Oral Anticoagulant Therapies: A Balancing Act

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Learning Objectives
At the conclusion of this presentation, participants will be able to
• Identify risk factors for bleeding complications with oral anticoagulant agents
• Discuss strategies for minimizing the risk of bleeding with oral anticoagulant agents

Background
• Due to increase in the U.S. elderly population, prevalence of thrombosis related complications and bleeding associated with anticoagulants is constantly rising
• Various tools exist to assess thrombotic risk but assessment of bleeding risk is often ignored

Warfarin
• Widely used to prevent thromboembolism
• 2009, warfarin Rx for 3 million U.S. patients
• Leading cause of serious drug-related AEs – Bleeding 15-20%/yr; life-threatening 1-3%/yr

WARNING: BLEEDING RISK
See full prescribing information for complete boxed warning.
• Warfarin sodium can cause major or fatal bleeding. (5.1)
• Perform regular monitoring of INR in all treated patients. (2.1)
• Drugs, dietary changes, and other factors affect INR levels achieved with warfarin therapy. (7)
• Instruct patients about prevention measures to minimize risk of bleeding and to report signs and symptoms of bleeding. (17)

Coumadin (warfarin sodium) prescribing information. 2011 Oct (URL in ref list).

INR = (Patient’s PT in Seconds) / Mean Normal PT in Seconds

INR = International Normalized Ratio
ISI = International Sensitivity Index
PT = Prothrombin Time

Anticoagulants: Mode of Action


Warfarin Pharmacokinetics
Elimination half-life of warfarin
• R-warfarin: 45 hours
• S-warfarin: 29 hours

Elimination half-life of vitamin K dependent clotting factors
• II 42-72 hours
• VII 4-6 hours
• IX 21-30 hours
• X 27-48 hours

PT measures depression in factors II, VII, X
Kinetics of Warfarin and Clotting Factors


Clinical Predictors of Prolonged Delay in Return of INR to Therapeutic Range

N 633 patients with INR > 6.0/various indications
Outcome % patients with INR > 4.0 after holding warfarin x 2 days
Age 69 (25-95) [36% > 75 years]

INR > 4 after holding 2 doses 37%

Age, per decade of life OR 1.18 p value 0.04
Index INR, per unit 1.25 <0.001
Clinical CHF 2.79 0.009
Active malignancy 2.48 0.03
Weekly warfarin dose per 10 mg increase 0.87 0.009


Properties of Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>Xa</td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
<td>40%</td>
</tr>
<tr>
<td>t½ in hours by CrCl (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt; 80</td>
<td>8-15</td>
<td>14-17</td>
<td>5-9h</td>
<td>9-11</td>
</tr>
<tr>
<td>CrCl 50 – 79</td>
<td>14.6</td>
<td>16.6</td>
<td>8.7</td>
<td>NA</td>
</tr>
<tr>
<td>CrCl 30 – 49</td>
<td>17.6</td>
<td>18.7</td>
<td>9.0</td>
<td>NA</td>
</tr>
<tr>
<td>CrCl &lt; 30</td>
<td>17.3</td>
<td>27.5</td>
<td>9.5</td>
<td>NA</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>Unlikely</td>
<td>Yes</td>
<td>Unlikely</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

Decreased renal function is associated with an increase in anticoagulant effect

NA = not available


Novel Anticoagulants for SPAF Safety Endpoint: Major Bleeding


Institute for Safe Medication Practices: Serious Bleeding with Dabigatran

- ISMP QuarterWatch Report 2011
- Dabigatran linked to
  - 3781 serious adverse events
  - 2367 cases of hemorrhage
  - 542 patient deaths

Table 4. Suspect drugs ranked by number of direct reports to ISMP 2011

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug Name</th>
<th>Year</th>
<th>Direct</th>
<th>Report Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DABIGATRAN</td>
<td>2010</td>
<td>617</td>
<td>Susp</td>
</tr>
<tr>
<td>2</td>
<td>RIVAROXAN</td>
<td>1998</td>
<td>498</td>
<td>Susp</td>
</tr>
<tr>
<td>3</td>
<td>LEUVORIDON</td>
<td>1996</td>
<td>393</td>
<td>Susp</td>
</tr>
<tr>
<td>4</td>
<td>CARBOPATIN</td>
<td>1989</td>
<td>376</td>
<td>Susp</td>
</tr>
</tbody>
</table>


Ying – Yang Principle: Thrombosis vs. Bleeding

- With every approach to reduce thrombosis, there is an accompanying risk of increasing bleeding complications
- Conversely, reducing bleeding complications may increase thrombotic events
  - Both increase morbidity and mortality
- Balancing both ends of the spectrum is essential, and an individualized approach to therapy is advocated
Patient Case

