Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

Presented as a Midday Symposium at the 47th ASHP Midyear Clinical Meeting and Exhibition

Monday, December 3, 2012
Las Vegas, Nevada

Planned and conducted by ASHP Advantage and supported by an educational grant from CSL Behring
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**AGENDA**

11:30 a.m. – 11:40 a.m.  **Welcome and Introductions**  
Edith A. Nutescu, Pharm.D., FCCP

11:40 a.m. – 12:00 p.m.  **Oral Anticoagulant Therapies: A Balancing Act**  
Edith A. Nutescu, Pharm.D., FCCP

12:00 p.m. – 12:40 p.m.  **Options for Reversing the Effects of Oral Anticoagulants**  
James S. Kalus, Pharm.D., BCPS (AQ-Cardiology)

12:40 p.m. – 1:10 p.m.  **Practical Issues in Developing an Oral Anticoagulant Reversal Strategy**  
William E. Dager, Pharm.D., BCPS (AQ-Cardiology)

1:10 p.m. – 1:30 p.m.  **Faculty Discussion and Audience Questions**  
All Faculty

**FACULTY**

**Edith A. Nutescu, Pharm.D., FCCP**  
*Activity Chair and Moderator*  
Clinical Professor  
The University of Illinois at Chicago College of Pharmacy  
Director, Antithrombosis Center  
The University of Illinois Hospital and Health Sciences System  
Chicago, Illinois

**James S. Kalus, Pharm.D., BCPS (AQ-Cardiology)**  
Senior Manager, Patient Care Services  
Department of Pharmacy Services  
Henry Ford Hospital  
Detroit, Michigan

**William E. Dager, Pharm.D., BCPS (AQ-Cardiology)**  
Pharmacist Specialist  
UC Davis Medical Center  
Sacramento, California
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The faculty and planners report the following relationships:

Edith A. Nutescu, Pharm.D., FCCP, Activity Chair

Dr. Nutescu declares that she has has served as a consultant for Daiichi-Sankyo Inc. and received a research grant and served as a consultant for Janssen Pharmaceuticals, Inc.

James S. Kalus, Pharm.D., BCPS (AQ-Cardiology)

Dr. Kalus declares that he has no relationships pertinent to this activity.

William E. Dager, Pharm.D., BCPS (AQ-Cardiology)

Dr. Dager declares that he has no relationships pertinent to this activity.

Susan R. Dombrowski, M.S., B.S.Pharm.

Ms. Dombrowski declares that she has no relationships pertinent to this activity.

Carla J. Brink, M.S., B.S.Pharm.

Ms. Brink declares that she has no relationships pertinent to this activity.

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Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

ACTIVITY OVERVIEW

As the armamentarium of oral agents for prevention and treatment of thrombosis expands, practitioners must develop strategies to deal with the proper management of anticoagulant-related bleeding complications. Patients on oral anticoagulants who are at high risk of bleeding, are actively bleeding, or require emergency invasive procedures will need adjunct therapies that reverse or remove anticoagulant effects sooner than withholding the drug.

This activity will provide an overview of the challenges associated with oral anticoagulant therapies, including risks for developing bleeding complications. Therapeutic options for reversing the effects of oral anticoagulants will be described, focusing on new and emerging options for reversal. Using different patient scenarios, the faculty will explore practical issues in developing a reversal strategy for oral anticoagulant therapy.

ACTIVITY OBJECTIVES

After attending this application-based educational activity, participants should be able to

- Identify risk factors for bleeding complications with oral anticoagulant agents.
- Apply strategies for minimizing the risk of bleeding with oral anticoagulant agents.
- Describe the relative benefits and limitations of emergent anticoagulant reversal strategies.
- Discuss the clinical evidence supporting the use of emergent anticoagulant reversal strategies.
- 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.
Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 2.0 hours (0.2 CEUs) of continuing pharmacy education credit (ACPE activity #0204-0000-12-438-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP CE Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are on the next page. Be sure to record the session code beginning with “A” announced during the activity.

New! PRACTICE REMINDER EMAIL

During this educational activity, we encourage you to jot down points about what YOU want to remember to do as a result of what you are learning.

