Update on Stroke Prevention in Atrial Fibrillation

A knowledge-based CPE activity presented during the NYSCHP 2012 Downstate Midyear Meeting

Tuesday, September 11, 2012
LaGuardia, NY
9:00 am – 10:00 am

Planned and conducted by ASHP Advantage.
Supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.
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 (PGY1) 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. Of note, 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. He is board-certified as a pharmacotherapy specialist with added qualifications in cardiology.

In his research, Dr. Kalus focuses on atrial fibrillation (AF), including the pathophysiology of AF occurring after cardiac surgery and novel strategies for the treatment and prevention of AF. 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, 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.
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**ACTIVITY OVERVIEW**

With new therapeutic options and recent updates to evidence-based practice guidelines now available, this is a dynamic time for stroke prevention in atrial fibrillation (AF). This symposium will provide an overview of the basics related to preventing stroke in this patient population, as well as methods of assessing risk. It will then focus on changes in this practice area, including recent guideline updates and clinical data related to new and emerging therapeutic options. Potential strategies that pharmacists can use to address challenges related to stroke prevention and improve the care of patients with AF will be described.

**LEARNING OBJECTIVES**

At the conclusion of this knowledge-based CPE activity, participants should be able to

- Describe new and emerging therapeutic options for stroke prevention in AF.
- Describe the primary changes related to stroke prevention in the 2011 focused updates to the ACCF/AHA/HRS guideline on the management of patients with AF.
- Identify current and potential challenges and opportunities in stroke prevention in AF.

**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 1 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #204-000-12-401-L01P).

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

Complete instructions for receiving your CPE statement of credit online are on the next page. **Be sure to record the session code announced during this activity.**
Instructions for Processing Continuing Education

To obtain CE statements for live symposia, webinars, or webcasts, please visit the ASHP CE Center at [http://ce.ashp.org](http://ce.ashp.org).

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4. 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 and Session Codes** are announced at the end of the activity. Click **Submit** when prompted and then click on the **Start** link to the right of the activity title.

5. Enter the session code, which starts with the letter “A” and was announced during the activity, and select the number of hours equal to your participation in the activity. Participants should only claim credit for the amount of time they participate in an activity.

6. Click **Submit** to receive the attestation page.

7. Confirm your participation and click **Submit**.

8. Print and/or save your CE statement as appropriate.

9. Complete activity evaluation by selecting the **My Account** tab and continue to **My Transcript**.

10. Select the applicable year from the drop down menu and locate the activity.

11. Click **Complete Evaluation** under the **Status** column to be taken to the evaluation page.

12. Complete all evaluation questions and click **Finish**.

<table>
<thead>
<tr>
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<th>Activity Code</th>
<th>Session Code (announced during the live activity)</th>
<th>CE credit hours</th>
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</tr>
</tbody>
</table>

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Update on Stroke Prevention in Atrial Fibrillation

Objectives

• Describe new and emerging therapeutic options for stroke prevention in atrial fibrillation (AF).
• Describe the primary changes related to stroke prevention in the 2011 focused updates to the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guideline on the management of patients with AF.
• Identify current and potential challenges and opportunities in stroke prevention in AF.

Epidemiology of AF

• Most common arrhythmia in U.S.
  – Projected to affect 2.7-6.1 million in 2010
• Affects men more than women
• Incidence and prevalence increase with age
  – 70% of patients with AF between 65-85 yr
• Lifetime risk of AF in men and women ≥40 yr ~ 25%

Stroke in AF

• Incidence of all-cause stroke in patients with AF is 5%
• AF is an independent risk factor for stroke (↑ risk of stroke by 4-5-fold)
  – ~15-20% of all strokes in the U.S. are caused by AF
• Risk for stroke ↑ with age
• Stroke risk persists even in asymptomatic AF
• ↑ risk of mortality

New Antithrombotic Agents:

Ideal Characteristics

• Broad therapeutic window
  – Low inter- and intra-patient variability
  – No need for routine monitoring
• Oral administration
• No need for parenteral to oral switch
  – Use as single agent in acute and chronic indications and in both the hospital and home settings
• No drug or diet interactions
• Safe with low or no adverse effects
• Easily reversible with or without an antidote

Stroke Risk Stratification in AF

• CHADS2 score
  – Congestive heart failure = 1 point
  – Hypertension = 1 point
  – Age ≥75 years = 1 point
  – Diabetes = 1 point
  – Stroke/TIA = 2 points

TIA = transient ischemic attack
Update on Stroke Prevention in Atrial Fibrillation

