Warfar–IN or Warfar–OUT? And Other Updates in the Management of Atrial Fibrillation

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Conflict of Interest

• I have no conflicts of interest to disclose

Objectives for Pharmacists

• Review general management principles in the treatment of atrial fibrillation
• Summarize updates in the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines
• Utilize risk stratification schemes to balance risks and benefits to antithrombotic therapy
• Discuss the role of various anticoagulants in stroke prevention management in patients with atrial fibrillation

Objectives for Technicians

• Identify novel oral anticoagulants (NOACs)
• Describe atrial fibrillation and discuss its complications
• Recognize the different doses for the NOACs available on the market

Atrial Fibrillation

• Definition
  • Supraventricular tachyarrhythmia characterized by uncoordinated atrial activity which results in impaired mechanical function
• Epidemiology
  • Affects between 2.3 and 6.1 million American adults
  • Expected to double over the next 25 years
  • Adds $26 billion in U.S. healthcare bill
• Prognosis
  • Mortality is double that of patients in normal sinus rhythm
  • Non-valvular AF: 5-fold increase risk of stroke
  • Mitral stenosis: 20-fold increase risk of stroke

Pathophysiology

Normal Sinus Rhythm  Atrial Fibrillation

• Normal sinus rhythm
  • SA node → AV node → ventricular response
• Atrial fibrillation
  • ≥ 3 rapidly firing foci, multiple reentrant wavelets, spiral or wave re-entrant circuits
Pathophysiology

- Normal sinus rhythm
  - Every atrial impulse (SA node) generates a ventricular response
  - 1:1 conduction
  - Atrial and ventricular rate 60-100bpm
- Atrial Fibrillation
  - Multiple atrial stimuli blocked in a random fashion by the AV node
  - Variable conduction
  - Atrial rate ≥300bpm, ventricular rate variable

Symptoms

- Non-existent → severe
  - Fatigue, dizziness, palpitations, dyspnea, hypotension, syncope, heart failure
  - Decreased cardiac output
    - Suboptimal ventricular rate (too fast/slow)
    - Loss of coordinated atrial contraction
    - Beat to beat variability

Pharmacist: Question #1

- JC is a 47 year old male with atrial fibrillation interested in the NOACs. JC states that commercials on TV for the NOACs mention atrial fibrillation "not due to a heart valve problem." He turns to you for clarification. Which of the following conditions is considered a heart valve problem? (valvular AF)

A. Rheumatic mitral stenosis
B. Mechanical heart valve
C. Bioprosthetic heart valve
D. Mitral valve repair
E. All of the above

Classification Updated**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>AF that terminates spontaneously or with intervention within 7 d of onset</td>
</tr>
<tr>
<td>Persistent</td>
<td>Continuous AF that is sustained &gt; 7d</td>
</tr>
<tr>
<td>Longstanding persistent</td>
<td>Continuous AF of &gt;12 mo duration</td>
</tr>
<tr>
<td>Permanent</td>
<td>When there is a joint decision by the patient and clinician to cease further attempts to restore sinus rhythm</td>
</tr>
<tr>
<td>Nonvalvular</td>
<td>AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral repair</td>
</tr>
</tbody>
</table>

Simplified scheme for AF classification, no more “lone” AF
Technician: Question #2

- Which of the following is a devastating consequence of atrial fibrillation?

A. Deep venous thrombosis (DVT)
B. Stroke and systemic embolism
C. High blood pressure
D. Coronary artery disease

Pathophysiology

- Embolism formation
  - Loss of organized atrial contraction causes decreased blood velocity and stasis in the left atrium and left atrial appendage

Management

- Rate control
- Rhythm control
- Anticoagulation

Rate Control

- Improves quality of life, decreases potential for tachycardia induced cardiomyopathy, reduces mortality
- Patients remain in atrial fibrillation
  - Little to no effect on atrial rate or rhythm
  - Decreases conduction through the AV node
  - Slower ventricular rate (heart rate)

*depending on cause

RACE-II Trial

- Prevention of: Composite of death from CV causes, hospitalization for HF, stroke, systemic embolism, bleeding, life threatening arrhythmias
- <110bpm vs. <80bpm
- Lenient heart rate control is non-inferior to strict heart rate control
  - 12.9% vs 14.9%, HR 0.84 (0.58-1.21)

PALLAS Trial

- Dronedarone increased risk of heart failure, stroke and death from CV causes in patients with permanent AF
2014 Rate Control Update**
- Less than 80 bpm resting (Class IIa)
- Less than 110 bpm (Class IIb)
- Rate controlling agents
  - Beta blockers (Class I)
  - Non-dihydropyridine CCBs (Class I)
  - Digoxin
  - Amiodarone (Class IIb)
  - Dronedarone NOT recommended for rate control in permanent AF (Class III)

Pharmacist: Question 3
- According to the 2014 Guidelines, which of the following is an appropriate management strategy for a patient in atrial fibrillation?
  A. Dronedarone for rate control
  B. Resting heart rate target of < 110
  C. Diltiazem for rate control in a patient with an EF < 40%
  D. None of the above are appropriate

