Atrial Fibrillation: New Therapies for an Old Problem

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Disclosures
Mr. Thibodeau is a consultant for Daichii Sankyo.

Educational Objectives
At the conclusion of this session, the participant will be able to:
– Recognize the importance of rate and rhythm control in patients with atrial fibrillation.
– Identify current management strategies for atrial fibrillation.
– Develop and apply a treatment regimen for patients with atrial fibrillation with selected comorbidities.
– Identify new management strategies for atrial fibrillation.
– Explain how PAs can take the lead in atrial fibrillation management.

This activity is funded through an educational grant from Bristol-Myers Squibb/Pfizer Pharmaceuticals Partnership to the TEAM-A Collaborative to support activities that improve the treatment of patients with Atrial Fibrillation.

The Physicians’ Institute is a member of TEAM-A and retains full control over the distribution of individual grants under this collaborative grant program.
Pre-Activity Questions

Please rate each statement as it relates to your present level of ability to administer antithrombotic therapy for patients with atrial fibrillation.

Assessment Question 1
Document the risk of stroke using a validated assessment tool.
Low                    High
1      2     3     4     5

Assessment Question 2
Discuss antithrombotic therapy with the patient in order to make an informed therapy decision.
Low                    High
1      2     3     4     5

Assessment Question 3
Select the appropriate antithrombotic therapy.
Low                    High
1      2     3     4     5

Atrial Fibrillation

- Arrhythmia characterized by uncoordinated atrial activation, with consequent deterioration of atrial mechanical function.
- A-fib is the most common type of arrhythmia.

Circulation 2011; 123: e269-e367
Atrial Fibrillation

- Estimated 2.66 million people have atrial fibrillation
- Up to 12 million will have it by 2050\(^1\)
- Median age
  - Men 66.8 years
  - Women 74.6
- For last 20 years incidence of death related to atrial fibrillation is increasing


Atrial Fibrillation

- Symptoms of atrial fibrillation:
  - Palpitations
  - Feelings of an irregular heartbeat
  - Lightheadedness
  - Fatigue
  - Shortness of breath
  - Chest pain
Atrial Fibrillation

Atrial Fibrillation

Atrial Fibrillation

Atrial Fibrillation
Atrial Fibrillation

- Stroke and Heart Failure are the two most common complications from a-fib
- 20% of strokes are a result from a-fib
  - Strokes from a-fib tend to have greater severity
- Hospital admissions for a-fib have increased 60% in last 20 years
- Heart Failure has a high incidence of patients with a-fib
  - 4.5 to 5.9 fold increase in risk of future a-fib

Atrial Fibrillation- Treatment

- Rate control
  - β blockers (metoprolol)
  - Calcium channel blockers (diltiazem)
  - Amiodarone
  - Digoxin

- Rhythm control
  - Pharmacologic
  - Cardioversion
  - Ablation therapy

Atrial Fibrillation

- Multiple treatment plans
  - Rate control
  - Rhythm control (some cases)
  - Other factors (thyroid, electrolytes, CAD)
- Anticoagulation is a mainstay in treatment
  - Only 50-64% of patients with atrial fibrillation receive anticoagulation
- Patients with A-fib have the highest rate of stroke reoccurrence of any population
**Atrial Fibrillation**

- A-fib is complex - limited knowledge by clinicians
- Careful analysis of patient risk is paramount
- Careful management required
- Proper education
  - For the clinician
  - For the patient and family
- Team approach to management
  - Patient-centered medical home
## Stroke Risk- CHADS\textsubscript{2} Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS\textsubscript{2} Score (%/yr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age ( \geq 75 )</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Maximum Score</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>


## Bleeding Risk- HAS-Bled Score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristics</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal Liver Function or Renal Function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age ( \geq 65 ))</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

## HAS-BLED Risk

<table>
<thead>
<tr>
<th>Score/Points</th>
<th>Major Bleed/100 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>5 or more</td>
<td>12.5</td>
</tr>
</tbody>
</table>

## Fall Risk

- Most clinicians subjectively assess fall risk
- Use Morse or Hendrich fall risk guides
- Evaluate using a functional mobility assessment
- Determine any preventable reasons for falls
  - Medication side effects or sedation
- Find ways to reduce fall risk:
  - Functional mobility physical therapy
  - Vision assessment
  - Home hazard assessment
  - Limiting sedating medications
  - Home social support and family/caregivers
### ACC/AHA/ESC Guidelines