New and Emerging Oral Antithrombotic Agents

- Direct thrombin inhibitors
  - Dabigatran
- Factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Idraparinux
  - Betrixaban
  - Edoxaban
  - Idrabiotaparinux

Comparison of New/Emerging Antithrombotic Agents

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10/10: Approved by FDA for stroke prevention in AF</td>
<td>7/11: Approved by FDA for VTE prophylaxis in ortho patients</td>
<td>11/11: Approved in Europe</td>
</tr>
<tr>
<td></td>
<td>6/12: Rejected by FDA for ACS indication</td>
<td>11/11: Approved by FDA for VTE prophylaxis in ortho patients</td>
<td>6/12: FDA grants priority-review for stroke prevention in AF indication</td>
</tr>
</tbody>
</table>

Direct Thrombin Inhibitors: Clinical Trials

RE-LY: Study Design

Atrial fibrillation ≥ 1 Risk Factor for Stroke
Randomized, non-inferiority
Open-Label Blinded
Warfarin
INR 2.0-3.0
n = 6022
Dabigatran 110 mg po BID
n = 6015
Dabigatran 150 mg po BID
n = 6076
Primary Efficacy Endpoint: Stroke or Systemic Embolism
Primary Safety Endpoint: Major Bleeding


RE-LY: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg (n = 6015)</th>
<th>Dabigatran 150 mg (n = 6076)</th>
<th>Warfarin (n = 6022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>71.4</td>
<td>71.5</td>
<td>71.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Stroke/TIA (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ASA (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin Naive (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


RE-LY: Primary Outcome

Composite: Stroke or Systemic Embolism

1.69%/yr
1.53%/yr (p<0.001)
1.11%/yr (p<0.001)

* Warfarin time-in-range = 64%

**Update on Stroke Prevention in Atrial Fibrillation**

**RE-LY: Primary Outcome**

Composite: Stroke or Systemic Embolism

- Dabigatran 110 mg vs. Warfarin
  - RR (95% CI): 0.91 (0.74 – 1.11)
  - NON-INFERIORITY MARGIN

- Dabigatran 150 mg vs. Warfarin
  - RR (95% CI): 0.66 (0.53 – 0.82)

Dabigatran 150 mg results driven by reduction in stroke


**RE-LY: Primary Safety Outcome**

Risk of Myocardial Ischemic Events with Dabigatran

<table>
<thead>
<tr>
<th>Study</th>
<th>Dabigatran</th>
<th>Control</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE</td>
<td>13</td>
<td>239</td>
<td>0.71 (0.30-1.67)</td>
</tr>
<tr>
<td>RE-MODEL</td>
<td>13</td>
<td>239</td>
<td>1.26 (0.39-4.02)</td>
</tr>
<tr>
<td>RE-NOVATE II</td>
<td>10</td>
<td>200</td>
<td>0.99 (0.08-16.96)</td>
</tr>
<tr>
<td>PETRO</td>
<td>2</td>
<td>143</td>
<td>0.78 (0.04-16.13)</td>
</tr>
<tr>
<td>RE-LY</td>
<td>179</td>
<td>260</td>
<td>1.38 (1.04-1.86)</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>4</td>
<td>169</td>
<td>1.98 (0.36-10.90)</td>
</tr>
<tr>
<td>RE-DEEM</td>
<td>32</td>
<td>415</td>
<td>1.72 (0.60-4.89)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.33 (1.03-1.71)</td>
</tr>
</tbody>
</table>

DVT prophylaxis trials: RE-NOVATE, RE-MODEL, RE-NOVATE II
AF trials: PETRO, RE-LY
DVT treatment trial: RE-COVER
ACS trial: RE-DEEM
ACE = acute coronary events


**RE-LY Secondary Analyses**

**Major Findings**

- **Time in therapeutic range**
  - The benefits of dabigatran were consistent irrespective of centers’ quality of INR control.
  - Advantages of dabigatran were greater at sites with poor INR control than at those with good INR control.

- **Risk of bleeding in older vs. younger patients**
  - Both doses of dabigatran have lower risks of intracranial and extracranial bleeding in patients <75 yr.
  - In patients ≥75 yr, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

- **Previous TIA or stroke**
  - The effects are consistent with other patients in RE-LY.

- **Cardioversion**
  - The frequencies of stroke and major bleeding within 30 days of cardioversion on dabigatran were low and comparable warfarin with or without TEE guidance.


