Update on Stroke Prevention in Atrial Fibrillation

A knowledge-based CPE activity presented during the
2012 ICHP Annual Meeting

Friday, March 23, 2012
Normal, Illinois
12:00 pm – 1:00 pm

Planned and conducted by ASHP Advantage.
Supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

Update on Stroke Prevention in Atrial Fibrillation

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ACTIVITY FACULTY

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Cynthia A. Sanoski, Pharm.D., FCCP, BCPS, is Chair and Associate Professor in the Department of Pharmacy Practice at the Jefferson School of Pharmacy at Thomas Jefferson University in Philadelphia, Pennsylvania. She has played an integral role in the development and implementation of the curriculum and the recruitment and mentoring of pharmacy practice faculty in this newly established school. Previously, she served as Associate Professor of Clinical Pharmacy in the Philadelphia College of Pharmacy at the University of the Sciences in Philadelphia.

After earning her Bachelor of Science in Pharmacy degree at Duquesne University in Pittsburgh, Pennsylvania, and her Doctor of Pharmacy degree from The Ohio State University College of Pharmacy in Columbus, Dr. Sanoski completed a two-year fellowship in cardiovascular pharmacotherapy at the University of Illinois at Chicago College of Pharmacy.

Dr. Sanoski has given numerous presentations on the management of various cardiovascular diseases, including cardiac arrhythmias, acute coronary syndrome, and acute decompensated heart failure. She has published in a number of peer-reviewed journals, including *Archives of Internal Medicine*, *Formulary*, *Pharmacotherapy*, *Chest*, *Journal of Pharmacy Practice*, and *Journal of Managed Care Pharmacy.* She has also written several book chapters on the management of acute and chronic arrhythmias and medication-induced cardiovascular adverse effects. Dr. Sanoski is a reviewer for several journals, some of which include *Pharmacotherapy*, *Clinical Therapeutics*, *Journal of Pharmacy Practice*, *Current Medical Research and Opinion*, and *American Journal of Managed Care.* She also serves on the editorial boards of the *Journal of Pharmacy Practice* and *Current Medical Research and Opinion*.

Dr. Sanoski is an active member of the American Association of Colleges of Pharmacy (AACP), American College of Clinical Pharmacy (ACCP), and American Society of Health-System Pharmacists. Within ACCP, she has served as Chair and Secretary of the Cardiology Practice and Research Network (PRN) and Secretary-Treasurer of the Education and Training PRN. In 2007, Dr. Sanoski was elected as a fellow of ACCP. She is currently serving a three-year term as Treasurer of ACCP and is a member of the ACCP Board of Regents. Dr. Sanoski recently completed Academic Leadership Fellows Program sponsored by AACP. While at the University of the Sciences in Philadelphia, she was awarded the University's Faculty Special Recognition Award. In 2010, she was also the recipient of the Distinguished Alumnus Award from the Mylan School of Pharmacy at Duquesne University.

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Update on Stroke Prevention in Atrial Fibrillation

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.

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Be sure to record the session code announced during this activity.

Update on Stroke Prevention in Atrial Fibrillation

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1. Select **Process Meeting CE** from bottom left. Log in to the ASHP CE Center using your e-mail address and password.
2. **If you have not logged in to the new ASHP CE Center (launched August 2008) and are not a member of ASHP,** you will need to create a free account by clicking on **Register** at the bottom of the **Register as a New User** panel.
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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.**
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Date of Activity	Activity Code	Session Code (announced during the live activity)	CE credit hours
March 23, 2012	12401	A _ _ _ _ _	1.0

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Objectives

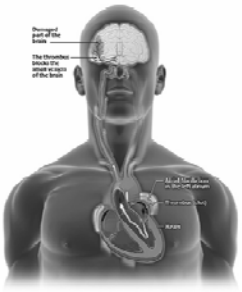
- Describe new and emerging therapeutic options for stroke prevention in atrial fibrillation (AF).
- Describe the primary changes related to stroke prevention in the 2011 focused updates to the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guideline 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%

Roger VL et al. *Circulation*. 2012; 125:e2-e220.
Go AS et al. *JAMA*. 2001; 285:2370-5.
Feinberg WM et al. *Arch Intern Med*. 1995; 155:469-73.
Lloyd-Jones DM et al. *Circulation*. 2004;110:1042-6.