- 69-year-old African American woman
- HTN (uncontrolled 165/95), DM, CRI (CrCl 35 mL/min) and HLD
- Presents to ER with dizziness and palpitations
- EKG: Atrial fibrillation, rate of 110 bpm
- Exam: normal, Labs: WNL, Cr 1.5
- Meds: lisinopril, simvastatin, glipizide
- SH: ETOH (+), 2-3 drinks/day
- Patient started on oral diltiazem XR 120 mg daily

Q1: This patient’s risk of a cardioembolic stroke is
a. Low
b. Moderate
c. High
d. Super high…ticking time bomb

Q2: This patient’s risk of bleeding is
a. Low
b. Moderate
c. High
d. Super high…ticking time bomb

Q3: What is this patient’s HAS-BLED score?

- a. 1
- b. 2
- c. 3
- d. 4
Stroke Prevention in Atrial Fibrillation
Balancing Stroke and Bleeding Risk

***HEMORR2HAGES Score***

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic or renal disease</td>
<td>1 ea</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Older age: &gt; 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Reduced platelet count or FxM</td>
<td>1 ea</td>
</tr>
<tr>
<td>Re-bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension, uncontrolled</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>1</td>
</tr>
<tr>
<td>Elevated taf risk a</td>
<td>1</td>
</tr>
<tr>
<td>Neumropsychiatric disease</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
</tbody>
</table>

**MAXIMUM** 14

***HAS-BLED Score***

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, SBP &gt; 160 mmHg</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function</td>
<td>1 ea</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding history or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Class IIIa or IVla INRs</td>
<td>2</td>
</tr>
<tr>
<td>Elderly: age &gt; 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol use: &gt; 8 servings/week</td>
<td>1</td>
</tr>
</tbody>
</table>

**MAXIMUM** 11


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Perioperative Management Considerations

**Bleeding**

SURGERY / INVASIVE PROCEDURE

**Thrombosis**

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**PRE-operative Management Considerations**

- Minor surgery
  - Low bleeding risk
  - Can have some residual AC effect at time of surgery
- Major surgery
  - High bleeding risk
  - Spinal anesthesia
  - Aim to have minimum or NO residual AC effect at time of surgery

- Allow longer period of time before surgery
  - Elderly
  - Known impaired renal function
  - Known clinical factors to cause delay in INR drop or drug elimination for novel oral anticoagulants

**Number of half-lives elapsed** | % of Drug Effect Remaining
---------------------------------|------------------------
1                                  | 50                     |
2                                  | 25                     |
3                                  | 12.5                   |
4                                  | 6.25                   |
5                                  | 3.125                  |

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**Postoperative Management Considerations**

- Consider the effect of surgery, risk of bleeding, and bowel motility
- Resume once adequate hemostasis has been achieved

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**Stroke Prevention in Atrial Fibrillation: ESC 2012 Guidelines**

Recommendations for prevention of thromboembolism in non-valvular AF—bleeding

Recommendations for Timing of Warfarin around Invasive Procedures

Discontinuation 5 days before scheduled procedure

Resumption "12-24 hours after surgery and when there is adequate hemostasis"

(To minimize bleeding risk, use patient’s pre-operative dose rather than reloading)


Interruption of Novel Oral Anticoagulant Therapy for Invasive Procedures and Surgery

<table>
<thead>
<tr>
<th>Drug (Renal Function)</th>
<th>No. of Doses to Skip before Minor Procedure</th>
<th>No. of Doses to Skip before Major Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (CrCl &gt; 50 mL/min)</td>
<td>1 or 2</td>
<td>4</td>
</tr>
<tr>
<td>Dabigatran (CrCl ≤ 50 mL/min)</td>
<td>3 or 4</td>
<td>6-8</td>
</tr>
<tr>
<td>Rivaroxaban (CrCl &gt; 50 mL/min)</td>
<td>1 or 2</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1 or 2</td>
<td>3 or 4</td>
</tr>
</tbody>
</table>

*Resume therapy 24-48 hr after minor procedure, 48-72 hr after major surgery. If UFH or LMWH is used as bridging therapy in patients with atrial fibrillation, mechanical heart valve, or venous thromboembolism who are at high risk for thromboembolism, oral anticoagulant therapy should be resumed at least 1 hr after UFH infusion is discontinued and at least 10 hr after last dose of LMWH.

bAssuming dabigatran is taken twice daily, rivaroxaban is taken once daily, and apixaban is taken twice daily.