**Factor Xa Inhibitors: Clinical Trials**
Update on Stroke Prevention in Atrial Fibrillation

ROCKET-AF: Study Design

Atrial Fibrillation
≥2 Risk Factors for Stroke
Randomized, Double-Blind, Double Dummy, Non-inferiority

Rivaroxaban
20 mg daily
(15 mg for CrCl 30-49 mL/min)
n = 7131

Warfarin
INR = 2-3
n = 7133

Primary Efficacy Endpoint: Stroke or Systemic Embolism
Primary Safety Endpoint: Major and Non-Major Clinically Relevant Bleeding
Median duration of treatment exposure 590 days

ROCKET-AF: Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rivaroxaban (n=7131)</th>
<th>Warfarin (n=7133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age—yr; median</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>BMI; median</td>
<td>28.3</td>
<td>28.1</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>2831 (39.7)</td>
<td>2832 (39.7)</td>
</tr>
<tr>
<td>Previous VKA use—no. (%)</td>
<td>4443 (62.3)</td>
<td>4461 (62.5)</td>
</tr>
<tr>
<td>CHADS2 score; mean</td>
<td>3.48 ± 0.94</td>
<td>3.46 ± 0.95</td>
</tr>
<tr>
<td>CHADS2 score; mean</td>
<td>3.48 ± 0.94</td>
<td>3.46 ± 0.95</td>
</tr>
<tr>
<td>CHF—no. (%)</td>
<td>3916 (54.9)</td>
<td>3895 (54.6)</td>
</tr>
<tr>
<td>Previous stroke or TIA—no. (%)</td>
<td>3916 (54.9)</td>
<td>3895 (54.6)</td>
</tr>
<tr>
<td>CHF—no. (%)</td>
<td>3916 (54.9)</td>
<td>3895 (54.6)</td>
</tr>
</tbody>
</table>

ROCKET AF: Primary Endpoint
Composite: Stroke or Systemic Embolism
On-Treatment Analysis

<table>
<thead>
<tr>
<th>Event Rate (%/pt-yr)</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.71</td>
<td></td>
<td>2.16</td>
</tr>
</tbody>
</table>

HR (95% CI): 0.79 (0.66-0.96)
p-value Non-Inferiority: <0.001

ROCKET AF: Primary Endpoint Results
Composite: Stroke or Systemic Embolism
On Treatment Analysis

<table>
<thead>
<tr>
<th>NON-INFERIORITY MARGIN</th>
</tr>
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<tbody>
<tr>
<td>0.79 (0.66 - 0.96)</td>
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</tbody>
</table>

ROCKET AF: Bleeding Rates

Major and Non-Major Clinically Relevant
Major
Non-Major Clinically Relevant
ICH

<table>
<thead>
<tr>
<th>%/100 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major and Non-Major Clinically Relevant</td>
</tr>
<tr>
<td>Major</td>
</tr>
<tr>
<td>Non-Major Clinically Relevant</td>
</tr>
</tbody>
</table>

ICH = intracranial hemorrhage

ROCKET-AF: Study Design

Atrial Fibrillation
CHADS2 score ≥1
Failed or unsuitable for warfarin therapy
Randomized, Double-Blind, Double Dummy, Superiority Trial

Apixaban 5 mg BID
(2.5 mg BID for pts with ≥2 of following:
≥80 yrs, wt ≤60 kg, SCr ≥1.5 mg/dL)
n = 2808

Primary Efficacy Endpoint: Stroke or Systemic Embolism
Primary Safety Endpoint: Major Bleeding

Early termination of study since primary outcome was met
Mean duration of follow-up = 1.1 years

AVERROES: Study Design

Atrial Fibrillation
CHADS2 score ≥1
Failed or unsuitable for warfarin therapy
Randomized, Double-Blind, Double Dummy, Superiority Trial

Apixaban 5 mg BID
Aspirin 81-324 mg daily
n = 2791

Primary Efficacy Endpoint: Stroke or Systemic Embolism
Primary Safety Endpoint: Major Bleeding

Early termination of study since primary outcome was met
Mean duration of follow-up = 1.1 years

Update on Stroke Prevention in Atrial Fibrillation

### AVERROES: Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Apixaban (n=2808)</th>
<th>Aspirin (n=2791)</th>
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<tbody>
<tr>
<td>Age—yr</td>
<td>70 ± 9</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 5</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Male sex—no. (%)</td>
<td>1660 (59)</td>
<td>1617 (58)</td>
</tr>
<tr>
<td>CHADS2 score— mean</td>
<td>2.0 ± 1.1</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>Score – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>1004 (36)</td>
<td>1022 (37)</td>
</tr>
<tr>
<td>≥2</td>
<td>758 (27)</td>
<td>812 (29)</td>
</tr>
<tr>
<td>Use of VKA within 30 days before screening –no. (%)</td>
<td>401 (14)</td>
<td>426 (15)</td>
</tr>
<tr>
<td>Use of ASA within 30 days before screening –no. (%)</td>
<td>2137 (76)</td>
<td>2081 (75)</td>
</tr>
</tbody>
</table>


