Novel Anticoagulation for Prevention of Stroke in Patients with Atrial Fibrillation

Objectives

1. Review current evidence on use of warfarin in individuals with atrial fibrillation
2. Compare the three novel anticoagulants indicated for use in individuals with atrial fibrillation for primary and secondary prevention of stroke
3. Discuss treatment decision support based on best practice when evidence is limited
4. Review current evidence on use of Vitamin K antagonists/anticoagulants in individuals with atrial fibrillation
5. Compare and contrast the three novel anticoagulants based on current evidence

Atrial Fibrillation (AF)

- Most common cardiac arrhythmia
- Characterized by uncoordinated activation of the atria
- Causes deterioration in cardiac function
- Associated with increased morbidity, mortality, and cost, specifically associated with stroke
Atrial Fibrillation and Stroke

- After stratifying for the risk factors most common for stroke (e.g., age, hypertension, heart failure), AF is associated with up to a 5-fold increased risk of ischemic stroke
- In 2009, 1 million people were hospitalized for stroke in the nation, of whom, 12% were diagnosed with AF as a comorbid condition

Warfarin

- Oral antithrombotic therapy; largely considered evidence-based and best practice for years
- Pooled Analysis 5 trials
  - Primary prevention: Benefit
- EAFTR
  - Warfarin vs Aspirin 300mg vs placebo
  - Greater risk reduction with warfarin compared to aspirin and placebo
- ACTIVE W
  - Aspirin + Plavix vs Warfarin
  - Trial stopped early due to superiority of warfarin
- SPAF III
  - Warfarin vs low dose Warfarin (INR 1.2-1.5) vs Aspirin 325mg
  - Stopped early due to more strokes in low dose arm
Coagulation Cascade

Warfarin

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Oral: Rapid, complete</td>
</tr>
<tr>
<td>Distribution</td>
<td>0.14 L/kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic, primarily via CYP2C9; minor pathways include CYP2C8, 2C19, 2C9, 3A2, and 3A4</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (92%), primarily as metabolites</td>
</tr>
<tr>
<td>Half-life</td>
<td>20-60 hours</td>
</tr>
</tbody>
</table>
Warfarin

- **Onset of action:**
  - 5-7 days
  - May requiring bridging

- **Antidote:**
  - Vitamin K, FFP, PRBC

- **Interactions:**
  - Foods with high vitamin K content

Warfarin

- **Medications**
  - Anticoagulants
  - Aspirin/NSAIDS (ibuprofen)
  - 2-[[3-Chlorophenyl]amino]benzamide (Acyclovir)
  - Fluorouracil (5FU)
  - Fluorinated steroids (ciprofloxacin)
  - Griseofulvin
  - Hemodial
  - Macrolides (azithromycin)
  - Metoclopramide
  - NSAIDs
  - Penicillin (methicillin)
  - Prednisone
  - Rifampin
  - Sulfamethoxazole/trimethoprim
  - Ticarcillin/Amoxicillin

- **Herbals**
  - Ginger
  - Ginkgo
  - Fenugreek
  - Chamomile
  - St. John's Wort

Warfarin

- **ADRs**
  - Bleeding/Hemorrhage/Hematuria
  - Vasculitis
  - Dermatitis, pruritus, urticaria
  - Abdominal pain, N/V/D
  - Anemia
  - Skin necrosis, gangrene, “purple toes” syndrome
Dabigatran

- MOA: direct thrombin inhibitor which inhibits:
  - Both free and fibrin-bound thrombin
  - Cleavage of fibrinogen to fibrin
  - Activation of factors V, VIII, XI, and XIII
  - Thrombin-induced platelet aggregation

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<tr>
<td>Half-life</td>
</tr>
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</table>
Dabigatran

- Monitoring
  - PPT

- Onset: 1 hour, delayed by food

- Antidote: None

- ADRs
  - Bleeding (8% to 33%; major ≤ 6%)
  - Dyspepsia (11%)