Measurement of Anticoagulation Effect

- Under- or overdosing
- Drug interactions
- Progressive renal insufficiency
- Adherence assessment
- Invasive procedures, surgery
- Thrombolytic therapy
- Triple antithrombotic therapy
- Extremes of age, weight

Hematology Testing: Novel Oral Anticoagulants

Usefulness of Lab Test

<table>
<thead>
<tr>
<th>Lab tests</th>
<th>Strong</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECT</td>
<td></td>
<td>Chromogenic anti-Xa</td>
<td>Chromogenic anti-Xa</td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td></td>
<td>aPTT, PT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aPTT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT/INR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Summary

- Assessment of bleeding risk must be objective with the use of bleeding risk scores
- Health care providers must maintain a fine balance between thrombosis and bleeding in choosing and managing oral anticoagulant therapy
- Novel agents with multiple doses and indications
  - Special attention to half-life and renal function
  - Various agents will require different algorithms for managing invasive procedures and reversal approaches
Options for Reversing the Effects of Oral Anticoagulants

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Senior Manager, Patient Care Services
Henry Ford Hospital
Detroit, Michigan

Learning Objectives
At the conclusion of this presentation, participants will be able to
• Describe the relative benefits and limitations of emergent anticoagulant reversal strategies
• Discuss the clinical evidence supporting the use of emergent anticoagulant reversal strategies

Q4: Which of the following patients taking warfarin would require pharmacologic reversal of anticoagulation? Select all that apply.

a. INR of 4, presenting to ED with complaints of hematemesis
b. INR of 12 and no signs or symptoms of bleeding
c. INR of 2.2, requiring emergent coronary artery bypass graft surgery
d. INR of 7 and no signs or symptoms of bleeding

Clinical Scenarios for Reversal

Basis for Understanding Reversal
**Vitamin K Dependent Factor Formation**

Vitamin K Dependent Factor Precursor → Reduced Vitamin K → Vitamin K Oxidase Reductase → Oxidized Vitamin K → Vitamin K Dependent Factor

**Basis for Understanding Reversal**

- **Intrinsic Pathway**
  - Tissue Factor → VIIa → XI → XII → IXa
  - Thrombin (IIa) → Fibrinogen → Fibrin
- **Extrinsic Pathway**
  - Platelet Activation → Fibrinogen → Fibrin

**Reversal with Vitamin K**

- **Intrinsic Pathway**
  - Exogenous vitamin K allows liver to produce more II, VII, IX, X...
- **Extrinsic Pathway**
  - Tissue Factor → VIIa → XI → XII → IXa

**Vitamin K**

- **Dosing issues**
  - Supratherapeutic INR
    - Oral is preferred
  - Urgent situations
    - IV is preferred
    - NO subcutaneous or IM
- **Adverse events**
  - Anaphylactic reaction to IV
  - May be refractory to warfarin when restarted
    - Use lowest dose possible to avoid

**IV Vitamin K for Reversal of Warfarin**

- INR decline with IV Vitamin K

**Warfarin Reversal: Vitamin K**

<table>
<thead>
<tr>
<th>INR</th>
<th>Hold</th>
<th>PO Vitamin K</th>
<th>IV Vitamin K</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 – 10</td>
<td>Yes</td>
<td>No advantage to vitamin K use in these patients</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>Yes</td>
<td>2 – 2.5 mg</td>
<td>No</td>
</tr>
<tr>
<td>Any + bleeding</td>
<td>Yes</td>
<td>No</td>
<td>5 – 10 mg slow</td>
</tr>
</tbody>
</table>

Evidence: INR > 10 and No Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Oral Vitamin K Dose</th>
<th>Any Bleeding (n)</th>
<th>Major Bleeding (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunther 2004</td>
<td>2 mg</td>
<td>Vitamin K = 0a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>16b</td>
<td>f1b</td>
</tr>
</tbody>
</table>

*Day 3
1Day 7

Low rate of bleeding with oral vitamin K
No patients refractory to warfarin with oral vitamin K


Reversal of Warfarin: Bleeding or Need for Emergent Surgery

Options
- IV vitamin K
- Fresh frozen plasma (FFP)
- Prothrombin complex concentrate (PCC)

Options
- Recombinant factor VIIa (rFVIIa)
- Activated PCC (aPCC)

Fresh Frozen Plasma

- How does it work?
  - Contains all blood factors found in plasma
- Dosing
  - 1 unit = 200 – 250 mL
    - Weight based
    - 10 – 20 mL/kg → 20 – 30% increase in any factor level
  - 2 units FFP
- Disadvantages
  - Volume of fluid administration – 400 mL or more!
  - Thawing may delay therapy
  - Infectious disease concerns
  - Hemolytic transfusion reactions and hypersensitivity