### AVERROES: Results

<table>
<thead>
<tr>
<th>%/year</th>
<th>Apixaban</th>
<th>Aspirin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>3</td>
<td>3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>1.6</td>
<td>1.2</td>
<td>0.57</td>
</tr>
<tr>
<td>3.5</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
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</tbody>
</table>

ICH = intracranial hemorrhage


### ARISTOTLE: Study Design

- **Atrial Fibrillation CHADS2 score ≥ 1**
- Randomized, Double-Blind, Double Dummy, Non-inferiority Trial
- **Apixaban 5 mg BID** (2.5 mg BID for pts with ≥2 of following:
  1. ≥70 yrs
  2. wt ≤60 kg
  3. SCr ≥1.5 mg/dL) n = 9120
- **Warfarin INR 2-3** n = 9081

Primary Efficacy Endpoint: Stroke or Systemic Embolism
Primary Safety Endpoint: Major Bleeding

Median duration of follow-up = 1.8 years


### ARISTOTLE: Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Apixaban (n=9120)</th>
<th>Warfarin (n=9081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age—yr</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Weight—kg</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Female sex—no. (%)</td>
<td>3234 (35.5)</td>
<td>3182 (35.0)</td>
</tr>
<tr>
<td>Prior use of VKA for &gt;30 consec. days –no. (%)</td>
<td>5208 (57.1)</td>
<td>5193 (57.2)</td>
</tr>
<tr>
<td>CHADS2 score— mean</td>
<td>2.1 ± 1.1</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>≥1</td>
<td>3100 (34.0)</td>
<td>3083 (34.0)</td>
</tr>
<tr>
<td>2</td>
<td>3262 (35.8)</td>
<td>3254 (35.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>2758 (30.2)</td>
<td>2744 (30.2)</td>
</tr>
<tr>
<td>Age ≥75 yr—no. (%)</td>
<td>2890 (31.2)</td>
<td>2628 (31.1)</td>
</tr>
<tr>
<td>Prior stroke, TIA—no. (%)</td>
<td>1748 (19.2)</td>
<td>1790 (19.7)</td>
</tr>
<tr>
<td>CHF or reduced LVEF—no. (%)</td>
<td>3235 (35.5)</td>
<td>3216 (35.4)</td>
</tr>
</tbody>
</table>


### ARISTOTLE: Results

- **HR 0.79, 95% CI 0.66 -0.95; p=0.001 for non inferiority; p=0.01 for superiority**

Update on Stroke Prevention in Atrial Fibrillation

Study Differences

<table>
<thead>
<tr>
<th>Design</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
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<tbody>
<tr>
<td>Mean CHADS2 score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Mean TTR of warfarin</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>ASA use</td>
<td>Restrict to ≤ 100 mg/day</td>
<td>Restrict to ≤ 100 mg/day</td>
<td>Restrict to ≤ 165 mg/day</td>
</tr>
<tr>
<td>% ASA use at baseline</td>
<td>40% D 110 mg 38.7% D 165 mg 40.6% Warfarin</td>
<td>38.3% Riva 38.7% Warfarin 31.3% Apix 30.9% Warfarin</td>
<td></td>
</tr>
<tr>
<td>% prior stroke/TIA</td>
<td>19.9% D 110 mg 20.3% D 165 mg 19.8% Warfarin</td>
<td>54.9% Riva 54.6% Warfarin 19.2% Apix 19.7% Warfarin</td>
<td></td>
</tr>
</tbody>
</table>

Role of Dabigatran for Stroke Prevention in AF

- **2011 ACCF/AHA/HRS Guidelines**
  - Dabigatran given a Class I (LOE B) recommendation
  - Dabigatran is useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have the following:
    - Prosthetic heart valve or hemodynamically significant valve disease
    - CrCl <15 mL/min
    - Advanced liver disease

ACCP Recommendations: Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 = 0</td>
<td>No therapy (preferred) or aspirin (2B)</td>
</tr>
<tr>
<td>CHADS2 = 1</td>
<td>OAC preferred over no therapy (1B), aspirin (2B), or aspirin + clopidogrel (2B)</td>
</tr>
<tr>
<td>CHADS2 ≥ 2</td>
<td>OAC preferred over no therapy (1A), aspirin (1B), or aspirin + clopidogrel (1B)</td>
</tr>
</tbody>
</table>

