Should we “RELY” on Dabigatran for the Treatment of Non-Valvular Atrial Fibrillation?

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By the end of the presentation, you will be able to:
1. Identify appropriate screening and diagnosis for patients presenting with atrial fibrillation
2. Apply current guidelines for the treatment and management of atrial fibrillation to a patient case
3. Evaluate existing literature for treatment of atrial fibrillation in regards to new oral anticoagulants versus standard therapy
4. Discuss recommendations regarding pharmacotherapy for atrial fibrillation in regards to stroke risk, bleeding risk, and cost of medication and monitoring
I. Introduction

A. Definitions of Atrial Fibrillation (AF)\textsuperscript{1-3}

1. “Supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function”
2. “A rapid, irregular, sustained, wide-QRS, complex tachycardia strongly suggests AD with conduction over accessory pathway”

B. Epidemiology\textsuperscript{4,5}

1. Most common cardiac arrhythmia accounting for 1/3 of hospitalizations
2. National statistics: 2.3 million people in the United States; 0.4 to 1.0% in the general population
3. Local statistics: Stroke is the third leading cause of death in Texas (1999-2010; 2.8%)
4. Age: incidence of atrial fibrillation increases with age
   • 1.5% of women and 2% of men per year over the age of 70
   • 8% in patients >80 years of age
5. Race: Higher risk in Caucasians compared with African American population

\textbf{Figure 1. Prevalence of AF in the Framingham Heart Study and Cardiovascular Heart Study}^6

![Graph showing prevalence of AF from 50-80 years](source: Circulation 2001)

C. Pathophysiology\textsuperscript{4,6,7}

1. Most frequent change in AF is atrial fibrosis and loss of atrial muscle mass
2. “Lone” AF- uncertainties about its origin without reference to age or cardiovascular pathology
3. Theories of the mechanism of AF:
   • Enhanced automaticity in 1 or several rapidly depolarizing foci
   • Rapidly firing foci located in 1 or several superior pulmonary veins (PV), right atria (RA), superior vena cava (SVC), or coronary sinus
   • Three patterns of induced AF:
     o Type 1- single wave fronts propagating across the RA
     o Type 2- One or two wave fronts propagating across the RA
     o Type 3- multiple activation wavelets propagating in different directions
4. The AV node is the factor that limits conduction during AF; conduction over an accessory pathway can lead to a rapid ventricular response
5. Factors affecting hemodynamic function- loss of synchronous atrial mechanical activity, irregularity of ventricular response, and inappropriate rapid heart beat
6. Classification of clinical AF subtypes
   • \textbf{Paroxysmal}: Episodes that terminate spontaneously
   • \textbf{Persistent}: Paroxysmal AF sustained for more than seven days, or atrial fibrillation that terminates spontaneously
   • \textbf{Permanent}: AF that is unresponsive to cardioversion; cardioversion will not be reattempted
   • \textbf{Recurrent}: Two or more episodes of atrial fibrillation
Figure 2. Posterior view of principal electrophysiological mechanism of atrial fibrillation

<table>
<thead>
<tr>
<th>Risk Factors (Control group)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke or transient ischemic attack (TIA)</td>
<td>2.5</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.4</td>
</tr>
<tr>
<td>Advanced age (continuous, per decade)</td>
<td>1.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.7</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Source: Circulation 2006

D. Clinical Manifestation
1. Palpitations
2. Chest pain
3. Dyspnea
4. Fatigue
5. Lightheadedness

II. Complications
A. Clot formation
- Most frequently in the left atrial appendage (LAA) because of reduced flow velocities due to disorganized mechanical contraction

B. Stroke
- Patients with nonvalvular AF have a 6-fold increase of developing a stroke compared to a patient in normal sinus rhythm

III. Risk Factors
A. Advanced age
- Prevalence doubles with each advancing decade of age, 0.5% at age 50-59 years to almost 9% at age 80-89 years

B. Cardiovascular disease
1. Any heart condition can increase the risk of abnormal rhythm
   a. Rheumatic heart disease
2012 VMGarcia p.4

b. Hypertensive cardiovascular disease
c. Congestive Heart Failure
d. Cardiac abnormalities with atrial enlargement

2. Thyrotoxicosis
3. Post heart surgery

IV. Screening and Diagnosis\textsuperscript{3,6,8}

A. Screening
1. American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force (ACCF/AHA/HRS) Guidelines
   a. History and physical examination to determine
      i. Presence and nature of symptoms associated with AF
      ii. Clinical type (first episode, paroxysmal, persistent, or permanent)
      iii. Onset of first symptomatic attack or date of discovery of AF
      iv. Frequency, duration, precipitating factors and mode of termination
      v. Response to any medications that have been administered
      vi. Presence of underlying heart disease or other conditions (hyperthyroidism or alcohol consumption)- Successful treatment of the condition will rule out AF

B. Diagnosis
1. Electrocardiogram to identify:
   a. Rhythm (verify AF: atrial rate >100 bpm but usually 350-600, irregular and rapid ventricular rate of 120-180 bpm)
   b. Left ventricular (LV) hypertrophy
   c. P-wave duration and fibrillatory waves
   d. Prior MI