Concentrated Blood Factor Products

<table>
<thead>
<tr>
<th></th>
<th>rFVIIa</th>
<th>3-factor PCC</th>
<th>4-factor PCC</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand</td>
<td>Novo-Seven®</td>
<td>Bebulin VH®</td>
<td>Octaplex®</td>
<td>FEIBA®</td>
</tr>
<tr>
<td>Names</td>
<td>Profilnine SD®</td>
<td>Beriplex P/N®</td>
<td>Cofact®</td>
<td></td>
</tr>
<tr>
<td>Availability</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Factors Provided</td>
<td>VII</td>
<td>II, IX, X</td>
<td>II, VII, IX, X</td>
<td>II, VII, IX, X</td>
</tr>
<tr>
<td>Activated?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Prothrombin Complex Concentrates (PCCs)

Approximate Factor Concentrations in Available PCCsa,b

<table>
<thead>
<tr>
<th>Factor</th>
<th>Profilnine SD®</th>
<th>Beriplex P/N®</th>
<th>Octaplex®</th>
<th>Cofact®</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>≤ 35-40</td>
<td>31</td>
<td>38</td>
<td>14-35</td>
</tr>
<tr>
<td>VII</td>
<td>≤ 10</td>
<td>16</td>
<td>24</td>
<td>7-20</td>
</tr>
<tr>
<td>IX</td>
<td>25</td>
<td>29</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>X</td>
<td>≤ 25</td>
<td>41</td>
<td>30</td>
<td>14-35</td>
</tr>
</tbody>
</table>

*Concentration expressed as units/mL. Actual concentrations vary from lot to lot.
Profilnine SD (factor IX complex) prescribing information. 2010 Aug (URL in ref list).

Concentrated Blood Factors

- Dosing issues
  - Fixed dosing vs. weight based
  - Extrapolating results reported in literature
  - Variability in factor concentrations by PCC product
- Adverse events
  - Prothrombotic potential
    - Especially with “activated” products
      - rFVIIa, aPCC
    - Anticipated benefit must outweigh prothrombotic risk
      - WHO should be reversed will be discussed in the next presentation
Warfarin Reversal with a 3-Factor PCC

**Study**  Holland and Colleagues

<table>
<thead>
<tr>
<th>Patients</th>
<th>n = 40 PCC/42 Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>INR &gt; 5 with bleeding or at risk for bleeding</td>
</tr>
<tr>
<td></td>
<td>ICH excluded</td>
</tr>
<tr>
<td></td>
<td>Control group: historical controls</td>
</tr>
<tr>
<td>Dosing</td>
<td>PCC: 25 units/kg; High: 50 units/kg</td>
</tr>
<tr>
<td></td>
<td>FFP: 2 units per prescriber; Vitamin K 1 – 10 mg</td>
</tr>
<tr>
<td>Findings</td>
<td>Target INR &lt; 3 within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Baseline INR: 8.6 – 9.4</td>
</tr>
<tr>
<td></td>
<td>Low and high dose had similar effect on INR</td>
</tr>
<tr>
<td></td>
<td>PCC alone: 43 – 55% achieved INR target</td>
</tr>
<tr>
<td></td>
<td>FFP alone: 62% achieved INR target</td>
</tr>
<tr>
<td></td>
<td>PCC + FFP: 89 – 93% achieved INR target</td>
</tr>
</tbody>
</table>


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Warfarin Reversal with 3-Factor PCC

**Summary of Evidence**

- Shortened time to reduction in INR
  - Faster than FFP alone
  - Data limited by nonstandard monitoring after PCC
- 3-factor PCCs mostly studied in addition to FFP
  - Reduced FFP requirements
- Dose is typically 25 – 50 units/kg (IX)
- Lack of clinical outcome data


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Warfarin Reversal with a 4-Factor PCC

- Case series
  - 85 doses/82 patients
- Reversal strategy
  - Octaplex
  - Vitamin K (69/85 doses)
  - 4.9 + 5.5 mg
  - FFP – not used
- Results
  - Mean INR ↓
  - 3.98 ± 5.86
  - Thrombosis: 3
  - Death: 7
  - 4 surgical
  - 3 bleeding


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Warfarin Reversal with a 4-Factor PCC: Impact on Outcomes

- Reversal due to bleeding
  - n = 212
- Randomized, open-label
  - 4-factor PCC (25 – 50 units/kg, based on INR)
  - FFP (10 – 15 mL/kg, based on INR)

**KEY FINDINGS**

- Bleeding: similar at 24 hours
- INR correction: faster with 4-factor PCC
- Fluid overload: less with 4-factor PCC