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Risk Factors CHADS$_2$</td>
<td>Aspirin 81-325mg</td>
</tr>
<tr>
<td>One moderate risk factor CHADS$_2$= 1</td>
<td>Aspirin 81-325 mg Warfarin (INR 2.0-3.0, target 2.5)</td>
</tr>
<tr>
<td>&gt;1 moderate risk factor CHADS$_2$ ≥ 2</td>
<td>Warfarin (INR 2.0-3.0, target 2.5)</td>
</tr>
<tr>
<td>Mechanical prosthetic mitral valve</td>
<td>Warfarin (INR 2.5-3.5, target 3.0)</td>
</tr>
</tbody>
</table>

### STROKE PREVENTION IN AF: ASPIRIN VS. PLACEBO

- AFASAK-1 (432)
- SPAF I (57)
- EAFT (403)
- ESPS-II (404)
- LASAF (447)
- UK-TIA (46)

All Trials (n=6)

- Aspirin Worse
- Warfarin Better

19%


### STROKE PREVENTION IN AF: WARFARIN VS. ASPIRIN

- AFASAK I (432)
- AFASAK II (439)
- EAFT (403)
- PATAF (443)
- SPAF II (440)

All Trials (n=5)

- Aspirin Better
- Warfarin Worse

33%


### STROKE PREVENTION IN AF: WARFARIN VS. PLACEBO

- AFASAK-1 (432)
- SPAF (57)
- BAATAF (428)
- CAFA (436)
- SPINAF (437)
- EAFT (403)

All Trials (n=6)

- Warfarin Worse

62%

PROBLEMS WITH WARFARIN

1) Delayed onset/offset
2) Unpredictable dose response
3) Narrow therapeutic index
4) Drug-drug, drug-food interactions
5) Problematic monitoring
6) High bleeding rate
7) Slow reversibility

Inadequacy of Anticoagulation

Patients with AF in Primary Care Practice

<table>
<thead>
<tr>
<th>Condition</th>
<th>No warfarin</th>
<th>INR in range</th>
<th>Subtherapeutic INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR above target</td>
<td>6%</td>
<td>15%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Preventable Strokes

AF Patients with Stroke with no Known Contraindication to Anticoagulation

<table>
<thead>
<tr>
<th>Condition</th>
<th>No warfarin</th>
<th>INR in range</th>
<th>Subtherapeutic INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR in range</td>
<td>10%</td>
<td>15%</td>
<td>29%</td>
</tr>
</tbody>
</table>


**Novel Anticoagulants: Advantages**

- Immediate onset of action
- Fixed dose
- No laboratory coagulation monitoring
- Minimal drug-drug/ drug-food interactions
- Short half-life; therefore, no “bridging”

**Novel Oral Anticoagulants**

1. **Dabigatran**: an oral DTI—twice daily (renal clearance)
2. **Rivaroxaban**: direct factor Xa inhibitor (renal clearance)—once daily
3. **Apixaban**: direct factor Xa inhibitor (hepatic clearance)—twice daily
4. **Edoxaban**: direct factor Xa inhibitor (hepatic clearance)—once daily

**Sites of Action**

- **Rivaroxaban**
- **Apixaban**
- **Edoxaban**
- **Betrixaban**

**Comparison of New Anticoagulants with Warfarin**

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>New Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food Effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Comparison of Stroke Prevention in AF Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF-TIMI 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>18,113</td>
<td>14,284</td>
<td>18,206</td>
<td>21,107</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>150,110</td>
<td>20(15)QD</td>
<td>5 (2.5)BID</td>
<td>60,30 QD</td>
</tr>
<tr>
<td>Apixaban</td>
<td>None</td>
<td>20-&gt;15</td>
<td>5-&gt;2.5</td>
<td>60-&gt;30 30-&gt;15</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Dose adjustment for drug clearance | None | 20->15 | 5->2.5 | 60->30 30->15 |

<table>
<thead>
<tr>
<th>Design</th>
<th>Open</th>
<th>Double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
<td>Stroke/SEE</td>
<td></td>
</tr>
<tr>
<td>Non-inferiority HR boundary</td>
<td>1.46</td>
<td>1.38</td>
</tr>
</tbody>
</table>