2. Differential Diagnosis
   a. Thyroid function test
   b. Hemoglobin/hematocrit
   c. Alcohol level
   d. Electrolyte measurement
   e. Arterial blood gases and pH

V. Current Recommendation for Safety: National Patient Safety Goals\textsuperscript{9}

A. NPSG.03.05.01
   • Reduce the likelihood of resident harm associated with the use of anticoagulant therapy
     Note: This requirement applied only to organizations that provide anticoagulation therapy and/or long-term anticoagulation prophylaxis

B. Rationale for NPSG.03.05.01
1. National Patient Safety Goal
   a. Impact the safety of the patient which results in better outcomes
   b. Provide face-to-face patient education to ensure that the patient understands the risks and precautions involved with anticoagulants and INR monitoring
   c. Reduce the risk of adverse drug events (ADEs) associated with anticoagulant therapy

2. Elements of Performance for NPSG.03.05.01
   a. Use approved protocols for the initiation and maintenance of anticoagulation therapy
   b. Before starting a resident on warfarin, assess the patient’s baseline INR; for patients on warfarin therapy, adjust medication based on current INR
   c. Use appropriate guidelines and resources to manage potential food and drug interactions for patients on warfarin
   d. Written policies and procedures for baseline and ongoing laboratory tests are required for anticoagulants
e. Provide education about anticoagulation to prescribers, staff, residents, and families
   i. Importance of monitoring
   ii. Compliance
   iii. Drug-food interactions
   iv. Potential for adverse drug reactions and interactions
f. Evaluate anticoagulation safety practices, take action to improve practices, and measure the effectiveness of those actions

VI. Current Recommendations for Treatment\textsuperscript{11-15}

A. Newly Diagnosed Atrial Fibrillation
   1. Paroxysmal
      a. No therapy needed unless severe symptoms (e.g., hypotension, HF, angina pectoris)
      b. Anticoagulation as needed
   2. Persistent (Refer to Appendix C/D for Rate and Rhythm Control Recommendation)
      a. Permanent AF
         i. Anticoagulation and rate control as needed
      b. Rate Control or Coagulation needed
         i. Consider antiarrhythmic drug therapy
         ii. Cardioversion
         iii. Long-term anti-arrhythmic drug therapy unnecessary

B. Evaluate need for Anticoagulation Therapy
   1. Assess stroke risk with CHADS\textsubscript{2} risk stratification tool

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
Risk Factor & Points \\
\hline
Recent Congestive Heart Failure exacerbation & 1 \\
History of Hypertension & 1 \\
Age $\geq 75$ & 1 \\
Diabetes mellitus & 1 \\
Prior History of Stroke or Transient Ischemic Attack & 2 \\
\hline
\textbf{Maximum Score} & 6 \\
\hline
\end{tabular}
\caption{CHADS\textsubscript{2} Score for Assessment of Stroke Risk in Patients with Non-Rheumatic AF\textsuperscript{10}}
\end{table}

\textit{CHADS}\textsubscript{2} = congestive heart failure, hypertension, age $\geq 75$ years, diabetes mellitus, prior stroke or transient ischemic attack

2. Revised CHAD\textsubscript{2} risk stratification tool

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
Risk Factor & Score & \textit{CHA}_{2}\textit{DS}_{2}\textit{-VAS}_{t} & Patients (n=7329) & Adjusted stroke rate (%/year) \\
\hline
CHF/LV dysfunction & 1 & 0 & 1 & 0% \\
HTN & 1 & 1 & 422 & 1.3% \\
Age $\geq 75$ & 2 & 2 & 1230 & 2.2% \\
DM & 1 & 3 & 1730 & 3.2% \\
Stroke/TIA/thromboembolism & 2 & 4 & 1718 & 4.0% \\
Vascular disease & 1 & 5 & 1159 & 6.7% \\
Age 65-74 & 1 & 6 & 679 & 9.8% \\
Sex category (i.e. female sex) & 1 & 7 & 294 & 9.6% \\
\hline
\textbf{Maximum score} & 9 & 82 & 14 & 15.2% \\
\hline
\end{tabular}
\caption{Risk factor-based approach with the acronym \textit{CHA}_{2}\textit{DS}_{2}\textit{-VAS}_{t}\textsuperscript{14}}
\end{table}
C. Antithrombotic Treatment based on CHADS₂

1. American College of Chest Physicians (CHEST)/ACCF/AHA/HRS: Antithrombotic recommendations in patients with nonvalvular atrial fibrillation

<table>
<thead>
<tr>
<th>Indication</th>
<th>*Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Including Paroxysmal AF: CHADS₂ = 0</td>
<td>No therapy over antithrombotic therapy</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Patient that choose therapy: ASA 75 mg – 325 mg daily</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>ASA preferred over oral anticoagulation or combination of ASA and clopidogrel</td>
<td>2B</td>
</tr>
<tr>
<td>Including Paroxysmal AF: CHADS₂ =1</td>
<td>Oral anticoagulation over no therapy, ASA, or ASA plus clopidogrel</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Patient unable to take oral anticoagulation: ASA plus clopidogrel &gt; ASA</td>
<td>2B</td>
</tr>
<tr>
<td>Including Paroxysmal AF: CHADS₂ =2</td>
<td>Oral anticoagulation over no therapy, ASA, or ASA plus Clopidogrel</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>Patient unable to take oral anticoagulation: ASA plus clopidogrel &gt; ASA</td>
<td>1B</td>
</tr>
<tr>
<td>Oral Anticoagulation</td>
<td>Dabigatran 150 mg BID preferred over vitamin K antagonist</td>
<td>2B</td>
</tr>
</tbody>
</table>