Warfarin: Target INR 2.5 (range 2-3)
Aspirin: 75-325 mg daily

ACCP = American College of Chest Physicians
OAC = oral anticoagulant

Other Factor Xa Inhibitors in the Pipeline

- **Edoxaban** (Oral, daily)
  - ENGAGE AF TIMI-48: Ongoing (estimated completion in 2/2012); target enrollment >20,000
- **Retrêxaban** (Oral, daily)
  - EXPLORE Xa: Completed, dose ranging
- **Darexaban (YM150)** (Oral, once or twice daily)
  - Opal-2: Completed, dose ranging
- **Idraparinux** (SC injection, weekly)
  - AMADEUS: Stopped early, excessive bleeding risk
- **Idrabiotaparinux** (SC injection, weekly)
  - BOREALIS AF: Terminated

Update on Stroke Prevention in Atrial Fibrillation

Challenges and Opportunities for Pharmacists Related to Stroke Prevention in AF

Challenges
- Reversal
- Perioperative management

Opportunities
- Individualize therapy
  - Drug interactions
  - Organ dysfunction

Challenges for Pharmacists

Questions
- Has at least 1 patient presented to your institution with severe or life-threatening bleeding due to a new anticoagulant?
- Does your institution have an established systematic approach for managing patients requiring anticoagulant reversal (including the new agents)?

Theoretical Support for Reversal

Concentrated Blood Factor Products

<table>
<thead>
<tr>
<th></th>
<th>rFactor</th>
<th>3-factor PCC</th>
<th>4-factor PCC</th>
<th>Activated PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Names</td>
<td>Novo-Seven®</td>
<td>Babulin®</td>
<td>Octaplex®</td>
<td>FEIBA®</td>
</tr>
<tr>
<td>U.S. Availability</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Factors Provided</td>
<td>VII, IX, X</td>
<td>II, VII, 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>

PCC = prothrombin complex concentrate

**Update on Stroke Prevention in Atrial Fibrillation**

**Blood Factors: Considerations**
- Prothrombotic potential!
  - Especially with "activated" products
  - Recombinant Factor VIIa, Activated PCC (FEIBA®)
- Anticipated (largely unproven) benefit must outweigh prothrombotic risk
  - High risk patient populations?
- Agent selection?
  - Blood factor concentration varies by product
  - Dosing usually based on Factor IX

**Factor VIIa for Reversal**
- Works by downstream activation of factor IIa (thrombin)
  - Increased availability of Factor IIa
  - Oral direct thrombin inhibitor
  - Factor Xa antagonist
  - Lower bleeding risk?

**Animal Data: Dabigatran**
**ANIMAL MODEL #1**
- Rat tail model of bleeding
  - Dabigatran reversal attempted
    - High dose factor VIII (100 – 500 mcg/kg)
    - Activated PCC (FEIBA, 50 – 100 u/kg)
- Induced rat tail bleeding time
  - Control: 1455 ± 352 s
  - VIIIa: 186 ± 49 s
  - aPCC: 146 ± 11 s

**ANIMAL MODEL #2**

**Effect of Reversal on Hematoma Size**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11.9</td>
</tr>
<tr>
<td>No Reversal</td>
<td>17.9</td>
</tr>
<tr>
<td>fVIIa</td>
<td>15.0</td>
</tr>
<tr>
<td>aPCC</td>
<td>11.7</td>
</tr>
</tbody>
</table>

**Human Data: Dabigatran/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)
Update on Stroke Prevention in Atrial Fibrillation

Summary of LIMITED Reversal Data

- Dabigatran *
  - Factor VIIa: Animal data
  - Activated PCC: Animal data
  - 4-factor PCC: Animal data supports, human volunteer data does not support
  - 3-factor PCC: No data
- Rivaroxaban
  - PCC: Human and animal data
- Apixaban
  - ???

*Note: some data to support hemodialysis for removal of dabigatran only

Addressing Reversal Issues with New Anticoagulants

- Develop a standardized institutional approach
  - Guidelines
    - Local expert opinion based on limited data
    - Incorporation of BEST evidence
    - Safe doses of reversal agents
    - Consideration of risks of reversal agents
    - Approval process for reversal agents?