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Warfarin Reversal with a 4-Factor PCC

**Summary of Evidence**

- INR “normalized” in minutes to hours
  - May normalize in as little as 15 – 20 minutes
- 4-Factor PCCs effective for reducing INR without FFP
  - Effect on bleeding similar to FFP
- Dosing is often 25 – 50 units/kg (IX)
  - Maybe fixed doses or INR-specific doses
- Thromboembolic complications
  - Infrequent, but have occurred
- Surrogate endpoints


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Warfarin Reversal with Factor VIIa

**Retrospective, Observational Study**

≥ 18 y/o + traumatic ICH + warfarin use w/ INR > 1.3

**Standard Management (n = 20)**

- FFP ± vitamin K
- Other supportive measures or surgical interventions

**Factor VIIa Management (n = 20)**

- Factor VIIa (mean = 17.7 ± 5.2 u/mL/kg)
- FFP ± vitamin K
- Other supportive measures or surgical interventions

### Warfarin Reversal with Factor VIIa

<table>
<thead>
<tr>
<th></th>
<th>Standard (n=20)</th>
<th>FVIIa (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial INR</td>
<td>2.51</td>
<td>2.87</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>FFP (units)</td>
<td>4.6</td>
<td>2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>800%</td>
<td>95.0%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Time to surgery</td>
<td>74.6</td>
<td>5.6</td>
<td>0.30</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>35.0%</td>
<td>35.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>5.0%</td>
<td>20.0%</td>
<td>0.15</td>
</tr>
<tr>
<td>INR &lt; 1.3</td>
<td>68.4%</td>
<td>100%</td>
<td>0.02</td>
</tr>
<tr>
<td>Time to INR &lt; 1.3 (hr)</td>
<td>17.5</td>
<td>4.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


### Warfarin Reversal: 3-Factor PCC vs. Factor VIIa

#### Design: Retrospective cohort

**Patients:** Adult patients presenting with ICH, taking warfarin

<table>
<thead>
<tr>
<th></th>
<th>Factor VIIa (n = 15)</th>
<th>PCC* (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline INR</td>
<td>6.1a</td>
<td>2.3^</td>
</tr>
<tr>
<td>1-hour INR</td>
<td>1.1a</td>
<td>1.48^</td>
</tr>
<tr>
<td>Treatment dose</td>
<td>53.4 mcg/kg</td>
<td>27.8 units/kg</td>
</tr>
<tr>
<td>Vitamin K dose</td>
<td>17.8 ± 14.6 mg</td>
<td>17.1 ± 12.9 mg</td>
</tr>
<tr>
<td>FFP</td>
<td>1025 ± 828 mL</td>
<td>778 ± 484 mL</td>
</tr>
</tbody>
</table>

*aBebulin VH, 3-factor PCC


### “Building” a 4-Factor PCC

**Patients**
- Warfarin related ICH, INR ≥ 1.6 (46)
- Historical controls (12)

**Reversal strategy**
- IV Vitamin K 5 mg slow IV
- PCC 4000 units
- Factor VIIa 1 mg

**Complications**
- 2 NSTEMI
  - 1 occurred 8 hours post PCC+FVIIa
  - 1 occurred 3 days later
- Mortality
  - 24 hours – 5/46
  - 72 hours – 8/46

**Options for Reversal of Warfarin**

**Patients requiring reversal (n = 72)**
- Historical controls receiving FFP (n = 69)

**Reversal strategy**
- IV Vitamin K 10 mg slow IV
- aPCC 500 units if INR < 5
- aPCC 1000 units if INR ≥ 5
- FFP dosing in control patients
  - Discretion of prescriber (~2 units)

**Other results**
- Time to INR < 1.4
  - 2 hr vs. 25 hr (p = 0.006)

**Thromboembolic complications**
- 1 venous thromboembolism
- 3 possible episodes of cardiac ischemia

**Options for Reversal of Warfarin**

- Hold
- PO Vitamin K
- IV Vitamin K
- Factors*

*Generally reflects co-administration of vitamin K ± FFP


### Warfarin Reversal: 3-Factor PCC vs. Factor VIIa

#### Unexpected response to PCC due to low use of FFP ± vitamin K?


### Warfarin Reversal: aPCC

**Patients**
- Patients requiring reversal (n = 72)
- Historical controls receiving FFP (n = 69)

**Reversal strategy**
- IV Vitamin K 10 mg slow IV
- aPCC 500 units if INR < 5
- aPCC 1000 units if INR ≥ 5
- FFP dosing in control patients
  - Discretion of prescriber (~2 units)