*Duration for all indications and therapy is indefinite

CHEST 2012; 141(2):e531S-e575S; Circulation 2012; 43;1-12

2. European Society of Cardiology: Antithrombotic recommendations in patients with nonvalvular atrial fibrillation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic therapy to prevent thromboembolism for all patients with AF, except in those patients (both male and female) who are at low risk (aged &lt;65 years and lone AF), or with contraindications</td>
<td>A</td>
</tr>
<tr>
<td>The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient</td>
<td>A</td>
</tr>
<tr>
<td>The CHA₂DS₂-VAS₂ score is recommended as a means of assessing stroke risk of non-valvular AF</td>
<td>A</td>
</tr>
<tr>
<td>In patients with a CHA₂DS₂-VAS₂ score of 0 (i.e., aged &lt;65 years with long AF) who are at low risk, with none of the risk factors, no recommendation is recommended</td>
<td>B</td>
</tr>
<tr>
<td>In patients with a CHA₂DS₂-VAS₂ score ≥2, oral anticoagulation therapy with: adjust-dose VKA (INR 2-3); direct thrombin inhibitor (dabigatran); oral factor Xa inhibitor (e.g., rivaroxaban, apixaban); Should consider the risk of bleeding complications and patient preference</td>
<td>A</td>
</tr>
<tr>
<td>Female patients who are aged &lt;65 and have lone AF (but still have a CHA₂DS₂-VAS₂ score of 1 by virtue of their gender) are low risk and no antithrombotic should be considered</td>
<td>A</td>
</tr>
<tr>
<td>When patients refuse the use of oral anticoagulation therapy, antiplatelet therapy should be considered, using a combination therapy with ASA 75-100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding), or less effectively, ASA 75-325 mg daily</td>
<td>B</td>
</tr>
</tbody>
</table>

ESC 2012; 33: 2719-2747
### VI. Pharmacologic Agents

#### Pharmacological agents for the prevention of stroke in patients with nonvalvular atrial fibrillation

<table>
<thead>
<tr>
<th>MOA</th>
<th>Aspirin (Plavix®)</th>
<th>Clopidogrel (Plavix®)</th>
<th>Warfarin (Coumadin®)</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversibly inhibits cyclooxygenase-1 and 2 (COX 1 and 2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandins derivative, thromboxane A₂, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation; has antipyretic, analgesic, and anti-inflammatory properties</td>
<td>Active metabolite irreversibly blocks the P2Y₁₂ component of ADP receptors on the platelet surface, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Platelets blocked by clopidogrel are affected for the remainder of their lifespan (~7-10 days).</td>
<td>Hepatic synthesis of coagulation factors II, VII, IX, and X, as well as protein C and S, requires the presence of vitamin K. These clotting factors are biologically activated by the addition of carboxyl groups to key glutamic acid residues within the protein's structure. In the process, &quot;active&quot; vitamin K is oxidatively converted to an &quot;inactive&quot; form, which is then subsequently reactivated by vitamin K epoxide reductase complex (VKORC1).</td>
<td>Prodrug lacking anticoagulant activity that is converted in vivo to the active dabigatran, a specific, reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Inhibits coagulation by preventing thrombin-mediated effects, including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI, and XIII, and inhibition of thrombin-induced platelet aggregation</td>
<td>Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of factor Xa (FXa) in both the intrinsic and extrinsic coagulation pathways. FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, factor II and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>75 to 325 mg daily</td>
<td>75 mg daily</td>
<td>Initiate 2-5 mg once daily for 2 days or for healthy individuals, 10 mg daily once daily for 2 days</td>
<td>150 mg BID</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>GI ulceration and rash</td>
<td>Bleeding, GI hemorrhage, and rash</td>
<td>Signs/symptoms of bleeding</td>
<td>Dyspepsia, bleeding, GI hemorrhage</td>
<td>Bleeding, AST/ALT elevations, extremity pain</td>
</tr>
<tr>
<td>Antidote</td>
<td>Not available</td>
<td>Not available</td>
<td>Vitamin K</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Cost</td>
<td>$145/year (yr)</td>
<td>$2,459/yr</td>
<td>$167/yr (generic), $610 (brand), INR monitoring $1642</td>
<td>$3,000/yr</td>
<td>$3,000/yr</td>
</tr>
</tbody>
</table>

### VII. Goals and Monitoring

#### A. PT/INR

1. Goal of 2 to 3 in patients with nonvalvular atrial fibrillation

#### Table 6. Considerations of Adjustments of Warfarin Maintenance Dose (after at least 7 days of continuous dosing)

<table>
<thead>
<tr>
<th>International normalized ratio (INR)</th>
<th>Suggested Change in Total “Weekly” Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>Give extra daily dose once and increase weekly by 10% to 20%</td>
</tr>
<tr>
<td>1.5-1.9</td>
<td>Increase weekly dose by 5% to 15% (may give extra daily dose times 1)⁶</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>Maintain same dose</td>
</tr>
<tr>
<td>3.1-4a</td>
<td>Hold up to one daily dose and decrease weekly dose by 5% to 20%</td>
</tr>
<tr>
<td>4.1-5a</td>
<td>Hold up to two daily doses and decrease weekly dose by 10% to 20%</td>
</tr>
<tr>
<td>≥5</td>
<td>Possible vitamin K use</td>
</tr>
</tbody>
</table>