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

Roger VL et al. *Circulation*. 2012;125:e2-e220.
Benjamin EJ et al. *Circulation*. 1998;98:946-52.
Page RL et al. *Circulation*. 2003;107:1141-5..
Henriksson KM et al. *Int J Cardiol*. 2010:141:18-23.

Stroke Risk Stratification in AF

- $CHADS_2$ 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

Gage BF et al. *JAMA*. 2001; 285:2864-70.

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

New and Emerging Oral Antithrombotic Agents

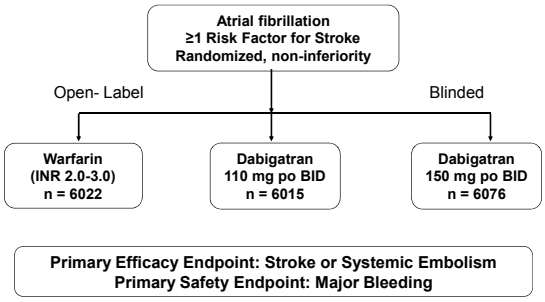
- Direct thrombin inhibitors
  - Dabigatran
- Factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Idraparinux
  - Betrixaban
  - Edoxaban
  - Idrabiotaparinux

Comparison of New/Emerging Antithrombotic Agents

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Mechanism of Action	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Approval Status	2008: Approved in Europe/Canada (VTE prophylaxis in ortho patients) 10/10: Approved by FDA for stroke prevention in AF	2008: Approved in Europe/Canada (VTE prophylaxis in ortho patients) 7/11: Approved by FDA for VTE prophylaxis in ortho patients 11/11 Approved by FDA for stroke prevention in AF	5/11: Approved in Europe (VTE prophylaxis in ortho patients) 11/11 FDA grants priority-review for stroke prevention in AF indication (decision due by end of 3/12)

Direct Thrombin Inhibitors: Clinical Trials

RE-LY: Study Design



Connolly SJ et al. *N Engl J Med*. 2009;361:1139-51.

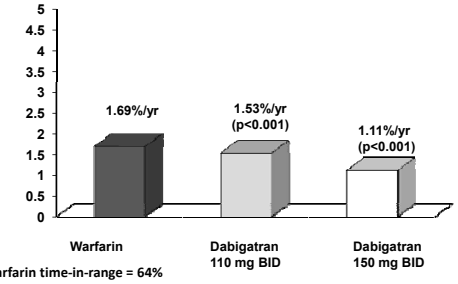
RE-LY: Baseline Characteristics

	Dabigatran 110 mg (n = 6015)	Dabigatran 150 mg (n = 6076)	Warfarin (n = 6022)
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
$CHADS_2$ score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior Stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

Connolly SJ et al. *N Engl J Med*. 2009;361:1139-51.

RE-LY: Primary Outcome

Composite: Stroke or Systemic Embolism

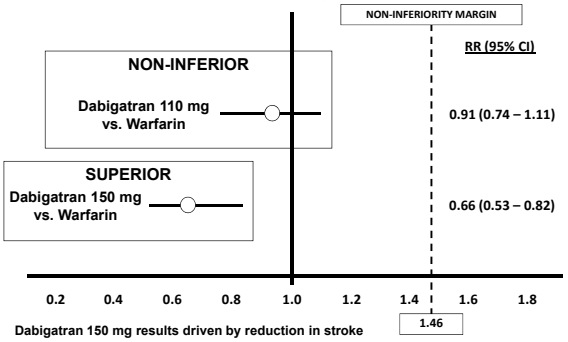


• Warfarin time-in-range = 64%

Connolly SJ et al. *N Engl J Med*. 2009; 361:1139-51.

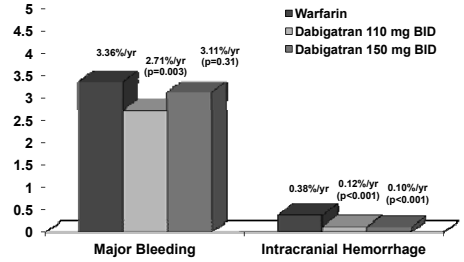
RE-LY: Primary Outcome

Composite: Stroke or Systemic Embolism



Connolly SJ et al. *N Engl J Med*. 2009;361:1139-51.