**Other results**
- Time to INR < 1.4
  - 2 hr vs. 25 hr (p = 0.006)

**Thromboembolic complications**
- 1 venous thromboembolism
- 3 possible episodes of cardiac ischemia

Urgent Warfarin Reversal: Bleeding or Surgery

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Reversal Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>Vitamin K 5 – 10 mg slow IV + 4-factor PCC†</td>
</tr>
<tr>
<td>Surgery in &lt; 24 hours</td>
<td>IV vitamin K 5 – 10 mg slow IV + Either 4-factor PCC*, factor VIIa or aPCC‡</td>
</tr>
<tr>
<td>Surgery in &gt; 24 hours</td>
<td>May have time to use IV vitamin K alone‡</td>
</tr>
</tbody>
</table>

†Recommendation based on CHEST Guidelines (2C).
‡Recommendation based on published literature and pharmacodynamics of vitamin K.
*Note: 4 factor PCC not yet available in the United States, FFP or factor VIIa may be needed in addition to a 3-factor PCC to achieve desired effect on INR.


What can we do in the United States?

- Add FFP to either 3-factor PCC or factor VIIa
- FFP may not be tolerated by all
- 3-factor PCC + Factor VIIa
- aPCC alone

4-factor PCC approval soon?

Cost Implications of Reversal

<table>
<thead>
<tr>
<th>Agent</th>
<th>FFP + PCC</th>
<th>PCC + VIIa</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP (15 mL/kg)</td>
<td>$300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-factor PCC (25 units/kg)</td>
<td>$1932</td>
<td>$1932</td>
<td></td>
</tr>
<tr>
<td>Factor VIIa (20 mcg/kg)</td>
<td></td>
<td>$2820</td>
<td></td>
</tr>
<tr>
<td>aPCC (1000 units)</td>
<td></td>
<td></td>
<td>$1800</td>
</tr>
<tr>
<td>Cost/reversal regimen</td>
<td>$2232</td>
<td>$4752</td>
<td>$1800</td>
</tr>
</tbody>
</table>

* Assumes 80-kg patient and rounding to nearest vial size.
+ Acquisition cost (average wholesale price) for FFP = $60 per unit, PCC = $0.97/unit, factor VIIa = $1410/1-mg vial, aPCC = $1800/1056 units.

Q5: 75-year-old patient presents with new onset loss of consciousness and is found to have ICH. She takes warfarin 2.5 mg daily, and her INR is 3.2 today. Which of the following could be used alone to lower her INR?

a. Oral vitamin K
b. An activated PCC
c. A 3-factor PCC
d. IV vitamin K

DABIGATRAN and RIVAROXABAN

How do we reverse them?

- Not really sure
- Largely theoretical
- Based on very limited data
  - Animal models
  - Healthy volunteer studies
  - Case reports
Theoretical Support for Reversal

Animal Data

Human Data: Dabigatran and Rivaroxaban

Ex Vivo Study: Dabigatran and Rivaroxaban
Dabigatran: Factor VIIa and Hemodialysis

- 79-year-old man, CrCl = 36 mL/min
- Dabigatran 150 mg twice daily
- Required aortic valve replacement/CABG
  - Dabigatran held x 2 days prior to surgery
- Massive bleeding postoperatively
  - Managed with 5 doses of factor VIIa
  - Hemodialysis x 6 hours
- Supports previous pharmacokinetics study data suggesting 60 – 70% removal of dabigatran dose


Dabigatran: Perioperative Management

<table>
<thead>
<tr>
<th>Renal function (CrCl, mL/min)</th>
<th>Half-life (hours)</th>
<th>Time of last dabigatran dose before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 50 to 80</td>
<td>15</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 30 to 50</td>
<td>18</td>
<td>At least 48 hours</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>27</td>
<td>2 – 5 days</td>
</tr>
</tbody>
</table>

A high bleeding risk is associated with cardiac surgery, neurosurgery, abdominal surgery, and surgeries involving a major organ, advanced age, spinal anesthesia and other procedures in which complete hemostatic function is required, comorbid conditions (e.g., major cardiac, respiratory, or liver disease) and concomitant use of antiplatelet therapy.