⁵ Assumes no active bleeding
⁶ If cause identified, may not need to increase or decrease weekly dose
B. Monitoring

1. INR monitoring should be performed every 7 to 14 days until stable and every 4 to 8 weeks thereafter; patients who are very stable may have intervals as long as 12 weeks.
2. Patient/family should be educated on signs/symptoms of bleeding, stroke, and DVT/PE.
3. At each visit, evaluate consumption/use of the following:
   a. New medications including herbal products and vitamins
   b. Alcohol
   c. Smoking
   d. Cranberry Juice
   e. Green Tea
   f. Diet
4. Ask patient about missed doses, falls, and signs/symptoms of bleeding
5. Evaluate risk for bleeding with one of the following scoring systems

<table>
<thead>
<tr>
<th>Scoring System</th>
<th>Criteria</th>
<th>Point Scores</th>
<th>Risk of Major Bleeding (MB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient Bleeding Risk Index</strong></td>
<td>Age &gt; 65</td>
<td>1</td>
<td>Score MB Pt-yr</td>
</tr>
<tr>
<td></td>
<td>History of GI bleed</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>History of stroke</td>
<td>1</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>One or more of diabetes, hematocrit &lt;30, SCr &gt; 1.5 or recent MI</td>
<td>1</td>
<td>3-4</td>
</tr>
<tr>
<td><strong>HEMORR_HAGES</strong></td>
<td>Hepatic or renal disease</td>
<td>1</td>
<td>Score MB Pt-yr</td>
</tr>
<tr>
<td></td>
<td>Ethanol abuse</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Older (age &gt;75)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Reduced platelet count or function</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Rebleeding risk</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Hypertension (uncontrolled)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Genetic factors (CYP 2C9 polymorphism)</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Excessive fall risk</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td><strong>HAS-BLED</strong></td>
<td>Hypertension</td>
<td>1</td>
<td>Score MB Pt-yr</td>
</tr>
<tr>
<td></td>
<td>Abnormal renal/liver function</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bleeding history or predisposition</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Labile INR (&lt;60% time in range)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Elderly (age &gt; 75)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Drugs/alcohol concomitantly</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

CYP= cytochrome p450; GI= gastrointestinal; MI= myocardial infarction; pt-yr= patient-year; SCr= serum creatinine
VIII. Literature Review

A. Safety and Efficacy Trial


**Study Design** Randomized, noninferiority trial

**Study Site(s)** 951 clinics in 44 countries

**Objective** To evaluate stroke or systemic embolism with dabigatran 110 mg and 150 mg BID compared to warfarin

**Subjects**

18,113 patients with atrial fibrillation and risk of stroke

**Inclusion Criteria**

- Atrial fibrillation documented with electrocardiography at screening or within 6 months and at least one of the following: previous stroke or transient ischemic attack, a left ventricular ejection fraction of <40%, NYHA Class II or higher heart failure symptoms within 6 months before screening, age of at least 75 or 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease

**Exclusion Criteria**

- Presence of severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased risk of hemorrhage, a creatinine clearance of <30 mL/min, active liver disease, and pregnancy

**Methods**

- Randomization occurred with dabigatran 110 and 150 mg BID with unblinded use of warfarin tablets of 1, 3, or 5 mg
- International normalized ratio (INR) goal of 2.0 to 3.0, with INR monitoring occurring monthly
- Follow-up occurred 14 days after randomization, 1 and 3 months, then every 3 months in the first year, and every 4 months until the completion of the study

**Statistics**

- Cox proportional-hazards modeling to determine if dabigatran 110 mg and 150 mg BID demonstrated noninferiority to warfarin
- Two one-sided P-values were used to determine noninferiority, and once noninferiority was established, two-tail tests were used to determine superiority
- Relative risk, confidence intervals, and P-values were calculated using the Cox regression analysis
- Chi-square testing was used to compare adverse events and medication discontinuation

<table>
<thead>
<tr>
<th>Event Outcome</th>
<th>Dabigatran 110 mg (N=6015)</th>
<th>Dabigatran 110 mg vs Warfarin</th>
<th>Dabigatran 150 mg (N=6076)</th>
<th>Dabigatran 150 mg vs Warfarin</th>
<th>Warfarin (N= 6022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/systemic embolism</td>
<td>182 1.53</td>
<td>0.91 &lt;0.001, 0.34</td>
<td>134 1.11</td>
<td>0.66 &lt;0.001, &lt;0.01</td>
<td>199 1.69</td>
</tr>
<tr>
<td>Stroke</td>
<td>171 1.44</td>
<td>0.92 0.41</td>
<td>122 1.01</td>
<td>0.64 &lt;0.001</td>
<td>185 1.57</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>86 0.72</td>
<td>1.35 0.07</td>
<td>89 0.74</td>
<td>1.38 0.048</td>
<td>63 0.53</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>14 0.12</td>
<td>1.26 0.56</td>
<td>18 0.15</td>
<td>1.61 0.21</td>
<td>11 0.09</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>2311 19.4</td>
<td>0.92 0.003</td>
<td>2430 20.2</td>
<td>0.97 0.34</td>
<td>2458 20.8</td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>289 2.43</td>
<td>0.90 0.21</td>
<td>274 2.28</td>
<td>0.85 0.04</td>
<td>317 2.69</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>446 3.75</td>
<td>0.91 0.13</td>
<td>438 3.64</td>
<td>0.88 0.051</td>
<td>487 4.13</td>
</tr>
</tbody>
</table>