RE-LY: Primary Safety Outcome



Connolly SJ et al. *N Engl J Med.* 2009; 361:1139-51.

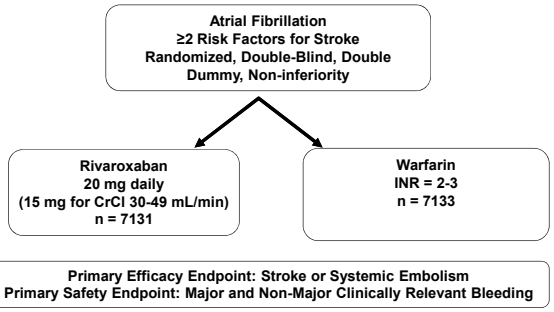
RE-LY Secondary Analyses

Sub-group	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.

Wallentin L et al. *Lancet.* 2010; 376:975-83.
Eikelboom JW et al. *Circulation*. 2011;123:2363-72.
Diener HC et al. *Lancet Neurol.* 2010; 9:1157–63.
Nagarakanti R et al. *Circulation.* 2011; 123:131-6.

Factor Xa Inhibitors: Clinical Trials

ROCKET-AF: Study Design



Median duration of treatment exposure 590 days

Patel MR et al. *N Engl J Med* 2011;365:883-91.

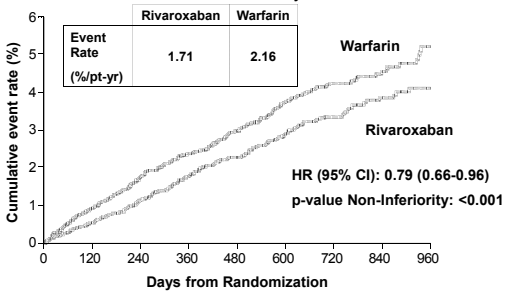
ROCKET-AF: Baseline Characteristics

Variable	Rivaroxaban (n=7131)	Warfarin (n=7133)
Age—yr; median	73	73
BMI; median	28.3	28.1
Female sex -- no. (%)	2831 (39.7)	2832 (39.7)
Previous VKA use—no. (%)	4443 (62.3)	4461 (62.5)
$CHADS_2$ score; mean	3.48 ± 0.94	3.46 ± 0.95
2	925 (13.0)	934 (13.1)
3	3058 (42.9)	3158 (44.3)
4	2092 (29.3)	1999 (28.0)
5	932 (13.1)	881 (12.4)
6	123 (1.7)	159 (2.2)
Previous stroke or TIA—no. (%)	3916 (54.9)	3895 (54.6)
CHF—no. (%)	4467 (62.6)	4441 (62.3)

Patel MR et al. *N Engl J Med* 2011;365:883-91.

ROCKET AF: Primary Endpoint

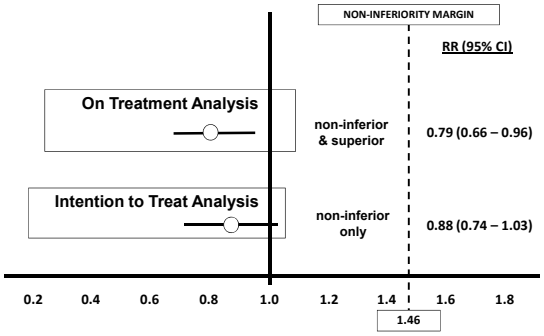
Composite: Stroke or Systemic Embolism
On-Treatment Analysis



Patel MR et al. *N Engl J Med* 2011;365:883-91.