Rivaroxaban: Perioperative Management

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>&gt;80 (n = 8)</th>
<th>50 – 79 (n = 8)</th>
<th>30 – 49 (n = 8)</th>
<th>&lt;30 (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (hr)</td>
<td>8.3</td>
<td>8.7</td>
<td>9.0</td>
<td>9.5</td>
</tr>
</tbody>
</table>

- AUC ↑ as CrCl ↓
- Most rivaroxaban clearance
  - Non-renal (hepatic)
  - Renal secretion
- High protein binding
- Limited clearance by glomerular filtration


Urgent Reversal of Novel Anticoagulants: Bleeding or Surgery

Possible strategies
- aPCC
  - Supported by animal and limited human data
- 3-factor PCC plus factor VIIa
  - Mimic effects of aPCC
- Maybe a 4-factor PCC
  - Conflicting animal data, limited human data

Urgent Reversal of Novel Anticoagulants: Practical Considerations

**Dabigatran**
- Charcoal after recent ingestion
- Renal impairment complicates reversal
  - Role for hemodialysis

**Rivaroxaban**
- Less reliance on renal clearance

**Dosing**
- Very little guidance
  - Higher doses than usual?

**Patient selection**
- Risk vs. benefit

**Conclusions**

Warfarin reversal
- Concentrated blood factors > FFP alone
  - All studies have some methodologic limitations

Reversal of dabigatran and rivaroxaban
- Concentrated blood factors may have a role
  - aPCC or 4-factor PCCs may be best approach
  - Extremely limited data
  - Human data lacking
- Lack of clear benefit + risk of blood factor products
- Proper patient selection is critical
Practical Issues in Developing an Oral Anticoagulant Reversal Strategy

William E. Dager, Pharm.D., BCPS (AQ-Cardiology)
Pharmacist Specialist
UC Davis Medical Center
Sacramento, California

Learning Objectives
At the conclusion of this presentation, participants will be able to
• Explain patient-specific treatment options for reversing the effects of oral anticoagulants using laboratory observations
• Develop an approach to managing major bleeding in a patient on oral anticoagulation therapy

Warfarin Situations
• 75 yo with AF, CKD V, heart failure, and CVA on warfarin 1 mg/day and has a GI bleed. INR = 12
• 56 yo with mechanical MVR brought into ED after crashing his motorcycle. Had notable abdominal injuries with hemorrhage apparent. INR = 3.0
• 27 yo with PE 1 year ago being assessed for colonoscopy. Warfarin 15 mg/day. INR = 2.5

Skill: Assess the Situation
• Bleeding?
  • Site: risk of a complication
  • Level of anticoagulation
    – Laboratory assay
    – Antiplatelet agents?
  • Hold anticoagulant

Skill: Explore Options
• Mechanical intervention
• Pharmacologic intervention
  • Intensity of anticoagulation (prior and post)
  • Goal or need for re-initiating therapy
  • Neutralize the drug
  • Reverse the effects of the drug independently

Skill: Consider the Entire Needs of the Patient
• Replace losses
• Optimize management of co-morbid situations
• Create a plan and request necessary follow up
• Evaluate thrombosis risks
Reversing Warfarin

Vitamin K (IV or PO) – 0.25 – 10 mg
Fresh frozen plasma (FFP)
Prothrombin complex concentrate (PCC)
  • PCC3 vs. PCC4 vs. activated PCC
  • 25-50 units/kg depending on patient’s weight, INR, and bleeding
Recombinant activated factor VII (rFVIIa)
  • Low (1-2 mg) vs. high dose

How Reliable Is the Laboratory Information?

• Single value?
• Rapidly rising vs falling
• INR: What is the difference between 6 and 12?


Warfarin

INR assay (How High)
  • Rising vs. falling INR (? 1.8 > 2.2)
  – Not reliable in first days (factor VII driven)
  • False DTI, UFH elevation
  – UFH (neutralization step in Lab?)
Hylek et al: INR > 6 → Risk Factors - INR ≥ 4 post 2-day hold
  • Age per decade of life
  • Initial INR (per 1.0 unit)
  • Heart failure
  • Weekly warfarin dose (per 10-mg increase)
  • Active cancer

Using Vitamin K

• What dose?
  – How fast do we need a response
• What route?
  – PO or IV (avoid SC or IM)
• Are other more rapid therapies planned (PCC, rFVIIa, FFP)
• Administration
  – Infusion rate – Max 1 mg/min (over ~15 – 20 min)
  – Light sensitive (~50 mL, avoid delay using large volumes)
  – Anaphylaxis concerns (3:10,000 risk)


Vitamin K for Reversing Warfarin

• Vit K IV: doses > 2 mg IV
  • Did not increase rate of reversal
  • ↑ dose → prolonged periods of bridging therapy


How Reliable Is the Laboratory Information?

Vitamin K for Reversing Warfarin

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Vitamin K for Reversing Warfarin

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What Improves Outcomes in Warfarin-related ICH?