• Use your smart device to link directly to the reminder tool and type in your ideas.
• Next month, we will send you an email as a reminder from YOURSELF about what YOU want to do after attending this activity.
• Do it more than once...multiple entries for this activity from the same email address will be combined into one email.
• If you do not have a smart device, go to the reminder tool on the activity website. http://www.ashpadvantage.com/reversal/?remindme=1
Instructions for Processing CPE online at http://ce.ashp.org

The ASHP CE Center allows participants to obtain statements of continuing pharmacy education (CPE) conveniently and immediately using any computer with an internet connection. To obtain CPE statements for ASHP Advantage activities, please visit http://ce.ashp.org

1. Log in to the ASHP CE Center using your e-mail address and password.
   If you have not logged in to the ASHP CE Center (launched August 2008) and are not a member of ASHP, you will need to set up an account by clicking on “Become a user” and follow the instructions.

2. Once logged in to the site, click on Process Meeting CE.

3. If you are a registered attendee at the ASHP Midyear Clinical Meeting, click on the start button to the right of ASHP Midyear Clinical Meeting 2012.
   If you are not registered to attend the ASHP Midyear Clinical Meeting, click on the start link to the right of the activity title. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The activity code is noted below. Click submit when prompted and then click on the start link to the right of the activity title. Do not click on “remove” next to an activity title unless you did not attend that activity.

4. Click on the click here link to view sessions associated with the day of the activity.

5. Enter the session code announced during the activity (e.g., A12XXX and note that the letter is case sensitive) and select the number of hours equal to your participation in the activity.

6. Click submit to receive the attestation page.

7. Confirm your participation and click submit.

8. Complete the overall Midyear evaluation and click the finish button. You will then be able to view and print your transcript.

<table>
<thead>
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<th>Activity Code</th>
<th>Session Code (announced during the live activity)</th>
<th>CPE credit hours</th>
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Your educational opportunities related to the reversal of anticoagulant therapy extend beyond today’s symposium…

- **A live Ask the Experts webinar** on March 20, 2013, during which faculty will explore issues raised by participant questions in today’s symposium (1 hour CPE)

- **Informational podcasts** featuring the faculty in a roundtable discussion about important issues related to reversal of anticoagulant therapy

- **e-Newsletters** featuring tips for incorporating information from this symposium into practice, as well as updates on emerging information on anticoagulant therapy reversal

- **Web-based activity** based on today’s live symposium (2 hours of CPE, but please note that individuals who claim CPE credit for the live symposium or webcast are ineligible to claim credit for the web-based activity)

- **Supplement** to the *American Journal of Health-System Pharmacy* (CPE hours to be determined)

For more information and to sign up to receive e-mail updates about this educational series, go to

www.ashpadvantage.com/reversal
Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

Edith A. Nutescu, Pharm.D., FCCP
Activity Chair and Moderator
Clinical Professor
The University of Illinois at Chicago College of Pharmacy
Director, Antithrombosis Center
The University of Illinois Hospital and Health Sciences System
Chicago, Illinois

Edith A. Nutescu, Pharm.D., FCCP, is Clinical Professor in the Department of Pharmacy Practice, Department of Pharmacy Administration, and Center for Pharmacoeconomic Research at University of Illinois at Chicago College of Pharmacy. She also is Director of the Antithrombosis Center at the University of Illinois at Chicago Medical Center.

Dr. Nutescu earned her Doctor of Pharmacy degree with high honors at the University of Illinois at Chicago College of Pharmacy. After graduation, she went on to complete a pharmacy practice residency at Lutheran General Hospital–Advocate Health Care in Park Ridge, Illinois, and a primary care specialty residency at the University of Illinois at Chicago Medical Center, both accredited by the American Society of Health-System Pharmacists (ASHP).

Dr. Nutescu maintains an active clinical practice and research program. Her research and practice interests are in the areas of comparative effectiveness, health services, and outcomes, with emphasis in cardiovascular diseases, stroke, thrombosis, and antithrombotic therapies. She has authored over 100 scientific articles and book chapters, and she coauthored “Anticoagulation Therapy: A Point-of-care Guide” published by ASHP in 2011. Her research has been funded by the Department of Health and Human Services, Agency for Healthcare Research and Quality, and National Center for Research Resources. She is a recipient of the Ruth L. Kirchstein National Research Service Award for 2010-2012. She has lectured extensively both nationally and internationally on topics related to thrombosis, antithrombotic therapies, cardiovascular diseases, and stroke.