Dabigatran

- Contraindications
  - Hypersensitivity to dabigatran or any component
  - Active bleeding

- Warnings/Precautions
  - Bleeding
  - Renal impairment
  - Anticoagulants
  - Invasive/surgical invasions
  - P-gp inducers/inhibitors

Dabigatran

- Drug interactions
  - Category X: P-Gp inducers
  - Category D: Amiodarone, P-Gp inhibitors, quinidine, St. John’s Wort, verapamil
  - Category C: antacids, anticoagulants, antiplatelet agents, atorvastatin, dasatinib, ibritumomab, NSAIIDs, prostacyclin analogs, PPIs, salicylates, thrombolytic agents
Dabigatran

- FDA Bleeding Risk: [12-7-2011]
- Evaluating post-marketing reports of serious bleeding
- "Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies."

Dabigatran

- ISMP Medication Safety Alert: Quarter Watch [01-12-12]
- 932 serious adverse events for 1st quarter of 2011
  - 120 deaths
  - 25 cases of permanent disability
  - 543 cases requiring hospitalization
  - 505 cases involved hemorrhage; elderly patients (Median age of 80)
  - 120 cases of hemorrhagic stroke

Dabigatran

- FDA Drug Safety Communication: [11-02-2012]
  - "...FDA investigated the actual rates of gastrointestinal bleeding and intracranial hemorrhage for new users of [dabigatran] compared to new users of warfarin. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of [dabigatran] do not appear to be higher than bleeding rates associated with new use of warfarin ...."
Dabigatran


• "A clinical trial in Europe (the RE-ALIGN trial) was recently stopped because [dabigatran] users were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the [dabigatran] users than in the warfarin users. [dabigatran] is not approved for patients with AF caused by heart valve problems."

Updated FDA bleeding risk [5-13-14]

• “As a result of our latest findings, we still consider dabigatran to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use.”

Dabigatran

<table>
<thead>
<tr>
<th>MAY be appropriate</th>
<th>MAY NOT be appropriate</th>
<th>NOT appropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to comply with home daily drug regimen</td>
<td>History of non-compliance</td>
<td>Renal renal impairment (CrCl&lt;30 mL/min)</td>
</tr>
<tr>
<td>Unstable reflux on warfarin (related to adherence)</td>
<td>Stable reflux on warfarin</td>
<td>History of GI bleeding or recent ulcers</td>
</tr>
<tr>
<td>Difficulty initiating regular daily dosing</td>
<td>Advanced age (pts 65 and older, consider benefits and risks)</td>
<td>Active liver disease</td>
</tr>
<tr>
<td>Consider converting drug regimen on warfarin</td>
<td>History of renal failure</td>
<td>Pregnancy, at risk of pregnancy, or lactating</td>
</tr>
<tr>
<td>High risk of intracranial bleed</td>
<td>Medication regimen does not include drugs that interact with dabigatran</td>
<td>Need for concurrent treatment with P-glycoprotein (P-gp) inhibitors</td>
</tr>
<tr>
<td>Baseline function</td>
<td>No history of GI bleeding or recent ulcer</td>
<td>Moderate oral anticoagulation (IC-2) or coronary artery disease and the need for concurrent treatment with the P-gp inhibitors, verapamil, or amiodarone</td>
</tr>
<tr>
<td>No history of GI bleeding or recent ulcer</td>
<td></td>
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Dabigatran
Rivaroxaban

- MOA: selective/reversible direct inhibitor of factor Xa
- Prevents the conversion of prothrombin to thrombin
- Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin
Rivaroxaban

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<thead>
<tr>
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<tbody>
<tr>
<td>Absorption</td>
<td>Rapid</td>
</tr>
<tr>
<td>Distribution</td>
<td>Vd= 50 L</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (33%) via CYP3A4/5 and CYP2C19</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal (66% primarily via active tubular secretion), feces (28%)</td>
</tr>
<tr>
<td>Half-life</td>
<td>5.9 hours</td>
</tr>
</tbody>
</table>