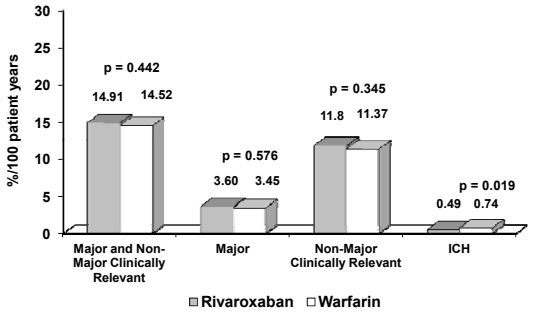
ROCKET AF: Primary Endpoint Results

Composite: Stroke or Systemic Embolism



Patel MR et al. *N Engl J Med* 2011; 365:883-91.

ROCKET AF: Bleeding Rates



ICH = intracranial hemorrhage

Patel MR et al. *N Engl J Med* 2011; 365:883-91.

AVERROES: Study Design

Atrial Fibrillation
$CHADS_2$ 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

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

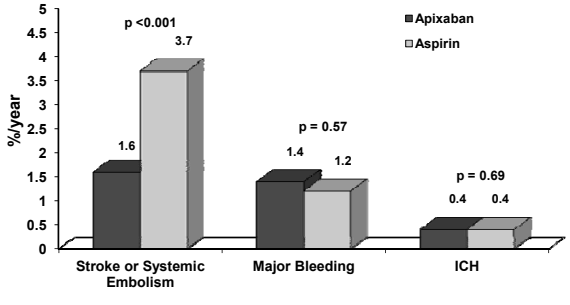
Connolly S et al. *N Engl J Med* 2011; 364:806-17.

AVERROES: Baseline Characteristics

Variable	Apixaban (n=2808)	Aspirin (n=2791)
Age—yr	70 ± 9	70 ±10
BMI	28 ±5	28 ± 5
Male sex -- no. (%)	1660 (59)	1617 (58)
$CHADS_2$ score-- mean	2.0 ± 1.1	2.1 ± 1.1
Score – no. (%)		
0 or 1	1004 (36)	1022 (37)
2	1045 (37)	954 (34)
≥3	758 (27)	812 (29)
Use of VKA within 30 days before screening –no. (%)	401 (14)	426 (15)
Use of ASA within 30 days before screening –no. (%)	2137 (76)	2081 (75)

Connolly SJ et al. *N Engl J Med* 2011;364:806-17.

AVERROES: Results



ICH = intracranial hemorrhage

Connolly S et al. *N Engl J Med* 2011;364:806-17.

ARISTOTLE: Study Design

Atrial Fibrillation
$CHADS_2$ score ≥1
Randomized, Double-Blind, Double Dummy, Non-inferiority 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 = 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

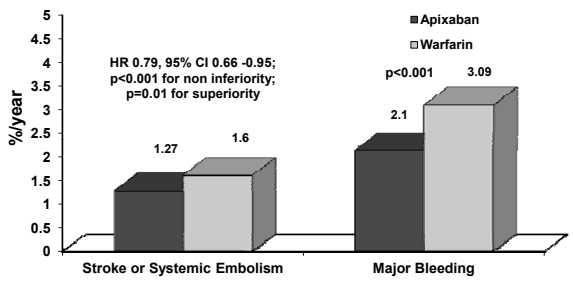
Granger CB et al. *N Engl J Med* 2011; 365:981-92.

ARISTOTLE: Baseline Characteristics

Variable	Apixaban (n= 9120)	Warfarin (n=9081)
Age—yr	70	70
Weight—kg	82	82
Female sex –no. (%)	3234 (35.5)	3182 (35.0)
Prior use of VKA for >30 consec. days –no. (%)	5208 (57.1)	5193 (57.2)
$CHADS_2$ score; mean	2.1 ± 1.1	2.1 ± 1.1
1	3100 (34.0)	3083 (34.0)
2	3262 (35.8)	3254 (35.8)
≥3	2758 (30.2)	2744 (30.2)
Age ≥75 yr—no. (%)	2850 (31.2)	2828 (31.1)
Prior stroke, TIA—no. (%)	1748 (19.2)	1790 (19.7)
CHF or reduced LVEF—no. (%)	3235 (35.5)	3216 (35.4)

Granger CB et al. *N Engl J Med* 2011; 365:981-92.