Dr. Nutescu serves on the editorial boards for Pharmacotherapy, Annals of Pharmacotherapy, and Thrombosis, and she previously was on the editorial board for the American Journal of Health-System Pharmacy. Dr. Nutescu is active in several professional organizations, and she currently is a member of the Board of Regents for the American College of Clinical Pharmacy (ACCP), Board of Directors for Pharmacotherapy, and Board of Directors of the Anticoagulation Forum. She has served on the Oral Anticoagulant National Advisory Board of the National Consumers League Senior Outpatient Medication Safety Coalition and was the only pharmacist member nominated to serve on the steering committee of the National Quality Forum and The Joint Commission that developed “National Consensus Standards for the Prevention and Care of Venous Thrombosis.” Dr. Nutescu has been recognized as a fellow of ACCP and is the recipient of the ACCP 2009 Clinical Practice Award and ASHP Section of Home and Ambulatory Care Practitioners 2010 Distinguished Service Award.
Oral Anticoagulant Therapies: A Balancing Act

Edith A. Nutescu, Pharm.D., FCCP
Clinical Professor
The University of Illinois at Chicago College of Pharmacy
Director, Antithrombosis Center
The University of Illinois Hospital and Health Sciences System
Chicago, Illinois

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

Anticoagulants: Mode of Action

**Intrinsic system (surface contact)**
- X: Activates IX, X, XI, XII
- IX: Activates VIII
- VIII: Activates IX, X, XI
- XI: Activates IX
- XII: Activates IX

**Extrinsic system (tissue damage)**
- Tissue factor activates X
- X: Activates IX, X, XI
- IX: Activates VIII
- VIII: Activates IX, X, XI

**Heparins**
- Direct thrombin inhibitors
- Factor Xa inhibitors
- Vitamin K antagonists


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**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)
- 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).

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**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

\[ \text{INR} = \left( \frac{\text{Patient's PT in Seconds}}{\text{Mean Normal PT in Seconds}} \right) \]

PT = Prothrombin time
INR = International Normalized Ratio
ISI = International Sensitivity Index
Kinetics of Warfarin and Clotting Factors

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

Properties of Novel Oral Anticoagulants


Novel Anticoagulants for SPAF
Safety Endpoint: Major Bleeding

![Graph showing the comparison of novel anticoagulants for SPAF.

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>
<thead>
<tr>
<th>Rank</th>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Approved</th>
<th>Year</th>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>2010</td>
<td>2010</td>
<td>SAE</td>
</tr>
<tr>
<td>2</td>
<td>Warfarin</td>
<td>Coumadin</td>
<td>1954</td>
<td>1954</td>
<td>SAE</td>
</tr>
<tr>
<td>3</td>
<td>Apixaban</td>
<td>Brevanti</td>
<td>2001</td>
<td>2001</td>
<td>SAE</td>
</tr>
<tr>
<td>4</td>
<td>Edoxaban</td>
<td>Savaysa</td>
<td>2011</td>
<td>2011</td>
<td>SAE</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

Stroke Prevention in Atrial Fibrillation: Assessing Stroke Risk

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>CHA2DS2-Vasc Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
<td>Score</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA history</td>
<td>2</td>
</tr>
<tr>
<td>MAXIMUM</td>
<td>6</td>
</tr>
<tr>
<td>Age 65 – 74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category/female</td>
<td>1</td>
</tr>
<tr>
<td>MAXIMUM</td>
<td>9</td>
</tr>
</tbody>
</table>

Stroke Prevention in Atrial Fibrillation: Guideline Recommendations

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Chest (Grade of rec)</th>
<th>ACCF/AHA/HRS (Class of rec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (low)</td>
<td>No therapy (2B)</td>
<td>Aspirin (I)</td>
</tr>
<tr>
<td>1 (moderate)</td>
<td>OAC (1B)</td>
<td>OAC or aspirin (IIa)</td>
</tr>
<tr>
<td></td>
<td>Dabi &gt; warfarin*</td>
<td>Dabi alt to warfarin†</td>
</tr>
<tr>
<td>≥ 2 (high)</td>
<td>OAC (1A)</td>
<td>OAC (I)</td>
</tr>
<tr>
<td></td>
<td>Dabi &gt; warfarin*</td>
<td>Dabi alt to warfarin†</td>
</tr>
</tbody>
</table>