*Relative risk (95% Confidence interval)*

- Hemorrhagic stroke: 0.12% in the Dabigatran 110 mg group, 0.10% in the Dabigatran 150 mg group, and 0.38% in the warfarin group
- Life-threatening bleeding, intracranial bleeding, and major or minor bleeding: warfarin (1.8%, 0.74%, and 18.15%), Dabigatran 110 mg (1.22%, 0.23%, and 14.62%), Dabigatran 150 mg (1.45%, 0.30%, and 16.42%) (P<0.05 for all groups)

**Author’s Conclusions**

Dabigatran 150 mg BID is safe and effective alternative to warfarin for the use of atrial fibrillation in patients at risk for stroke and systemic embolism.

**Weaknesses:**

- Open-labeled warfarin, 1/3 of patients with CHADS2 score >2
- Unexpected rates of myocardial infarction in the three treatment groups
- 20% of patients in each group were on concomitant ASA
- Uses intent-to-treat vs. per protocol

**Strengths:**

- Safety measures were monitored
- Evaluated two doses of dabigatran
### B. Cost-Effectiveness Trial

Shah SV and Gage BF. Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation. *Circulation* 2011;123: 2562-2570.21

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Site(s)</td>
<td>951 clinics in 44 countries (RE-LY Trial)</td>
</tr>
<tr>
<td>Objective</td>
<td>70-year-old patients with atrial fibrillation who had a moderate risk of stroke and no contraindication to therapy</td>
</tr>
</tbody>
</table>
| Subjects | **Inclusion Criteria** (RE-LY Trial)  
- Atrial fibrillation documented with electrocardiography at screening or within 6 months and at least one of the following: previous stroke or transient ischemic attack, a left ventricular ejection fraction of <40%, NYHA Class II or higher heart failure symptoms within 6 months before screening, age of at least 75 or 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease  
**Exclusion Criteria**  
- Presence of severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased risk of hemorrhage, a creatinine clearance of <30 ml/min, active liver disease, and pregnancy |
| Methods | **Cost Effectiveness**  
- Costs and quality-adjusted life-years (QALYs) were gathered each month depending on the health of the patient  
- Applied utilities and cost to each outcome over its expected duration  
- Used a Markov model to perform a decision analysis comparing the treatments and outcomes (ischemic stroke, transient ischemic attack (TIA), intracranial hemorrhage, major and minor noncerebral hemorrhage, MI, dyspepsia, and death)  
- Quality-adjusted survival and net cost over a maximum of 20 years was calculated for each treatment option  
**Cost** vs **QALY**  
- Cost per quality-adjusted life-year was examined over probable ranges for various variables (e.g., ASA, ASA and clopidogrel, warfarin, dabigatran, cost of INR, short-term cost of neurological event, long-term cost of event, bleeding) |
| Statistics | **Table 2. Projected Costs and Quality-Adjusted Life Years (QALYs) in the Base Case**  

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost $</th>
<th>QALYs</th>
<th>Marginal Cost per QALY vs Aspirin, $</th>
<th>Marginal Cost per QALY vs Warfarin, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg twice daily</td>
<td>43,000</td>
<td>8.65</td>
<td>50,000</td>
<td>86,000</td>
</tr>
<tr>
<td>Dabigatran 110 mg twice daily</td>
<td>44,300</td>
<td>8.54</td>
<td>66,000</td>
<td>150,000</td>
</tr>
<tr>
<td>Warfarin</td>
<td>23,000</td>
<td>8.40</td>
<td>12,500</td>
<td>N/A</td>
</tr>
<tr>
<td>Aspirin and clopidogrel</td>
<td>34,000</td>
<td>8.32</td>
<td>99,000</td>
<td>Dominated</td>
</tr>
<tr>
<td>Aspirin</td>
<td>20,000</td>
<td>8.17</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*QALY= quality-adjusted life-year; N/A= not applicable  
- Patients with a CHADS2 score of ≥3 and any hemorrhage rate, dabigatran 150 mg BID was cost-effective at less than $3500/y  
- Dabigatran 110 mg BID and Aspirin plus clopidogrel were both not cost-effective |

| Author’s Conclusions | Dabigatran 150 mg BID is a cost-effective alternative in patients with a high risk of hemorrhage or stroke (CHADS2 score ≥3) unless the patient is within therapeutic range >72.6% of the time while on warfarin. Patients with a moderate stroke risk (CHADS2 score 1 or 2) are recommended to be on warfarin unless the INR is not within therapeutic range <57.1% of the time. |
| Comments | In another study, Freeman et al. found that dabigatran 150 mg was more cost-effective ($45,372 per QALY) compared to dabigatran 110 mg ($86,000 per QALY). Testing for genetic polymorphisms in patients with hemorrhage risks may be useful to determine cost-effective therapy, but genotype testing continues to be costly.  
**Weaknesses:**  
- Dabigatran’s effectiveness only based on RE-LY trial  
- Long-term adverse effects were not determined with warfarin and dabigatran  
- Warfarin was not blinded  
**Strengths:**  
+ Percentage in therapeutic range averaged 64% |
C. Safety Trial