ARISTOTLE: Results



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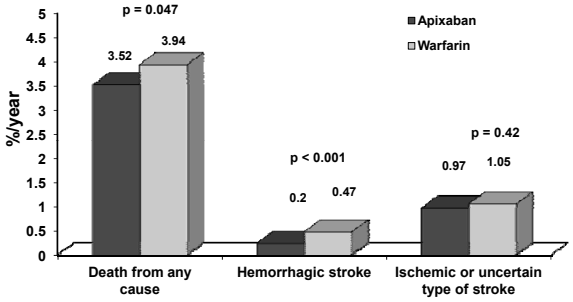
ARISTOTLE: Results



Granger CB et al. *N Engl J Med* 2011; 365:981-92.

Study Differences

	RE-LY	ROCKET-AF	ARISTOTLE
Design	Open-label	Double-blind	Double-blind
Mean $CHADS_2$ score	2.1	3.5	2.1
Mean TTR of warfarin	64%	55%	62%
ASA use	Restrict to ≤ 100 mg/day	Restrict to ≤ 100 mg/day	Restrict to ≤ 165 mg/day
% ASA use at baseline	40% D 110 mg 38.7% D 150 mg 40.6% Warfarin	38.3% Riva 38.7% Warfarin	31.3% Apix 30.5% Warfarin
% prior stroke/TIA	19.9% D 110 mg 20.3% D 150 mg 19.8% Warfarin	54.9% Riva 54.6% Warfarin	19.2% Apix 19.7% Warfarin

Connolly SJ et al. *N Engl J Med.* 2009; 361:1139-51.
Patel MR et al. *N Engl J Med.* 2011; 365:883-91.
Granger CB et al. *N Engl J Med* 2011; 365:981-92.

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

Wann LS et al. *Heart Rhythm.* 2011; 8:e1-e8.

Role of Dabigatran for Stroke Prevention in AF

- 2011 ACCF/AHA/HRS guidelines also state the following:
  - Patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran because of dabigatran's:
    - Twice-daily dosing
    - Greater risk of nonhemorrhagic side effects,
  - Selection of patients with AF and ≥1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual factors, including:
    - Ability to comply with twice-daily dosing
    - Availability of an anticoagulation management program to sustain routine monitoring of INR
    - Patient preferences
    - Cost
    - Other factors

Wann LS et al. *Heart Rhythm.* 2011; 8:e1-e8.

ACCP Recommendations: Antithrombotic Therapy

Risk Category	Recommendation
$CHADS_2 = 0$	No therapy (preferred) or aspirin (2B)
$CHADS_2 = 1$	OAC preferred over no therapy (1B), aspirin (2B), or aspirin + clopidogrel (2B)
	Not candidates for OAC (for reasons other than bleeding): aspirin + clopidogrel (2B)
$CHADS_2 \geq 2$	OAC preferred over no therapy (1A), aspirin (1B), or aspirin + clopidogrel (1B)
	Not candidates for OAC (for reasons other than bleeding): aspirin + clopidogrel (1B)

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

ACCP = American College of Chest Physicians
OAC = oral anticoagulant

You JJ et al. *Chest*. 2012;141 (2 Suppl):e531S-75S.

ACCP Recommendations: Antithrombotic Therapy

- For patients with AF where oral anticoagulation is recommended ($CHADS_2 \geq 1$), guidelines suggest using dabigatran rather than warfarin therapy (2B)

You JJ et al. *Chest*. 2012;141 (2 Suppl):e531S-75S.

Other Factor Xa Inhibitors in the Pipeline

Stroke Prevention in AF Clinical Trials

Edoxaban (Oral, daily)
- ENGAGE AF TIMI-48: Ongoing (estimated completion in 2/2012); target enrollment >20,000

Betrixaban (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

www.ClinicalTrials.gov
Ruff CT et al. *Am Heart J.* 2010; 160:635-41.
Alexander W. *P & T.* 2010; 35:291-4.
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Challenges and Opportunities for Pharmacists Related to Stroke Prevention in AF