*Except in patients with CrCl < 30 mL/min, mitral stenosis, stable CAD, recent ACS, or s/p intra coronary stent
†Except in patients with prosthetic heart valves, hemodynamically significant valvular heart disease, CrCl < 15 mL/min, or advanced liver disease

Rivaroxaban and apixaban not approved at time of guideline publication; not included


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
### ESC 2012 Guidelines

**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>Ethanol 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</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 fall risk a</td>
<td>1</td>
</tr>
<tr>
<td>neuropsychiatric disease</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td><strong>MAXIMUM</strong></td>
<td>14</td>
</tr>
</tbody>
</table>

**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>Liabile INRs</td>
<td>2</td>
</tr>
<tr>
<td>Elderly: age &gt; 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol use: &gt; 8 servings/week</td>
<td>1</td>
</tr>
<tr>
<td><strong>MAXIMUM</strong></td>
<td>11</td>
</tr>
</tbody>
</table>

Gage BF et al. Am Heart J. 2006; 151:713-9

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### Perioperative Management Considerations

**Bleeding**

**Thrombosis**
**Perioperative Management Considerations**

- **PRE-operative**
  - Timing of when AC is stopped is anchored on agent PK characteristics and half-life.
  - Aim to stop AC agent before surgery so there is minimal or NO residual AC effect at the time of surgery.

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

**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.

**Pre-Operative Management Considerations**

<table>
<thead>
<tr>
<th>Number of half-lives elapsed</th>
<th>% of Drug Effect Remaining</th>
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<tbody>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>6.25</td>
</tr>
<tr>
<td>5</td>
<td>3.125</td>
</tr>
</tbody>
</table>

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.
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 (CICl &gt; 50 mL/min)</td>
<td>1 or 2</td>
<td>4</td>
</tr>
<tr>
<td>Dabigatran (CICl ≤ 50 mL/min)</td>
<td>3 or 5</td>
<td>6-8</td>
</tr>
<tr>
<td>Rivaroxaban (CICl &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.

*Assuming dabigatran is taken twice daily, rivaroxaban is taken once daily, and apixaban is taken twice daily.


Measurement of Anticoagulation Effect

- Under- or overdosing
- Invasive procedures, surgery
- Drug interactions
- Thrombolytic therapy
- Progressive renal insufficiency
- Triple antithrombotic therapy
- Adherence assessment
- Extremes of age, weight
Hematology Testing: Novel Oral Anticoagulants

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

Kinetics of Warfarin and Clotting Factors


Stroke Prevention in Atrial Fibrillation: ESC 2012 Guidelines

Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

**CLOTTING ASSAYS**

Prothrombin time (PT)
- Time in seconds for a clot to form after addition of calcium and thromboplastin to plasma

Thrombin time (TT)
- Measures the activity of thrombin in plasma

Ecarin clotting time (ECT)
- Directly measures thrombin generation

Activated partial thromboplastin time (aPTT)
- Measure of the intrinsic and final common pathway

Chromogenic anti-FXa assays
- Measure of coagulation during rivaroxaban and apixaban therapy

Others in development
- Dilute prothrombin time (dPT)
- Heptest (American Diagnostica, Stamford, CT)
- Prothrombinase-induced clotting time (PICT)
- Chromogenic anti-factor IIa assays

Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

SELECTED REFERENCES


Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy


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SELF–ASSESSMENT QUESTIONS

1. Which of the following scoring systems for bleeding risk assessment in patients with atrial fibrillation (AF) receiving oral anticoagulant therapy is recommended by the European Society of Cardiology?
   a. CHADS2.
   b. CHA2DS2-Vasc.
   c. HAS-BLED.
   d. HEMORR2HAGES.

2. CB is a 75-year-old woman with decompensated congestive heart failure, breast cancer, a creatinine clearance of 45 mL/min, and a new diagnosis of AF in whom stroke prophylaxis with a novel oral anticoagulant is contemplated. Which of these patient characteristics is most likely to affect the pharmacokinetics of novel oral anticoagulants and increase the risk for bleeding?
   a. Decompensated congestive heart failure.
   b. Advanced age.
   c. Renal impairment.
   d. Active cancer.