Study Design Randomized, controlled trial
Study Site(s) 53 centers in Denmark, Netherlands, Sweden, and United States
Objective To identify a safe dose of dabigatran in patients atrial fibrillation and high risk for thromboembolic events

Subjects
502 patients with atrial fibrillation and coronary artery disease plus ≥1 of the following: hypertension requiring treatment, DM (type 1 or 2), symptomatic heart failure or left ventricular dysfunction (ejection fraction <40%), previous stroke or transient ischemic attack, or age >75 years

Inclusion Criteria
- Documented atrial fibrillation with coronary artery disease plus ≥1 of the following: hypertension requiring treatment, DM (type 1 or 2), symptomatic heart failure or left ventricular dysfunction (ejection fraction <40%), previous stroke or transient ischemic attack, or age >75 years

Exclusion Criteria
- Mitral stenosis, prosthetic heart valves, planned cardioversion, recent myocardial infarction, recent stroke or transient ischemic attack, coronary stent placement within 6 months, any contraindication to or another indication for anticoagulation therapy, major hemorrhage in the past 6 months, severe renal impairment (glomerular filtration rate ≤30 ml/min), abnormal liver function, risk of pregnancy, investigational drug use within 30 days, or any other condition that would not allow participation in the study

Methods
- Randomization occurred with dabigatran 50, 150, and 300 mg and warfarin with unblinded use of aspirin treatment
- Warfarin group had INR goal of 2.0 to 3.0
- Follow-up occurred 1, 2, 4, 8, and 12 weeks after randomization
- Major bleeding defined as fatal or life-threatening retroperitoneal, intracranial, intracranial, or intraspinal bleeding; or bleeding requiring surgery or transfusion of ≥2 U or associated with a decrease in hemoglobin of ≥2.0 g/L

Statistics
- 1-sample Wilcoxon test was used to determine D-dimer statistical changes from baseline; data analyzed using the chi-square test or the Fisher exact test, quantitative data with 1-way analysis of variance or the Kruskal-Wallis test
- Data analysis was performed using SAS software

Table 3. Major or clinically relevant bleeding episodes and thromboembolic events

<table>
<thead>
<tr>
<th>Dabigatran Dose (mg twice daily)</th>
<th>Aspirin Dose (mg)</th>
<th># of Patients</th>
<th>Bleeding Events</th>
<th>Thromboembolic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Major</td>
<td>Clinically Relevant Plus Major</td>
<td>Total</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>50</td>
<td>81</td>
<td>21</td>
<td>1 (4.8%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>50</td>
<td>325</td>
<td>27</td>
<td>1 (3.7%)</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>150</td>
<td>0</td>
<td>100</td>
<td>9 (9%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>150</td>
<td>81</td>
<td>36</td>
<td>2 (5.6%)</td>
<td>8 (22.2%)</td>
</tr>
<tr>
<td>150</td>
<td>325</td>
<td>33</td>
<td>2 (6.1%)</td>
<td>7 (21.2%)</td>
</tr>
<tr>
<td>300</td>
<td>0</td>
<td>105</td>
<td>6 (5.7%)</td>
<td>14 (13.3%)</td>
</tr>
<tr>
<td>300</td>
<td>81</td>
<td>34</td>
<td>1 (2.9%)</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>300</td>
<td>325</td>
<td>30</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Warfarin once daily</td>
<td>0</td>
<td>70</td>
<td>0</td>
<td>4 (5.7%)</td>
</tr>
</tbody>
</table>

- In the warfarin group, patients were in therapeutic range 57.2% during the treatment
- Major bleeding occurred with the dabigatran 300 mg twice daily plus aspirin (4 of 64); major bleeding did not occur with patients treated with dabigatran 300 mg twice daily without aspirin (0 of 105, p <0.02)
- Two systemic thromboembolic events occurred in patients who received 50 mg dabigatran twice daily
- Most common adverse events seen with dabigatran were diarrhea, nausea, vomiting (26%); fatigue, edema (12%); dizziness and headache (12%), and infections

Author’s Conclusions Higher doses of dabigatran (300 mg twice daily) in combination with aspirin demonstrated a major and clinically significant bleeding events

Comments
Weaknesses:
- Open-labeled aspirin
- Duration of the study was 12 weeks long

Strengths:
+ Safety measures were monitored
+ Evaluated three doses of dabigatran and bleeding risks in combination with aspirin
IX. Other Considerations for Selecting Treatment

A. Provider Preference
   1. Comfort level/experience with warfarin versus dabigatran
   2. Warfarin use requires monitoring of INR