Rhythm Control
- Restoration and maintenance of sinus rhythm
  - Cardioversion
    - Electrical (Class I)
    - Chemical (Class I)
    - Catheter ablation***
  - Pharmacologic agents to maintain sinus rhythm
    - Increase refractory period
    - Decrease automaticity

Rate vs. Rhythm Control
- Meta-analysis: rate vs rhythm control
  - No mortality difference
  - Similar stroke risk, fewer adverse drug effects, hospitalizations

Drugs Recommended for Cardioversion

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*Notes: Class I: Strong recommendation; Class II: Moderate recommendation; Class III: Weak recommendation; **2014 Guidelines; ***Permanent AF; PHD: Prophylaxis; NST: Nonsustained tachycardia; OR: Odds Ratio; CI: Confidence Interval*
**Maintenance of Sinus Rhythm**

- No Structural Heart Disease
- Structural Heart Disease

**Rate vs. Rhythm Control**

- Tolerability of rhythm
  - Palpitations
  - Shortness of breath
  - Inability to adequately control rate
- Ability to maintain sinus rhythm
  - Reversibility of precipitants
    - Surgery
    - Alcohol intake
  - Structural changes
  - Number of occurrences

**Stroke and Systemic Embolism Prevention**

Individualized based on absolute and relative risk of stroke and bleeding and patient values and preferences (Class I)

**Risk Stratification Updated**

- CHADS, VASc scoring
- Irrespective of paroxysmal, persistent or permanent AF
- Limitation with CHADS,:
  - Lowest risk patients are not identified with CHADS, score of 1

### CHADS, VASc (Class I)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (Heart failure)</td>
<td>1</td>
</tr>
<tr>
<td>H (HTN)</td>
<td>1</td>
</tr>
<tr>
<td>Age (≥ 75 y)</td>
<td>1</td>
</tr>
<tr>
<td>D (diabetes)</td>
<td>1</td>
</tr>
<tr>
<td>S (stroke or TIA)</td>
<td>2</td>
</tr>
<tr>
<td>Total Score</td>
<td>6</td>
</tr>
</tbody>
</table>

- Non-valvular AF only
- Age is only counted once

**Technician: Question #4**

Which of the following agents is not yet approved by the FDA but has a new drug application submitted for stroke prevention in atrial fibrillation?

A. Edoxaban
B. Dabigatran
C. Vorapaxar
D. Apixaban
E. Rivaroxaban
Pharmacist: Question #5

RF is a 67 year old female with hypertension and type II diabetes. She has newly diagnosed atrial fibrillation and her primary care physician asks you to help estimate her annual risk of stroke.

What is her CHA2DS2-VASc score?
A. 1  
B. 2  
C. 3  
D. 4  
E. 5

Recommendations Updated**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors (CHA2DS2=0)</td>
<td>aspirin 81 to 325mg</td>
</tr>
<tr>
<td>1 moderate risk factor (CHA2DS2=1)</td>
<td>aspirin 81 to 325mg or warfarin</td>
</tr>
<tr>
<td>1 high risk* or 2 moderate risk factors</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

2014 Recommendations (CHA2DS2-VASc)§

- 0  Reasonable to omit therapy (Class IIa)**
- 1  No anticoagulation, oral anticoagulation or aspirin (Class IIb)**
- ≥ 2  Oral anticoagulation w/ dabigatran, apixaban, or rivaroxaban (Class I)**

HAS-BLED Score

- New scoring system to assess bleeding risk
- Not studied in combination with CHA2DS2-VASc
- No guideline recommendation on use

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (SBP &gt;160)</td>
<td>1</td>
</tr>
<tr>
<td>A (renal/hepatic)</td>
<td>1 each</td>
</tr>
<tr>
<td>S (stroke)</td>
<td>1</td>
</tr>
<tr>
<td>B (bleeding)</td>
<td>1</td>
</tr>
<tr>
<td>L (labile INR)</td>
<td>1</td>
</tr>
<tr>
<td>E (elderly &gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>D (drugs/alcohol)</td>
<td>1 each</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
</tr>
</tbody>
</table>

Helpful Hint

- Apixaban
- Rivaroxaban \{ Anti-Xa Inhibitors \}
- Edoxaban
- Dabigatran \{ Direct Thrombin Inhibitor \}

Dabigatran

- Oral direct thrombin inhibitor
- FDA approved October 19, 2010

RE-LY Trial

- Prevention of stroke or systemic embolism
  - Warfarin INR 2-3 (TTR 63%)
  - Dabigatran 150mg PO BID or 110mg PO BID
  - Mean CHADS2 = 2.1

<table>
<thead>
<tr>
<th>Dabigatran 150mg</th>
<th>Warfarin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.11%</td>
<td>1.69%</td>
</tr>
<tr>
<td>Bleeding Total</td>
<td>3.11%</td>
<td>3.36%</td>
</tr>
</tbody>
</table>

Dabigatran150mg BID is superior to warfarin in stroke and SE prevention
Similar bleeding risk
Dabigatran should NOT be used in patients with AF and mechanical heart valves (Class III recommendation).