3. CB’s CHA2DS2-Vasc score and risk for stroke is
   a. 3, very high.
   b. 2, high.
   c. 1, intermediate.
   d. 0, low.

4. LM is a 57-year-old woman receiving rivaroxaban for AF who has a creatinine clearance of 95 mL/min and plans to undergo elective coronary artery bypass graft surgery. How many doses should be withheld to prevent perioperative bleeding?
   a. None.
   b. 1 or 2.
   c. 3 or 4.
   d. 6-8.

Answers
1. c
2. c
3. b
4. c
Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy
Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

James S. Kalus, Pharm.D., BCPS (AQ-Cardiology)
Senior Manager, Patient Care Services
Department of Pharmacy Services
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James S. Kalus, Pharm.D., BCPS (AQ-Cardiology), is Senior Manager of Patient Care Services in the Department of Pharmacy Services at Henry Ford Hospital in Detroit, Michigan. In this position, Dr. Kalus is responsible for planning, implementing, and managing all pharmacy services related to patient care. He also is responsible for formulary management, evaluation, and control. In addition, he oversees staff training and development, as well as pharmacy research. He is Program Director for the postgraduate year one (PGY-1) residency at Henry Ford Hospital and precepts a general inpatient cardiology rotation for pharmacy students and residents.

Dr. Kalus earned both his Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees at the University of Toledo in Toledo, Ohio. After completing a residency at the Medical University of South Carolina in Charleston, he did a two-year cardiovascular research fellowship through Hartford Hospital and the University of Connecticut in Hartford, Connecticut. Dr. Kalus was honored with the Outstanding Young Alumnus Award from the University of Toledo in 2009.

Before assuming his current position, Dr. Kalus served as Assistant Professor at the Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University in Detroit, Michigan. He is board certified as a pharmacotherapy specialist with added qualifications in cardiology.

In his research, Dr. Kalus focuses on cardiovascular disease, including the pathophysiology of atrial fibrillation (AF) occurring after cardiac surgery, novel strategies for the treatment and prevention of AF, and practice-based research related to anticoagulation. He has authored several textbook chapters and many articles published in peer-reviewed journals, including the American Journal of Health-System Pharmacy, Annals of Pharmacotherapy, Annals of Thoracic Surgery, Circulation, Journal of Electrocardiology, Journal of Hospital Medicine, Pharmacoeconomics, and Pharmacotherapy. He also serves on the editorial board of The Annals of Pharmacotherapy, Cardiology Panel.

Complementing the practice and research interests of Dr. Kalus is his involvement in professional associations. An active member of the American Society of Health-System Pharmacists (ASHP), he regularly speaks at educational sessions at the ASHP Midyear Clinical Meeting. As a member of the 2007 Research Affairs Committee of the American College of Clinical Pharmacy, he co-authored the report, “Recommended Education for Pharmacists as Competitive Clinical Scientists,” published in March 2009. The Southeastern Michigan Society of Health-System Pharmacists honored him with the 2008 Preceptor of the Year Award and the 2006 Innovative Practice Award. He also has received the Drug Therapy Research Award from the ASHP Research and Education Foundation, and, in 2009, Dr. Kalus and his colleagues were finalists for the Foundation’s Excellence in Medication Use Safety Award.
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

Basis for Understanding Reversal

Reversal with Vitamin K

Exogenous vitamin K allows liver to produce more II, VII, IX, X…
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

Orthro

IV Vitamin K for Reversal of Warfarin

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>89</td>
<td>2 mg</td>
<td>Vitamin K = 0(^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No vitamin K = 3(^a) n/a</td>
</tr>
<tr>
<td>Crowther 2010</td>
<td>107</td>
<td>2.5 mg</td>
<td>16(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Day 3  
\(^b\)Day 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  
  PLUS  
- Fresh frozen plasma (FFP)  
  OR  
- Prothrombin complex concentrate (PCC)  
  OR  
- Recombinant factor VIIa (rFVIIa)  
  OR  
- 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 \(\rightarrow\) 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>Brand Names</th>
<th>3-factor PCC</th>
<th>4-factor PCC</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NovoSeven®</td>
<td>Bebulin VH®</td>
<td>Octaplex®</td>
<td>FEIBA®</td>
</tr>
<tr>
<td></td>
<td>Profilnine SD®</td>
<td>Beriplex P/N®</td>
<td>Cofact®</td>
</tr>
<tr>
<td></td>
<td>Kanokad®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. Availability</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Factors Provided</td>
<td>VII</td>
<td>II, IX, X</td>
<td>II, VII, IX, X</td>
</tr>
<tr>
<td>Activated?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


Prothrombin Complex Concentrates (PCCs)

Approximate Factor Concentrations in Available PCCs^{a,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.