B. Patient Preference
   1. Fear associated with use of oral anticoagulants
   2. Bleeding risk with oral anticoagulants

C. Accessibility
   1. Warfarin is available at a low cost, but requires INR monitoring (frequency determined by provider)
   2. Dabigatran and new anticoagulants are expensive, but do not require monitoring

X. Follow-up

A. Atrial fibrillation requiring standard therapy or new oral anticoagulants
   1. Indefinite treatment with oral anticoagulants when CHADS2 Score is > 1, unless risk outweighs benefit

XI. Summary/Conclusions (See Appendix A for Proposed Algorithm for Treating Atrial Fibrillation)

A. Screening/Diagnosis
   1. Patients should be screened for atrial fibrillation based on risk factors, irregular rate, and symptoms
   2. History and physical examination to define presence and symptoms associated with AF, clinical type, frequency and duration
   3. Electrocardiogram to identify rhythm and fibrillatory waves
   4. Blood tests of thyroid function when ventricular rate is difficult to control

B. Treatment
   1. Avoid complications of thromboembolism and risk of stroke by using anticoagulation therapy when necessary
   2. Patient should be treated with an oral anticoagulant in intermediate and high stroke risks
   3. If patient does not meet INR goal with warfarin in intermediate and high stroke risk, consider alternative treatment
   4. More evidence supports warfarin as first line, but dabigatran can be an alternative therapy in people who meet criteria
   5. Medication Assistant Program available for patients who qualify

C. Monitoring and Follow-up
   1. Warfarin therapy - patients should continue to visit their provider for frequent INR monitoring to determine if levels are within therapeutic range (INR between 2 and 3)
   2. Dabigatran - routine monitoring of coagulation tests not required

D. Future Considerations
   1. Randomized, controlled studies are needed to evaluate the safety and efficacy of dabigatran, optimal anticoagulation regimens, and to support current treatment guidelines
   2. Community pharmacist can play a role in management by discussing importance of monitoring, follow-up, and medication education
Appendix A: CSV’s Proposed Algorithm for Management of Atrial Fibrillation10,21 (Created by: Valerie Garcia, PharmD)

Low Risk Patient*

Intermediate Risk Patient*

High Risk Patient*

CHADS₂ = 0, additional risk factors of stroke, 65-74 yr, female gender, vascular disease

Hemorrhages score > 2

ASA 75-375 mg daily or clopidogrel

No therapy

Warfarin

Re-evaluate CHADS₂ Risk Score

Unsuitable (e.g., other than bleeding) for or choose not to take an oral anticoagulant- ASA 75-375 mg and clopidogrel

Oral Anticoagulant

Dabigatran or ASA 75-375 mg daily or

Intermediate Risk INR <60% *TR

Intermediate Risk INR >60% *TR

High Risk INR >80% *TR

**Table 2. Hemorrhages Bleeding Risk Score**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score MB</th>
<th>Pt-%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic or renal disease</td>
<td>1</td>
<td>0.9%</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1</td>
<td>2.3%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>5.3%</td>
</tr>
<tr>
<td>Older (age &gt;75)</td>
<td>2</td>
<td>8.4%</td>
</tr>
<tr>
<td>Reduced platelet count or function</td>
<td>1</td>
<td>4.0%</td>
</tr>
<tr>
<td>Rebleeding risk</td>
<td>2</td>
<td>10.4%</td>
</tr>
<tr>
<td>Hypertension (uncontrolled)</td>
<td>1</td>
<td>12.3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Genetic factors (CYP 2C9 polymorphism)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Excessive fall risk</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1. CHADS₂ Score Stroke Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS₂ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Congestive heart failure exacerbation</td>
<td>1</td>
<td>CHADS₂ = 0</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>1</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
<td>High Risk</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prior history of Stroke or transient ischemic attack</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Maximum Score</td>
<td>6</td>
<td>High Risk = ≥ 2</td>
</tr>
</tbody>
</table>

CHADS₂= congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack.

INR (Goal 2 – 3)

High Risk- *CHADS₂ ≥ 3 + any **hemorrhage risk score

Intermediate Risk- *CHADS₂ = 2 and risk of **hemorrhages ≥ 3 or at lower hemorrhage rates if it cost <$2500/y

No therapy

Intermediate Risk INR = 1

Dabigatran

Warfarin

High Risk

Intermediate Risk

Low Risk

*Table 1. CHADS₂ Score Stroke Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS₂ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Congestive heart failure exacerbation</td>
<td>1</td>
<td>CHADS₂ = 0</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>1</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
<td>High Risk</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prior history of Stroke or transient ischemic attack</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Maximum Score</td>
<td>6</td>
<td>High Risk = ≥ 2</td>
</tr>
</tbody>
</table>

CHADS₂= congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack.
Appendix B. Coagulation cascade and activity of anticoagulants

Figure 3. Coagulation cascade and activity of anticoagulants
Appendix C. Treatment Guidelines for the Maintenance of Normal Sinus Rhythm in Recurrent, Paroxysmal, or Persistent Atrial Fibrillation