- RE-ALIGN trial
  - Within 7 days (population A), 3 months out (population B)
  - Dabigatran 150, 220, or 300mg BID based on CrCl
    - Adjusted to serum level of 30ng/mL.
  - Stopped early due to a high incidence of thromboembolic and bleeding complications.

Technician: Question # 6

- Which of the following doses of Dabigatran is FDA approved?
  A. 220mg
  B. 150mg
  C. 110mg
  D. 300mg

Oral Anti-Xa Inhibitors

- Direct, competitive anti-Xa inhibitors
  - Does not require AT like fondaparinux
- Rivaroxaban
- Apixaban
- Edoxaban

Rivaroxaban

- Prevention of stroke and systemic embolism
  - Warfarin INR target 2.5 (TTR 57.8%)
  - Rivaroxaban 20mg daily, (15mg CrCl: 30-49)
- High Risk Patients
  - Mean CHADS2 = 3.4

<table>
<thead>
<tr>
<th>Rivaroxaban (n=7081)</th>
<th>Warfarin (n=7090)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.71%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.6%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

- Rivaroxaban is non-inferior to warfarin
- Similar bleeding risk
ARISTOTLE
- Prevention of stroke or systemic embolism
  - Warfarin targeted INR 2.5 (TTR 62.2%)
  - Apixaban 5mg BID*  
  - Mean CHADS2=2.1

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=9120)</th>
<th>Warfarin (n=9081)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.27%</td>
<td>1.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.13%</td>
<td>3.09%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- Apixaban is superior to warfarin
- Less bleeding than warfarin

AVERROES
- Prevention of stroke and systemic embolism prevention in pts unsuitable for VKA
  - Aspirin 81-324mg daily OR Apixaban 5mg BID
  - Mean CHADS2=2

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=2808)</th>
<th>ASA (n=2910)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.6%</td>
<td>3.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1.4%</td>
<td>1.2%</td>
<td>0.57</td>
</tr>
</tbody>
</table>

- Trial terminated early due to clear benefit of apixaban
- Apixaban appears to be superior to ASA
- Similar bleeding risk

ENGAGE AF-TIMI 48
- Prevention of stroke or systemic embolism
  - Edoxaban 60mg (30mg*) OR warfarin
  - Mean CHADS2=2.8

<table>
<thead>
<tr>
<th></th>
<th>High Dose Edoxaban</th>
<th>Low Dose Edoxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.18% (p&lt;0.01)</td>
<td>1.61% (p&lt;0.001)</td>
<td>1.5%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.75% (p&lt;0.01)</td>
<td>1.61% (p&lt;0.001)</td>
<td>3.43%</td>
</tr>
</tbody>
</table>

- Both doses are non-inferior to warfarin
- Both doses had lower rates of bleeding

Pharmacist: Question #7
- RF is our 67 year old female with hypertension and type II diabetes. Her PCP asks for your recommendation on which anticoagulant therapy to select for stroke prevention. What do you recommend?
  - Home meds: atorvastatin, lisinopril, metformin, metoprolol
  - CrCl: 60mL/min, weight: 85 kg
  - A. Apixaban 5mg BID
  - B. Rivaroxaban 20mg daily
  - C. Warfarin titrated to an INR of 2-3
  - D. Dabigatran 150mg BID

Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Dose</th>
<th>Renal Dose</th>
<th>Studied dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CrCl 15-50: 75mg BID CrCl &lt;15: avoid use</td>
<td>RELY: 150mg BID PK data: 75mg</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl 15-50: 15mg daily CrCl &lt;15: avoid use</td>
<td>ROCKET-AF CrCl 30-50:15mg</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5mg BID if 2 of Scr ≥1.5mg/dL, age ≥75, wt ≥80 kg</td>
<td>AVERROES/ARISTOTLE Excluded Scr ≥2.0mg/dL, CrCl ≥25</td>
</tr>
</tbody>
</table>

- For patients with non-valvular AF with a CHA2DS2-VASc of ≥2 and who have ESRD or are on HD, it is reasonable to prescribe warfarin (Class IIa)

End Stage Renal Disease
- FDA approval: Dose for ESRD patients maintained on hemodialysis (HD)
  - 5 mg orally twice daily
  - 2.5mg BID with ≥80 years or body weight ≤60 kg
- Pharmacokinetic study in 16 patients
  - 8 normal renal function, 8 ESRD
- 1 dose of apixaban
Special Circumstances Updated**

- Valvular AF
  - Mitral stenosis: warfarin
  - Mechanical valves: warfarin based on type and location of valve
- Post coronary revascularization w/ CHA2DS2-VASc ≥ 2
  - Reasonable to use clopidogrel with anticoagulant without ASA
- Cardioversion
  - Stable patients with 2-48 hrs in AF or Aflutter
    - Anticoagulation 1-4 wks after regardless of CHA2DS2-VASc
      - Warfarin (Class I)
      - NOACs (Class IIa)

References