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

<table>
<thead>
<tr>
<th>Study</th>
<th>Holland and Colleagues</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40 PCC/42 Controls</td>
</tr>
</tbody>
</table>

**Patients**
- INR > 5 with bleeding or at risk for bleeding
- ICH excluded
- Control group: historical controls

**Dosing**
- **PCC low**: prothrombin 25 units/kg; High: prothrombin 50 units/kg
- **FFP**: ~ 2 units per prescriber; Vitamin K: 1 - 10 mg

**Findings**
- Target INR < 3 within 24 hours
- Baseline INR: 8.6 – 9.4
- Low and high dose had similar effect on INR
- PCC alone: 43 – 55% achieved INR target
- FFP alone: 62% achieved INR target
- PCC + FFP: 89 – 93% achieved INR target

ICH = intracranial hemorrhage


---

**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


---

**Warfarin Reversal with a 4-Factor PCC**

- **Case series**
  - 85 doses/82 patients
- **Reversal strategy**
  - Octaplex
  - 1792 ± 601 units
  - Vitamin K (69/85 doses)
  - 4.9 ± 5.6 mg
  - FFP not used
- **Results**
  - Mean INR ↓
    - 3.98 ± 5.86
  - Thrombosis: 3
  - Death: 7
  - 4 surgical
  - 3 bleeding

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


---

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


---

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 = 11.7 ± 6.2 mcg/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>6.1</td>
<td>2.3</td>
</tr>
<tr>
<td>1-hour INR</td>
<td>1.1</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>

*Bebulin VH, 3-factor PCC

#n = 6; ^n = 5


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

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

“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+VIIa
- 1 occurred 3 days later

Mortality
24 hours – 5/46
72 hours – 8/46

*PCC+VIIa less than FFP and PCC+FFP (p=0.05)


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


Options for Reversal of Warfarin

INR
0 2 4 6 8 10
HOURS
0 6 12 18 24 30 36 42 48 54 60

Hold
PO Vitamin K
IV Vitamin K
Factors*

*Generally reflects co-administration of vitamin K ± FFP

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# 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

Intrinsic Pathway
- XIa
- IXa

Extrinsic Pathway
- Tissue Factor
- VIIa
- Xa
- Thrombin (IIa)

Pharmacologic reversal may provide enough blood factors to overwhelm the effects of the drug.

Animal Data
Effect on Bleeding Time or Models of Bleeding in Animals

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-factor PCC</td>
<td>???</td>
<td>???</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Factor VIIa</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>aPCC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FFP</td>
<td>No</td>
<td>???</td>
</tr>
</tbody>
</table>


Human Data: Dabigatran and Rivaroxaban

aPTT = activated partial thromboplastin time
ECT = ecarin clotting time
ETP = endogenous thrombin potential
PT = prothrombin time
TT = thrombin time

Healthy volunteers (n = 10)

Rivaroxaban 20 mg BID (n = 6)
Dabigatran 150 mg BID (n = 6)

4-factor PCC or Placebo

24-hour serial lab monitoring
Dabigatran: aPTT, ETP lag time, ECT, TT
Rivaroxaban: PT, ETP

**Human Data: Dabigatran and Rivaroxaban**

**Dabigatran**
- No effect of PCC on ANY measure of coagulation

**Rivaroxaban**
- PT
  - Normalized within 15 minutes (p<0.001)
- ETP
  - Normalized within 15 minutes (p<0.001)


**Ex Vivo Study: Dabigatran and Rivaroxaban**

**Dabigatran**
- 150-mg single dose

**Rivaroxaban**
- 20-mg single dose

**Blood Drawn**
- Endogenous thrombin potential (ETP)
- Peak thrombin generation (PEAK)
- Lag time (LT)
- Time to peak thrombin (TTP)