**FDA Approves Dabigatran 150 mg BID for SPAF:**
Dabigatran reduces stroke rate 34% compared to Warfarin
October 19, 2010

Dose of 150 mg for CrCl > 30 ml/ min
Dose of 75 mg for CrCl 15-30 ml/ min

**RE-LY: A Non-Inferiority Trial**

- Atrial fibrillation with ≥ 1 Risk Factor
- 951 centers in 44 countries

Blinded Event Adjudication

Warfarin
- Adjusted INR 2.0 – 3.0
- N=6,000

Dabigatran
- 110 mg BID N=6,000
- 150 mg BID N=6,000

**Stroke Prevention: 150 mg: 34% Fewer Strokes**

Dabigatran 110 vs. Warfarin

- Non-inferiority p-value: <0.001
- Superiority p-value: 0.34

Dabigatran 150 vs. Warfarin

- Non-inferiority p-value: <0.001
- Superiority p-value: <0.001

Margin = 1.46

Connolly SJ. NEJM 2009; 361: 1139-1151

Connolly SJ et al. NEJM 2009; 361: 1139-1151
150 mg: 60% LESS IC BLEEDING

- RR 0.31 (95% CI: 0.20–0.47) p<0.001
- RR 0.40 (95% CI: 0.27–0.60) p<0.001

Number of events:
- D110 mg BID: 0.23 %
- D150 mg BID: 0.30 %
- Warfarin: 0.74 %

RRR 69%  RRR 60%

Connolly SJ et al. NEJM 2009; 361: 1139-1151

DABIGATRAN: DISADVANTAGES

1. No specific antidote for overdose (“tincture of time”)
2. No anticoagulant effect if doses are “skipped” or “forgotten”
3. No lab test to monitor anticoagulant effect or intensity
4. Difficult to modulate dose
5. 2% discontinuation rate: GI distress
6. 0.2% increase in MI
7. Expensive if budgeting is “silo”

COST- DABIGATRAN VERSUS WARFARIN:

- Dabigatran retail: $240/month
- Warfarin discount retail: $4/month
- Will the high price of dabigatran (and other Factor X’s) cause poor medication adherence?
- “The cost of medical care looms as the single largest threat to the U.S. economy.”

WARFARIN IS FIGHTING TO “STAY ALIVE” WITH:

1) Excellent efficacy
2) Low Cost ($4 per month)
3) Long Track Record (1954)
4) Centralized Anticoagulation Clinics that maintain TTRs > 60%
5) Rapid turnaround genetic testing
6) Point-of-care testing

Avorn J. Circulation 2011; 123: 2519-2521
MEDICATION ADHERENCE FAILURE

- Failing to fill/refill a prescription
- Omitting doses
- Overdosing
- Prematurely discontinuing med
- Taking someone else’s medication
- Taking a med with prohibited foods
- Taking outdated medications

“Drugs don’t work in patients who don’t take them.”

C. Everett Koop, M.D.
Surgeon General 1981-1989

“SCRIPT YOUR FUTURE”

Regina M. Benjamin, M.D.
Surgeon General 2009-present

Top 10 Reasons for Medication Errors After Discharge

1. Nonintentional adherence
2. Discharge instructions were incomplete, inaccurate, or illegible
3. Conflicting information from different sources
4. Duplication of medications
5. Limited financial resources
6. Intentional nonadherence
7. Did not fill prescription
8. Incorrect label on prescription bottle
9. Medications prescribed with known allergies/intolerances
10. Patient confusion between brand and generic
What can PA’s do?

• Discussion with entire medical group
• Encourage CHADS2 risk assessment tools for hospital EMR’s
• Careful analysis of risk of patients in practice
• Proper education of professional colleagues about screening
• Education to patients about asking questions about anticoagulation
• Don’t sit on the sidelines

Summary

• Atrial fibrillation a growing concern
• Multifaceted approach to management
• Stroke prevention is key
• Choosing the right management for the right patients
• Education- patients and clinicians
**Post Activity Questions**

Please rate each statement as it relates to your present level of ability to administer antithrombotic therapy for patients with atrial fibrillation.

**Assessment Question 1**

Document the risk of stroke using a validated assessment tool.

<table>
<thead>
<tr>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Assessment Question 2**

Discuss antithrombotic therapy with the patient in order to make an informed therapy decision.