Perioperative Management

**DABIGATRAN**

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Half-life (hours)</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
<th>Standard bleeding risk</th>
<th>High bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11 – 22)</td>
<td>24 hours</td>
<td>2 – 4 days</td>
<td></td>
</tr>
<tr>
<td>&gt; 50 to 80</td>
<td>15 (12 – 34)</td>
<td>24 hours</td>
<td>2 – 4 days</td>
<td></td>
</tr>
<tr>
<td>&gt; 30 to 50</td>
<td>18 (13 – 23)</td>
<td>At least 48 hours</td>
<td>4 days</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>27 (22 – 35)</td>
<td>2 – 5 days</td>
<td>&gt; 5 days</td>
<td></td>
</tr>
</tbody>
</table>

Perioperative Management

**RIVAROXABAN**

<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 (h)</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
- Limited clearance by glomerular filtration

Opportunities for Pharmacists

Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-GP substrate</td>
<td>bleeding</td>
<td>T bleeding</td>
<td>T bleeding</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>N/A</td>
<td>Keilinazole - 160% T AUC Ritonavir - 150% T AUC Clarithromycin - 50% T AUC Erythromycin - 30% T AUC Fluconazole - 40% T AUC</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>N/A</td>
<td>Rifampin - 50% T AUC</td>
<td>T apixaban concentrations</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>N/A</td>
<td>T apixaban concentrations</td>
<td></td>
</tr>
</tbody>
</table>

Product Information, Pradaxa®
Product Information, Xarelto®
Update on Stroke Prevention in Atrial Fibrillation

Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-GP Inhibitors</td>
<td>Amiodarone: -50% ↑ AUC&lt;br&gt;Dronedarone: -73-99% ↑ AUC&lt;br&gt;Quinidine: -50% ↑ AUC&lt;br&gt;Verapamil: -250% ↑ AUC (1 hr post)&lt;br&gt;N-C AUC (2 hr after)</td>
<td>Ketoconazole: -100% ↑ AUC&lt;br&gt;Ritonavir: -150% ↑ AUC&lt;br&gt;Gatifloxacin: -50% ↑ AUC&lt;br&gt;Enzyte: -30% ↑ AUC</td>
<td>↑ apixaban concentrations</td>
</tr>
<tr>
<td>p-GP Inducers</td>
<td>Rifampin: -60% ↓ AUC&lt;br&gt;Barbiturates: -40% ↓ AUC</td>
<td>Rifampin: -50% ↓ AUC&lt;br&gt;Barbiturates: -30% ↓ AUC</td>
<td>↓ apixaban concentrations</td>
</tr>
<tr>
<td>p-GP Substrates</td>
<td>Digoxin: No interaction</td>
<td>Digoxin: No interaction</td>
<td>Not yet reported</td>
</tr>
</tbody>
</table>

Organ Dysfunction

<table>
<thead>
<tr>
<th>Kidney</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CrCl &gt;30 mL/min: 150 mg po BID&lt;br&gt;CrCl 15-30 mL/min: 75 mg po BID&lt;br&gt;CrCl &lt;15 mL/min: Not recommended</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt;50 mL/min: 20 mg po daily&lt;br&gt;CrCl 15-50 mL/min: 15 mg po daily&lt;br&gt;CrCl &lt;15 mL/min: Not recommended</td>
</tr>
<tr>
<td>Apixaban*</td>
<td>CrCl &lt;15 mL/min: Not recommended</td>
</tr>
</tbody>
</table>

* From European labeling

Drug Interaction Recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>p-GP inhibitors: ↓ dose to 75 mg BID with ketoconazole or dronedarone&lt;br&gt;CrCl 15-30 mL/min: Avoid concomitant use with p-GP inhibitors&lt;br&gt;p-GP inducers: Avoid concomitant use with rifampin</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>p-GP inhibitors and strong CYP3A4 inhibitors: Avoid concomitant use with COMBINED P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, conivaptan)&lt;br&gt;p-GP inducers and strong CYP3A4 inducers: Avoid concomitant use with COMBINED P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort)</td>
</tr>
<tr>
<td>Apixaban*</td>
<td>p-GP inhibitors and strong CYP3A4 inhibitors: Avoid concomitant use with COMBINED P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir)&lt;br&gt;p-GP inducers and strong CYP3A4 inducers: Use with caution with COMBINED P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, phenobarbital, St. John’s wort)</td>
</tr>
</tbody>
</table>

Product Information, Pradaxa®; Product Information, Xarelto®; Product Information, Eliquis®.

Patient Case

PL is a 76 yo WM who presents to the ED with left-sided facial weakness, slurred speech, and confusion. The symptoms started this morning (approx. 4 hours ago) and have begun to alleviate.

PMH: CHF (EF = 35%), HTN, dyslipidemia, CKD

The ED team finds AF on his ECG and is diagnosed with a TIA by neurology consult.

Baseline Labs: SCR 1.4 mg/dl, CrCl 42 ml/min, Hgb 9.2 g/dL, Hct 28%, Ptt 280,000/mm³

What is his CHADS² Score?