**Blood Exposed to**
- Factor VIIa
- 4-factor PCC
- 3 different concentrations of each

**Measures of thrombin generation**


**Ex Vivo Study: Dabigatran and Rivaroxaban**

**Summary of Findings**
- 4-factor PCC and factor VIIa
  - Inconsistent impact on thrombin generation
    - Dabigatran patient blood
    - Rivaroxaban patient blood
- aPCC
  - Consistent impact on thrombin generation
    - Rivaroxaban patient blood
  - Less consistent impact on thrombin generation
    - Dabigatran
      - Still better than PCC and factor VIIa

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
    - 2.4 mg/dose x 3 dose + 7.2 mg/dose x 2 doses
    - 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>Standard bleeding risk</td>
<td>High bleeding risk</td>
<td></td>
</tr>
<tr>
<td>&gt; 80</td>
<td>13</td>
<td>24 hours</td>
</tr>
<tr>
<td>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>≤ 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 antithrombotic 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>≤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
SELECTED REFERENCES


Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy


Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy


SELF–ASSESSMENT QUESTIONS

1. DB is an 85-year-old woman who underwent hip fracture surgery 2 weeks ago, receives warfarin for venous thromboembolism prophylaxis, and comes to the clinic for a checkup. Her INR is 8, but she has no signs or symptoms of bleeding. Which of the following interventions is indicated for DB?
   a. Vitamin K.
   b. Fresh frozen plasma (FFP).
   c. Three-factor prothrombin complex concentrate (PCC) + recombinant factor VIIa (rFVIIa).
   d. No intervention is needed.

2. Which of the following vitamin K doses should be given to DB if she returns a week later with confusion about what medications to take, an INR of 11, and no signs of bleeding?
   a. 2-2.5 mg orally.
   b. 5-10 mg orally.
   c. 2-2.5 mg by slow intravenous (i.v.) injection.
   d. 5-10 mg slow i.v. injection.

3. All of the following concentrated blood factor products could be added for DB if she requires additional surgery on an emergent basis, EXCEPT
   a. Four-factor PCC.
   b. Activated PCC (aPCC).
   c. rFVIIa.
   d. 3-factor PCC.

4. Which of the following concentrated blood factor products have been used in combination to build a four-factor PCC product for urgent reversal in patients with warfarin-related intracranial hemorrhage (ICH) and elevated INR values in the United States where four-factor PCC products currently are not available?
   a. FFP + aPCC.
   b. FFP + rFVIIa.
   c. rFVIIa + three-factor PCC.
   d. aPCC + rFVIIa.

Answers
1. d
2. a
3. d
4. c
Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy
Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

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William E. Dager, Pharm.D., BCPS (AQ-Cardiology), is a pharmacist specialist at UC Davis Medical Center in Sacramento, California, where he is responsible for managing challenging cases in anticoagulation, pharmacokinetics, and critical care. He also is clinically active with the cardiology service and serves as the director of the postgraduate year two (PGY-2) residency in cardiology at UC Davis. In addition, Dr. Dager holds three academic positions. He is Clinical Professor of Pharmacy at the University of California, San Francisco (UCSF) School of Pharmacy and Clinical Professor of Medicine at the University of California, Davis (UC Davis) School of Medicine. He also serves as Clinical Professor at the Touro School of Pharmacy in Vallejo, California.

Dr. Dager earned his Doctor of Pharmacy degree at UCSF and completed a residency at the UC Davis Medical Center in Sacramento. In addition, he completed the University of Pittsburgh Nephrology Pharmaceutical Care Preceptorship. He is a board-certified pharmacotherapy specialist and fellow of the American College of Clinical Pharmacy (ACCP), American Society of Health-System Pharmacists (ASHP), California Society of Hospital Pharmacists, and Society of Critical Care Medicine (SCCM).

