCC + dialysis if possible
B. aPCC + dialysis if possible
C. rFVIIa
D. Activated charcoal

How Can All This Information Be Implemented Into Practice?

Adapted from Garcia DA, Crowther MA. *Circulation*. 2012;125:2944-47.


### Cost Comparison of Factor Replacements

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost per Unit of Drug</th>
<th>Total Cost per Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Factor PCC (Kcentra®)</td>
<td>$1.27/unit</td>
<td>$3,175</td>
</tr>
<tr>
<td>3-Factor PCC (ProfilNine®)</td>
<td>$0.91/unit</td>
<td>$2,275</td>
</tr>
<tr>
<td>aPCC (FEIBA®)</td>
<td>$1.52/unit</td>
<td>$3,800</td>
</tr>
<tr>
<td>rFVIIa (NovoSeven®)</td>
<td>$1.52/mcg</td>
<td>$3,800</td>
</tr>
<tr>
<td>FFP (15 mL/kg)</td>
<td>$60/unit</td>
<td>$300</td>
</tr>
</tbody>
</table>

Cost of a single dose based on an 80 kg patient receiving 25 units/kg or 25 mcg/kg for rFVIIa.
Average cost of FFP $60/unit.
Price/unit based on GPO through Cardinal as of 10/2013.

### Strategies to Reduce Bleeding Events

**Warfarin**
- Improve the patient’s time in therapeutic range (TTR)
  - Ideally patients should be enrolled in an anticoagulation clinic
  - Standardized dosing nomograms, education, periprocedural management
  - Increase testing frequency
  - Self-testing or even self-management of warfarin
  - Improve transitions of care
  - Consider novel anticoagulants for patients consistently out of goal range

**Mechanical valve or valvular Afib**
- Warfarin
  - Increased risk of stroke, MI, and valve thrombosis

**Liver dysfunction**
- Warfarin
  - New agents require hepatic metabolism

**CrCl < 30 mL/min**
- Warfarin
  - Studies of new agents excluded patients with severe renal disease

**CrCl 30-50 mL/min**
- Warfarin
  - Rivaroxaban
  - Apixaban
  - Factor Xa inhibitors rely much less on renal function for elimination compared to dabigatran

**Recent GI Bleed**
- Warfarin
  - Rivaroxaban
  - Apixaban
  - Dabigatran and rivaroxaban associated with increased GI bleeding

**Recent ischemic stroke on warfarin**
- Dabigatran
  - Dabigatran 150mg BID associated lower risk of ischemic stroke than warfarin

**Recent ischemic stroke on novel anticoagulants**
- Apixaban
  - Not available

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3/17/2014
Acute Coronary Syndrome and A fibrillation

Triple therapy (dual antiplatelet therapy + anticoagulation) with newer agents at least doubles risk of bleeding after ACS

No literature to compare bleeding risk between warfarin or newer agents in patients with ACS and A fibrillation

Personalize therapy based on risk factors

Perioperative Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Days to Hold Prior to Minor Surgery</th>
<th>Number of Days to Hold Prior to Major Surgery</th>
<th>Surgical Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (CrCl &gt; 50 mL/min)</td>
<td>Hold 3 doses (1 day)</td>
<td>Hold 6 doses (2 days)</td>
<td>Increased risk of major surgery with high bleeding risk</td>
</tr>
<tr>
<td>Dabigatran (CrCl ≤ 50 mL/min)</td>
<td>Hold 4 doses (1 day)</td>
<td>Hold 8 doses (2 days)</td>
<td>Surgical intervention requiring complete hemostasis, cardiac, neurosurgical, abdominal, orthopedic, organ, spinal, or need for spinal anesthesia</td>
</tr>
</tbody>
</table>

Assessment of both bleeding and thrombotic potential should be completed prior to holding therapy.

Note: patients with warranting renal function will likely require more time to achieve adequate hemostasis prior to procedure, especially for dabigatran—consideration for holding therapy longer may be warranted.

References


Take Home Message

Be familiar with your institution’s policies on reversal

Limited data on reversal – create consensus among key players in your organization

Re-evaluate your anticoagulation patients for effective therapy

References


Questions?