Rivaroxaban

- Monitoring
  - Prothrombin time (PT)
  - CBC with differential
  - Renal/hepatic function

- Onset: 2-4 hours

- Antidote: None

Rivaroxaban

- ADRs
  - Pruritus (2%)
  - Bleeding
    - DVT prophylaxis: 6% [major: <1%]
    - Atrial fibrillation: 21% [major: 6%]
    - Thrombocytopenia (3%)
    - Increase in liver enzymes (7%-3%)
Rivaroxaban

- Contraindications
  - Hypersensitivity to rivaroxaban or any component
  - Active bleeding

- Drug Interactions
  - Category X: P-Gp or 3A4 inhibitors/inducers
  - Category C: anticoagulants, antiplatelet agents, NSAIDs, salicylates

Rivaroxaban

- Primary event: Thrombus
  - 358 cases, 44.4% of the total
- Hemorrhage
  - 121 cases, 34% of the total

Apixaban

- MOA: oral direct Xa inhibitor

- Dose: 5mg twice daily
  - Dose reduction to 2.5mg twice daily if 2+ of the following:
    - Age ≥80 years
    - Body weight ≤60kg
    - Scr ≥2.5 mg/dL
    - AVOID in CrCl <15 ml/min
Apixaban

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<tr>
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<tr>
<td><strong>Metabolism</strong></td>
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<td></td>
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<tr>
<td><strong>Excretion</strong></td>
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<td></td>
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<tr>
<td><strong>Half-life</strong></td>
</tr>
</tbody>
</table>

- Monitoring
  - Minimal impact on the PT, INR, or aPTT
  - Factor Xa inhibition

- Onset: 3-4 hours
- Antidote: None
## Clinical Evidence

![Clinical Evidence Table]

## Efficacy Comparison

![Efficacy Comparison Table]

## Safety Comparison

![Safety Comparison Table]
Latest AHA/ASA Recommendations

- AIS or TIA without apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event (Class IIa; Level of Evidence C).
- VKA therapy (Class I; Level of Evidence A), apixaban (Class I; Level of Evidence A), and dabigatran (Class I; Level of Evidence B) are all indicated for the prevention of recurrent stroke in patients with AF (Class IIa; Level of Evidence B).
- Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with AF (Class IIa; Level of Evidence B).
- Combination of oral anticoagulation (ie, warfarin or NOAC) with antiplatelet therapy is not recommended for all patients after IS or TIA but is reasonable in patients with clinically apparent CAD, particularly an ACS or stent placement (Class IIb; Level of Evidence C).

Is or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended (Class I; Level of Evidence A). The addition of clopidogrel to aspirin therapy, or aspirin therapy alone, might be reasonable (Class IIb; Level of Evidence B).

For most patients with IS or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (Class IIa; Level of Evidence B).

In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled HTN, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (Class IIa; Level of Evidence B).

The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with IS or TIA and AF is uncertain (Class IIb; Level of Evidence B).

Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>FDA Indicators</td>
<td>Nonvalvular AF</td>
<td>Nonvalvular AF</td>
<td>Nonvalvular AF</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>Twice daily</td>
<td>Daily with food</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Onset</td>
<td>1.3 day</td>
<td>2.4 hour</td>
<td>2.4 hour</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>14-17</td>
<td>7-12</td>
<td>6-14</td>
</tr>
<tr>
<td>Oral Adjust</td>
<td>1.25-3.75 mg/kg</td>
<td>Avoid ≥ 60 mg/day</td>
<td>Avoid ≥ 15 mg/day</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>P-gp</td>
<td>CYP2J2/P-gp</td>
<td>CYP2J2/P-gp</td>
</tr>
</tbody>
</table>

9/5/14