- A good stitch
  - STICH Trial: Any impact of neurosurgery on improved outcomes
- Dowlatshahi et al. Stroke. 2012
  - PCC rapidly reversed the INR, but did not change mortality and morbidity
- PCC shorten time to surgical procedures
  - Surgery may improve ICU-related outcomes
- Caution rebound
- Effects rapid
  - Retrospective studies may not have control on INR times


PCC Considerations

- INR > 4.5 may not have sufficient rFVIIa (needs confirmation)
- UFH in PCC may increase risk for HIT
- Not recommended if AT deficiency
- Balanced PCC may be advantage in VKA reversal to decrease complications (needs confirmation)
  - 1. Regulatory anticoagulant proteins C and S → ↑ thrombogenicity
- PCCs reduce the INR within 10 minutes
- PCC 4 in the USA soon?


Hemostatic Agents and Thrombosis: After all... the patient was being anticoagulated!

Hsia et al: Retrospective, single center analysis of off-label use (n=69)
  - Mean dose = 8.2 mg rFVIIa
  - 36 thrombotic events, mean 8.8 days post rFVIIa
  - MD questioner: Not aware of any thrombotic events in these patients

Thromboembolism: PCC4 (~1.8%) vs. PCC3 (0.7%)

rFVIIa or PCC → Tissue Factor Expression → Thrombosis

TF also expressed on monocytes


Warfarin Situations

- 75 yo with AF, CKD V, heart failure, and CVA on warfarin 1 mg/day and has a GI bleed. INR = 12
- 56 yo with mechanical MVR brought into ED after crashing his motorcycle. Had notable abdominal injuries with hemorrhage apparent. INR = 3.0
- 27 yo with PE 1 year ago being assessed for colonoscopy. Warfarin 15 mg/day. INR = 2.5

Dabigatran Reversal Case

AC Jr. is a 85 yo man with acute decompensated heart failure and receiving dabigatran 150 mg PO BID for AF. He has fallen and hit his head and is being admitted to the ED.

Q6: Which of the following tests would you NOT request?

a. PT/INR
b. Antifactor Xa activity
c. Thrombin time
d. Serum creatinine
AC Jr. is an 85 yo man with acute decompensated heart failure and receiving dabigatran 150 mg PO BID for AF. He has fallen and hit his head and is being admitted to the ED.

- Baseline INR in ED = 2.0
- Thrombin time = > 200 seconds
- Scr = 2.0 mg/dL

MD orders Vit K 10 mg IV and FFP

Q7: Will you process this order?

a. Yes
b. No
c. I'm not sure

Assessing Intensity of Anticoagulation Effects

<table>
<thead>
<tr>
<th>Drug present</th>
<th>Thrombin time</th>
<th>Chromogenic anti-factor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td>High sensitive INR</td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban</td>
<td></td>
<td>Chromogenic anti-factor Xa</td>
</tr>
</tbody>
</table>

Quantitative tests:
- Dilute thrombin time or Chromogenic ECT
- PT vs. aPTT (Point-of-care INR > central lab)
- aPTT > TT
- No or limited effect

- INR/aPTT - Potential for normal values at trough/active levels

What does a value mean?
- Is there a safe level to operate?
- Is it too high where the dose should be lowered?


Dialysis of Dabigatran

- Design: Dabigatran 50 mg x 1 + 2 HD sessions; CKD V
- Not 150 mg multiple doses or AKI
- Hemodialysis ~2/3rds removed
- 2 hr Cp Arterial 12.5 ng/mL > Cp Venous 4.4 ng/mL

Wanek et al: Case report. 2.5 hr HD (BFR 500 mL/hr): ↓ TT 90 – 60 sec

Reversing Dabigatran: A Case Experience

Setting: AF and undergoing ablation, on dabigatran

Situation: Transeptal perforation, pericardial window, and > 3L blood loss

Action: FFP, protamine, PRBCs with limited to no effect on bleeding

- aPCC: 25 units/kg over 15 minutes
- Bleeding slows in first few minutes and has stopped before infusion completed


Dabigatran Reversal Case

AC Jr. is a 85 yo man with acute decompensated heart failure and receiving dabigatran 150mg PO BID for AF. He has fallen and hit his head and is being admitted to the ED.

- Baseline INR in ED = 2.0
- Thrombin time = > 200 seconds
- Scr = 2.0 mg/dL

- CT scan to assess damage
- Arrange management options (dialysis, hemostatic agent, calcium if blood given)
- Check time of last dose
- Assess bleeding
- Consider anticoagulation options
- Patient and physician education

Systems Support

- 24-hour process
- Correct labs available
- Guidelines on how to use the available agents
  - Easy for clinicians to locate
- Rapid ability to implement management options