A. 2  B. 3  C. 4  D. 5  E. 6

The next day, the neurology team is discussing anticoagulation options for starting secondary stroke prophylaxis. Which of the following are reasonable options for PL?

A. Warfarin - titrate to goal INR 2-3.<br>B. Dabigatran 75 mg BID.<br>C. Dabigatran 150 mg BID.<br>D. ASA 81 mg daily.<br>E. Both A and C are correct.
Patient Case

BB, a 68 yo WF, is brought to the ED by a family member. She is currently unconscious and was complaining of a headache prior to losing consciousness. She has a history of type 2 DM, HTN and AF. Her medications include lisinopril 20 mg po daily, dabigatran 150 mg po BID, dronedarone 400 mg po BID and glipizide XL 10 mg po daily. Her vitals are BP 120/80 mmHg, HR 90 bpm. A head CT and labs are ordered, and she is found to have an intracranial hemorrhage and a CrCl of 25 mL/min.

What is the MOST likely drug-related cause for this admission?

A. Dabigatran overdose.
B. Drug interaction between dabigatran and dronedarone.
C. Untreated hypertension.
D. Medication non-compliance.

What is the LEAST evidence-based option for dealing with this patient’s intracranial hemorrhage?

A. Administer a 3-factor PCC.
B. Wait 5 days until the drug wears off.
C. Administer recombinant Factor VIIa.
D. Initiate hemodialysis.

Conclusions

• AF is a major and costly public health problem.
• Performing stroke risk stratification is essential in all patients with AF.
• Dabigatran and rivaroxaban are currently available and are viable alternatives to warfarin for stroke prevention in AF.
• Several other antithrombotic agents (including apixaban) are also in the pipeline.
• Pharmacists can play an important role in making decisions regarding reversal, perioperative management, drug interactions, and dosing with new oral antithrombotic agents.


Eikelboom JW, O'Donnell M, Yusuf S et al. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *Am Heart J*. 2010;159:348-53. e1.


Update on Stroke Prevention in Atrial Fibrillation


Update on Stroke Prevention in Atrial Fibrillation


**LIST OF ABBREVIATIONS**

ACCF = American College of Cardiology  
ACCP = American College of Chest Physicians  
AHA = American Heart Association  
AF = atrial fibrillation  
aPTT = activated partial thromboplastin time  
ASA = aspirin  
AT = antithrombin  
AUC = area under the curve  
CAD = coronary artery disease  
CKD = chronic kidney disease  
CrCl = creatinine clearance  
CHF = congestive heart failure  
Cmax = maximum concentration  
cTTR = Centre’s mean time in therapeutic range  
DM = diabetes mellitus  
DVT = deep vein thrombosis  
ECG = electrocardiogram  
ECT = ecarin clotting time  
ED = emergency department  
EF = ejection fraction  
ETP = endogenous thrombin potential  
FFP = fresh frozen plasma  
GCS = graduated compression stockings  
HRS = Heart Rhythm Society  
HTN = hypertension  
ICH = intracranial hemorrhage  
INR = international normalized ratio  
LDUH = low-dose unfractionated heparin  
LMWH = low molecular weight heparin  
LVEF = left ventricular ejection fraction  
MI = myocardial infarction  
NYHA = New York Heart Association classification of heart failure  
PCC = prothrombin complex concentrate  
PE = pulmonary embolism  
PMH = past medical history  
PRBC = packed red blood cells  
PT = prothrombin time  
RCT = randomized controlled trial  
SCr = serum creatinine  
TEE = transesophageal echocardiogram  
TIA = transient ischemic attack  
TT = thrombin time  
TTR = time in therapeutic range  
UFH = unfractionated heparin  
VKA = vitamin K antagonist  
VTE = venous thromboembolism
SELF – ASSESSMENT QUESTIONS

1. Which of the following patients with atrial fibrillation would be considered to be at HIGH risk for developing a stroke?
   a. A 23 year-old male college student who develops atrial fibrillation after binging on alcohol over the weekend.
   b. A 48 year-old female with a history of a transient ischemic attack who develops atrial fibrillation.
   c. A 58 year-old male with a history of coronary heart disease who develops atrial fibrillation.
   d. A 77 year-old male with a history of COPD who develops atrial fibrillation.

2. What is the recommended target INR range for an elderly patient with atrial fibrillation?
   a. 1.8 – 2.5
   b. 2 – 3
   c. 2.5 – 3.5
   d. Avoid warfarin.