<table>
<thead>
<tr>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Assessment Question 3**

Select the appropriate antithrombotic therapy.

<table>
<thead>
<tr>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Case Question 1**

A 77 year old man presents with permanent non-valvular atrial fibrillation of three years duration. He has a history of stroke, hypertension and mild congestive heart failure. He complains of frequent headaches, is moderately obese and has type II diabetes mellitus well controlled on an oral regimen.

Which individual element of this patient’s history is the strongest predictor of the risk of future stroke?

A. Age  
B. Previous Stroke  
C. Hypertension  
D. Congestive heart failure  
E. Diabetes
Post Activity Questions

Case Question 2-a
A 50-year-old man without past medical history has intermittent episodes of atrial fibrillation which he controls with episodic doses of oral metoprolol. The episodes typically last for less than one hour and resolve spontaneously. They occur less than once per year. He has been evaluated in the past with a normal chest x-ray, a normal echocardiogram, and normal thyroid function tests. He has no history of stroke, diabetes, hypertension, or congestive heart failure.

What would the approximate adjusted stroke rate be for this patient with non-valvular atrial fibrillation if not treated with anticoagulation?
A. Low  
B. Moderate  
C. High  
D. I don’t know

Post Activity Questions

Case Question 2-b
A 50-year-old man without past medical history has intermittent episodes of atrial fibrillation which he controls with episodic doses of oral metoprolol. The episodes typically last for less than one hour and resolve spontaneously. They occur less than once per year. He has been evaluated in the past with a normal chest x-ray, a normal echocardiogram, and normal thyroid function tests. He has no history of stroke, diabetes, hypertension, or congestive heart failure.

Which of the following therapies would you select initially for this patient?
A. No therapy or aspirin  
B. Aspirin and clopidogrel  
C. Oral anticoagulation

Post Activity Questions

Case Question 3-a
A 78-year-old woman with a history of hypertension and diabetes has permanent atrial fibrillation. She has dialysis-dependent renal failure due to diabetic nephropathy. There is no history of prior stroke, congestive heart failure, or left ventricular dysfunction. There is no history of valvular heart disease.

What would the approximate adjusted stroke rate be for this patient with non-valvular atrial fibrillation if not treated with anticoagulation?
A. Low  
B. Moderate  
C. High  
D. I don’t know

Post Activity Questions

Case Question 3-b
A 78-year-old woman with a history of hypertension and diabetes has permanent atrial fibrillation. She has dialysis-dependent renal failure due to diabetic nephropathy. There is no history of prior stroke, congestive heart failure, or left ventricular dysfunction. There is no history of valvular heart disease.

Which of the following therapies would you select initially for this patient?
A. No therapy or aspirin  
B. Apixaban  
C. Dabigatran  
D. Rivaroxaban  
E. Warfarin
**Post Activity Questions**

**Case Question 4**
An 80-year-old man with a history of hypertension and type II diabetes (orally controlled) has permanent atrial fibrillation and a pacemaker. He is active and fit. There is no history of prior stroke, congestive heart failure, or left ventricular dysfunction. There is no history of valvular heart disease.

Which of the following therapies would you select initially for this patient?

A. No therapy or aspirin  
B. Aspirin and clopidogrel  
C. Oral anticoagulation

---

**Post Activity Questions**

**Case Question 5**
A 55 year old female with hypertension and diabetes with chronic atrial fibrillation is planning to undergo an elective cholecystectomy. She takes dabigatran 150 mg twice daily.

How should her dabigatran be managed pre-procedurally?

A. Stop the dabigatran the evening before the procedure.  
B. Continue dabigatran throughout the procedure.  
C. Stop the dabigatran a day before the procedure.  
D. If the creatinine clearance is normal, stop the dabigatran 48 hours before the procedure.

---

**Post Activity Questions**

**Case Question 6**
A 78 year old male with a history of permanent atrial fibrillation, CHF, and prior stroke maintained on warfarin presents to the hospital with confusion, and is found to have an intracranial hemorrhage. INR is 4.0.

The next course of action is:

A. Continue warfarin.  
B. Allow the INR to drift down to 2.0 and resume warfarin.  
C. Administer vitamin K.  
D. Start subcutaneous heparin.

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For more information please visit www.teamanticoag.com