Challenges and Opportunities

Challenges
- Reversal
- Perioperative management

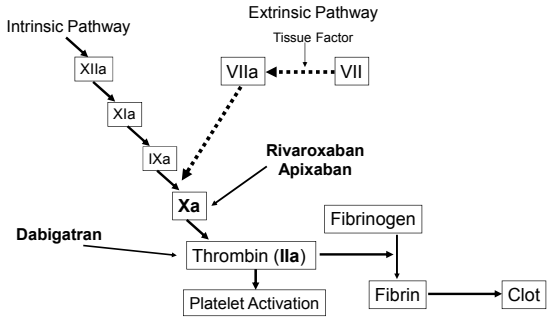
Opportunities
- Individualize therapy
  - Drug interactions
  - Organ dysfunction

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

	rFactor VIIa	3-factor PCC	4-factor PCC	Activated PCC
Brand Names	Novo-Seven®	Bebulin® Profilnine®	Octaplex® Others	FEIBA®
U.S. Availability	YES	YES	NO	YES
Factors Provided	VII	II, IX, X	II, VII, IX, X	II, VII, IX, X
Activated?	YES	NO	NO	YES

PCC = prothrombin complex concentrate

Samama CM. *Eur J Anaesth.* 2008; 25:784-9.

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

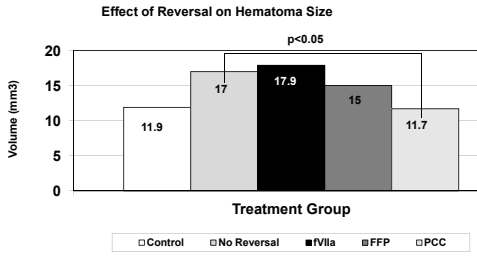
ANIMAL MODEL #1

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

van Ryn J et al. *Haematologica.* 2008;93(s1).

Animal Data: Dabigatran

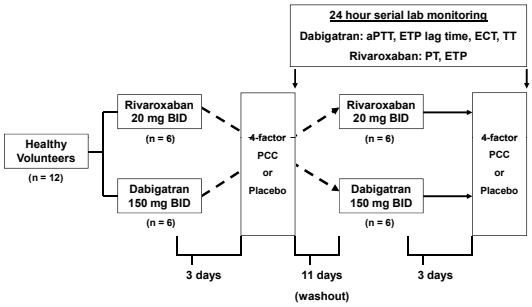
ANIMAL MODEL #2



PCC = Beriplex®

Zhou W et al. *Stroke.* 2011; 42.

Human Data: Dabigatran/Rivaroxaban



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

Eerenberg ES. *Circulation.* 2011; 124:1573-9.

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)

Eerenberg ES. *Circulation.* 2011; 124:1573-9.

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

CrCl (mL/min)	Half-life (hours)	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard bleeding risk	High bleeding risk
> 80	13 (11 – 22)	24 hours	2 – 4 days
> 50 to 80	15 (12 – 34)	24 hours	2 – 4 days
> 30 to 50	18 (13 – 23)	At least 48 hours	4 days
≤ 30	27 (22 – 35)	2 – 5 days	> 5 days

van Ryn J et al. *Thromb Haemost.* 2010;103:1116–27.

Perioperative Management

RIVAROXABAN

CrCl (mL/min)	>80 (n = 8)	50 – 79 (n = 8)	30 – 49 (n = 8)	<30 (n = 8)
Half-life (h)	8.3	8.7	9.0	9.5

- AUC ↑ as CrCl ↓
- Most rivaroxaban clearance
  - non-renal (hepatic)
  - renal secretion
- Limited clearance by glomerular filtration

Kubitza D et al. *Br J Clin Pharmacol.* 2010;70:703-12.

Opportunities for Pharmacists

Drug Interactions

	Dabigatran	Rivaroxaban	Apixaban
	p-GP substrate	CYP3A4 and p-GP substrate	CYP3A4 and p-GP substrate
Antithrombotic Agents	↑ bleeding	↑ bleeding	↑ bleeding
Antiplatelets Agents	↑ bleeding	↑ bleeding	↑ bleeding
CYP3A4 Inhibitors	N/A	Ketoconazole – 160% ↑ AUC Ritonavir – 150% ↑ AUC Clarithromycin - 50% ↑ AUC Erythromycin - 30% ↑ AUC Fluconazole - 40% ↑ AUC	↑ apixaban concentrations
CYP3A4 Inducers	N/A	Rifampin - 50% ↓ AUC	↓ apixaban concentrations

Nutescu E et al. *J Thromb Thrombolysis.* 2011;31:326-43.
Product Information, Pradaxa®.
Product Information, Xarelto®.