3. Most of the emerging alternatives for warfarin will be from which class of agents?
   a. Factor VII antagonists.
   b. Indirect thrombin inhibitors.
   c. Vitamin K antagonists.
   d. Factor Xa inhibitors.

4. Which of the following medications is NOT a factor Xa inhibitor?
   a. Rivaroxaban.
   b. Dabigatran.
   c. Apixaban.
   d. Betrixaban.

5. Which trial showed a reduction in all-cause mortality versus warfarin?
   a. Apixaban: ARISTOTLE.
   b. Dabigatran: RE-LY.
   c. Rivaroxaban: ROCKET-AF.
   d. Apixaban: AVERROES.

Answers:
1. b
2. b
3. d
4. b
5. a
ASHP Advantage appreciates your participation in this educational activity and values your feedback. Please complete this brief evaluation form to assist us in improving the quality of future educational activities.

1 = strongly disagree  2 = disagree  3 = neither agree nor disagree  4 = agree  5 = strongly agree

### Evaluation of Educational Objectives

<table>
<thead>
<tr>
<th>After attending this knowledge-based CPE activity, I am able to</th>
<th>Strongly Disagree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Describe new and emerging therapeutic options for stroke prevention in AF.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>2. Describe the primary changes related to stroke prevention in the 2011 focused updates to the ACCF/AHA/HRS guideline on the management of patients with AF.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>3. Identify current and potential challenges and opportunities in stroke prevention in AF.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>

### Evaluation Content

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The content presented was relevant to the target audience.</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>2. I will be able to apply the knowledge skills I learned</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>3. The activity fulfilled my education needs</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>4. The activity enhanced my ability to apply learning objectives to my practice</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>5. Based on my previous knowledge and experience, the content level of the activity for attending audience was:</td>
<td></td>
</tr>
<tr>
<td>□ Too basic □ Appropriate □ Too Complex</td>
<td></td>
</tr>
</tbody>
</table>

### Faculty/Instructional Materials

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. The teaching methods were effective</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>7. The instructional materials were effective</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

8. Please indicate the extent to which you agree or disagree with the following statement: “Faculty statements and therapeutic recommendations in this activity were based on supported evidence or professional opinion and did NOT evidence commercial bias.”

□ Strongly Disagree □ Disagree □ Agree □ Strongly Agree

9. If you answered strongly disagree or disagree to question 8, what commercial bias did you perceive in this activity?

________________________________________________________________________________________
________________________________________________________________________________________

Continue on next page
10. What did you find to be the most helpful aspect of this activity?
________________________________________________________________________________________
________________________________________________________________________________________

11. What was the least helpful aspect of this activity?
________________________________________________________________________________________
________________________________________________________________________________________

12. List ONE (and no more than three) changes that you intend to make in your practice as a result of this activity.

☐ Evaluate protocols at my practice site to ensure the protocols are consistent with recently released consensus guidelines (i.e., 2011 ACCF/AHA/HRS and 2012 ACCP guidelines) for stroke prevention in patients with atrial fibrillation.

☐ Adjust the dose of dabigatran or rivaroxaban in patients with renal dysfunction.

☐ Monitor patients for drug interactions with new anticoagulants (e.g., dabigatran, rivaroxaban).

☐ Develop a standardized institutional approach to reversing anticoagulation with new anticoagulants (e.g., dabigatran, rivaroxaban).

☐ Other. Please specify __________________________________________________________________
_______________________________________________________________________________________

13. How confident are you that you will be able to apply these changes in your practice?
   a. Very confident
   b. Somewhat confident
   c. Not confident

14. Please indicate any barriers you perceive to implementing these changes.
   a. Cost
   b. Lack of experience
   c. Lack of resources
   d. Lack of administrative support
   e. Other, please specify: __________________________________________________________________
_______________________________________________________________________________________

15. What question(s) do you still have about this topic?
_______________________________________________________________________________________

16. Based on your educational needs, list any topics you would like to see addressed in future educational activities.
_______________________________________________________________________________________

17. Other comments or suggested improvements:
_______________________________________________________________________________________
_______________________________________________________________________________________

18. Using the following scale, in the table below rate presentation skills, content knowledge, degree of balance, objectivity, and scientific rigor of faculty:


1 = very poor  2 = poor  3 = average  4 = above average  5 = excellent

<table>
<thead>
<tr>
<th></th>
<th>Presentation Skills</th>
<th>Knowledge of Content</th>
<th>Degree of Balance, Objectivity, &amp; Scientific Rigor</th>
</tr>
</thead>
<tbody>
<tr>
<td>James S. Kalus, Pharm.D., BCPS (AQ-Cardiology)</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>