**Figure 1. Maintenance of Sinus Rhythm**

**Table 1. Oral Agents for Heart Rate Control in Patients with Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
<th>Major Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem (Cardizem®)</td>
<td>N/A</td>
<td>120-360 mg daily in divided doses; slow release available</td>
<td>Hypotension, heart block, HF</td>
</tr>
<tr>
<td>Metoprolol (Lopressor®)</td>
<td>N/A</td>
<td>25-100 mg BID</td>
<td>Hypotension, heart block, bradycardia, asthma, HF</td>
</tr>
<tr>
<td>Propranolol (Inderal®)</td>
<td>N/A</td>
<td>80-240 mg daily in divided doses</td>
<td>Hypotension, heart block, bradycardia, asthma, HF</td>
</tr>
<tr>
<td>Verapamil (Calan®; Veralan®)</td>
<td>N/A</td>
<td>120-360 mg daily in divided doses; slow release available</td>
<td>Hypotension, heart block, HF, digoxin interaction</td>
</tr>
<tr>
<td>Amiodarone (Cardarone®)</td>
<td>800 mg daily for 1 week (wk) 600 mg daily for 1 wk 400 mg daily for 4-6 wk</td>
<td>200 mg daily</td>
<td>Pulmonary toxicity, skin discoloration, hypothyroidism, corneal deposits, optic neuropathy, warfarin interaction, proarrhythmia</td>
</tr>
<tr>
<td>Digoxin (Lanoxin®)</td>
<td>0.25 mg PO every 2 h; up to 1.5 mg</td>
<td>0.125-0.375 mg daily</td>
<td>Digitalis toxicity, heart block, bradycardia</td>
</tr>
</tbody>
</table>
### Table 1. Antiarrhythmic Medication for the Treatment of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Suggested dosage</th>
<th>Cost of generic (brand)*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (Cardarone®)</td>
<td>600 to 1,200 mg per day for one to two weeks, then taper to lowest possible dosage 200 mg per day for maintenance dosage</td>
<td>$29† ($136) for maintenance dosage</td>
<td>Adverse effects: abnormal cardiac conduction, anaphylaxis, heart failure, pulmonary toxicity, thyroid abnormalities, liver failure, lupus, thrombocytopenia</td>
</tr>
<tr>
<td>Dronedarone (Multaq®)</td>
<td>400 mg twice daily</td>
<td>$300</td>
<td>Adverse effects: QT prolongation, bradycardia, diarrhea</td>
</tr>
<tr>
<td>Disopyramide (Norpace®)</td>
<td>400 to 800 mg per day in divided doses</td>
<td>$63 ($198)</td>
<td>Adverse effects: torsades de pointes, hepatotoxicity, hypoglycemia, heart failure</td>
</tr>
<tr>
<td>Dofetilide (Tikosyn®)</td>
<td>500 mcg orally every 12 hours at initiation of therapy, titrate downward on QT response</td>
<td>Not available (NA) ($234)</td>
<td>Adverse effects: prolonged QT interval Use is restricted to trained prescribers and facilities In-house ECG monitoring required for at least 3 days</td>
</tr>
<tr>
<td>Flecainide (Tambocor®)</td>
<td>100 to 150 mg taken at onset of atrial fibrillation (may be taken BID for prevention)</td>
<td>$58 ($146)</td>
<td>Adverse effects: proarrhythmias, torsades de pointes</td>
</tr>
<tr>
<td>Ibutilide (Corver®)</td>
<td>A one-time 1 mg intravenous dosage, may repeat once after 10 minutes if no response</td>
<td>$336 ($452) for 1 mg per 10 mg vial‡</td>
<td>Adverse effects: ventricular tachycardia, hypotension, headache Caution in patients with QT prolongation, hypokalemia, hypomagnesemia, bradycardia Continuous ECG monitoring for four hours after last dosage</td>
</tr>
<tr>
<td>Procaainamide</td>
<td>Up to 50 mg per kg per day in divided doses</td>
<td>$37 (NA) for 500 mg every 6 hours‡</td>
<td>Adverse effects: agranulocytosis, asplastic anemia, coagulation disorder, arrhythmia, hepatotoxicity, drug-induced lupus</td>
</tr>
<tr>
<td>Propafenone (Rythmol®)</td>
<td>225 to 425 mg orally every 12 hours</td>
<td>$80 ($340)</td>
<td>Adverse effects: granulocytosis angina, chest pain, heart failure, AV block, hypotension, palpitations, sinus arrest</td>
</tr>
<tr>
<td>Quinidine</td>
<td>324 to 648 mg; one to two tablets every eight to 12 hours</td>
<td>$60 (NA)</td>
<td>Adverse effects: proarrhythmias, torsades de pointes, hepatotoxicity, kidney disease</td>
</tr>
<tr>
<td>Sotalol (Betapace®)</td>
<td>80 to 160 mg BID per day</td>
<td>$21† ($249)</td>
<td>Adverse effects: torsades de pointes, various proarrhythmias, heart failure, bradycardia, asthma Continuous ECG for 3 days after initiation of therapy Avoid in patients with renal insufficiency</td>
</tr>
</tbody>
</table>

NA= no available; *- from www.drugstore.com; †- may be available at discounted prices; ‡- estimated cost based on Red Book average wholesale prices; Adopted from: http://www.aafp.org/afp/2011/0101/p61.html
Acknowledgements

- Amanda Loya, PharmD
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- Margie Padilla, PharmD, CDE

References