Drug Interactions

	Dabigatran	Rivaroxaban	Apixaban
p-GP Inhibitors	Amiodarone - 50% ↑ AUC Dronedarone – 73-99% ↑ AUC Ketoconazole - 150% ↑ AUC Quinidine - 50% ↑ AUC Verapamil - 250% ↑ AUC (1 hr pre); NC AUC (2 hr after)	Ketoconazole - 160% ↑ AUC Ritonavir - 150% ↑ AUC Clarithromycin - 50% ↑ AUC Erythromycin - 30% ↑ AUC	↑ apixaban concentrations
p-GP Inducers	Rifampin - 60% ↓ AUC	Rifampin - 50% ↓ AUC	↓ apixaban concentrations
p-GP Substrates	Digoxin - No interaction	Digoxin - No interaction	Not yet reported

Nutescu E et al. *J Thromb Thrombolysis.* 2011;31:326-43.
Product Information, Pradaxa®.
Product Information, Xarelto®.

Drug Interaction Recommendations

Drug	Recommendation
Dabigatran	p-GP inhibitors: CrCl 30-50 mL/min: ↓ dose to 75 mg BID with ketoconazole or dronedarone CrCl 15-30 mL/min: AVOID concomitant use with p-GP inhibitors
	p-GP inducers: AVOID concomitant use with rifampin
Rivaroxaban	p-GP inhibitors and strong CYP3A4 inhibitors: Avoid concomitant use with COMBINED P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, conivaptan)
	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)
Apixaban (from European PI)	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)
	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)

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

Organ Dysfunction

	Kidney	Liver
Dabigatran	CrCl >30 mL/min: 150 mg po BID CrCl 15-29 mL/min: 75 mg po BID CrCl <15 mL/min: Not recommended	No issues
Rivaroxaban	CrCl >50 mL/min: 20 mg po daily CrCl 15-50 mL/min: 15 mg po daily CrCl <15 mL/min: Not recommended	Avoid in moderate or severe liver impairment
Apixaban*	CrCl <15 mL/min: Not recommended	Avoid in severe liver impairment

* From European labeling

Granger CB et al. *N Engl J Med.* 2011;365:981-92.
Alexander JH et al. *N Engl J Med.* 2011;365:699-708.
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%, Plt 280,000/mm^3

What is his $CHADS_2$ 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.
B. Dabigatran 75 mg BID.
C. Dabigatran 150 mg BID.
D. ASA 81 mg daily.
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.

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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

S E L F – A S S E S S M E N T Q U E S T I O N S

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

Update on Stroke Prevention in Atrial Fibrillation

Activity Evaluation Form

March 23, 2012 **Cynthia A. Sanoski, Pharm.D., FCCP, BCPS** ***Normal, IL***

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

After attending this knowledge-based CPE activity, I am able to	**Strongly Disagree**				**Strongly Agree**
1. Describe new and emerging therapeutic options for stroke prevention in AF.	1	2	3	4	5
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.	1	2	3	4	5
3. Identify current and potential challenges and opportunities in stroke prevention in AF.	1	2	3	4	5

Evaluation Content

	Strongly Disagree				**Strongly Agree**
1. The content presented was relevant to the target audience……..	1	2	3	4	5
2. I will be able to apply the knowledge skills I learned ……..	1	2	3	4	5
3. The activity fulfilled my education needs ……..	1	2	3	4	5
4. The activity enhanced my ability to apply learning objectives to my practice …….	1	2	3	4	5

5. Based on my previous knowledge and experience, the content level of the activity for attending audience was:
   ☐ Too basic ☐ Appropriate ☐ Too Complex

Faculty/Instructional Materials

	Strongly				**Strongly**
6. The teaching methods were effective……	1	2	3	4	5
7. The instructional materials were effective ……	1	2	3	4	5

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

	Presentation Skills	Knowledge of Content	Degree of Balance, Objectivity, & Scientific Rigor
Cynthia A. Sanoski, Pharm.D., FCCP, BCPS	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5