Dr. Dager's research interests focus on anticoagulation, critical care medicine, cardiovascular disease, and pharmacokinetics and pharmacodynamics. He has authored numerous articles, book chapters, and scientific reviews, and he coauthored “Anticoagulation Therapy: A Point-of-care Guide” published by ASHP in 2011. He also regularly makes presentations at national and international educational conferences. Dr. Dager serves as a reviewer and editorial board member for several medical journals, and he currently is chair of the Editorial Advisory Board Panel on Anticoagulation for The Annals of Pharmacotherapy. He has served as a site coordinator for the ASHP Research and Education Foundation Antithrombotic Pharmacotherapy Traineeship. Dr. Dager has received multiple teaching and professional awards, including the 2008 ACCP Best Practice Award.
Practical Issues in Developing an Oral Anticoagulant Reversal Strategy

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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

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


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%)


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)
  - Regulatory anticoagulant proteins C and S → ↑ thrombogenicity
- PCCs reduce the INR within 10 minutes
- PCC 4 in the USA soon?

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
Dabigatran Reversal Case

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

Is There a Way to Reverse these Agents?

<table>
<thead>
<tr>
<th>ETP</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>T ½</td>
<td>14-17 hr</td>
<td>5-9 hr; Elderly 11-13 hr</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Yes ~23 in 2 hr</td>
<td>Not expected (&gt; 90% bound) (Apixaban: 87% bound)</td>
</tr>
<tr>
<td>Antidote</td>
<td>In development</td>
<td></td>
</tr>
<tr>
<td>Hemostatic Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCC4 (50 units/kg)</td>
<td>- Did not restore aPTT, ECT, TT - rFVIIa alt. ETP lag time - PCC corrected ETP responsive &gt; rFVIIa</td>
<td>PT reversed, normalized ETP (114% Normal) PCC corrected ETP</td>
</tr>
<tr>
<td>Activated PCC (aPCC) (25-50 units/kg)</td>
<td>Altered ETP lag time Corrected all parameters</td>
<td></td>
</tr>
<tr>
<td>rFVIIa (high dose)</td>
<td>Effective – single case</td>
<td></td>
</tr>
</tbody>
</table>

Assessing Intensity of Anticoagulation Effects

<table>
<thead>
<tr>
<th>Drug present</th>
<th>Thrombin time</th>
<th>? Chromogenic anti-factor Xa</th>
<th>High sensitive INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>? Dilute thrombin time or Chromogenic ECT</td>
<td>Chromogenic anti-factor Xa</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban</td>
<td>PT &gt; aPTT</td>
<td>PT &gt; aPTT</td>
<td></td>
</tr>
</tbody>
</table>

Quantitative test

- 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
- Result: 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

Hemodialysis of Patients on Dabigatran

UCDMC experience
- Chromogenic dabigatran assay available
- Delays in initiating dialysis noted
- Plasma Cp rebound occurs
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

- Limited impact on TT, ECT, INR, or aPTT
- Low dose effective
- Single case report – Use caution


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
Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy

SELECTED REFERENCES


SELF-ASSESSMENT QUESTIONS

1. Adding rFVIIa to three-factor PCC in warfarin-treated patients with elevated INR values has been proposed to
   a. Enhance the rate of INR reduction.
   b. Reduce the risk for thromboembolism.
   c. Reduce costs.
   d. Reduce the risk for hypersensitivity reactions.

2. RD is a 66-year-old man with AF and a creatinine clearance of 28 mL/min who receives dabigatran 75 mg orally twice daily for stroke prevention. He comes to the clinic for a routine checkup and has no overt signs or symptoms of bleeding. Which of the following statements about the process for detecting bleeding in RD is correct?
   a. The absence of overt signs and symptoms of bleeding suffices to exclude the possibility of bleeding.
   b. Complete blood counts should be monitored for decreases reflecting blood loss.
   c. Laboratory coagulation assays are not needed because they do not provide useful information.
   d. Formal monitoring for bleeding is not needed because this complication is rare.

3. RD develops bleeding, and hemodialysis is used to remove dabigatran and reverse its anticoagulant effect. However, a rebound increase in plasma dabigatran concentration is observed after the end of the hemodialysis session. This rebound probably reflects
   a. The limited renal clearance of the drug.
   b. The small volume of distribution.
   c. The large volume of distribution and distribution of the drug into tissues.
   d. The large volume of distribution and redistribution of the drug from tissues to plasma.

4. Which of the following coagulation tests would be most useful as a qualitative test for the presence of dabigatran in RD after the drug is discontinued?
   a. TT.
   b. ECT.
   c. Point-of-care INR.
   d. A chromogenic anti-factor Xa assay.

Answers
1. a
2. b
3. d
4. a