Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

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Background—Recent studies have investigated alternatives to warfarin for stroke prophylaxis in patients with atrial fibrillation (AF), but whether these alternatives are cost-effective is unknown.

Methods and Results—On the basis of the results from Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) and other trials, we developed a decision-analysis model to compare the cost and quality-adjusted survival of various antithrombotic therapies. We ran our Markov model in a hypothetical cohort of 70-year-old patients with AF using a cost-effectiveness threshold of $50 000/quality-adjusted life-year. We estimated the cost of dabigatran as US $9 a day. For a patient with an average risk of major hemorrhage (≈3%/y), the most cost-effective therapy depended on stroke risk. For patients with the lowest stroke rate (CHADS2 score of 0), only aspirin was cost-effective. For patients with a moderate stroke rate (CHADS2 score of 1 or 2), warfarin was cost-effective unless the risk of hemorrhage was high or quality of international normalized ratio control was poor (time in the therapeutic range <57.1%). For patients with a high stroke risk (CHADS2 stroke score ≥3), dabigatran 150 mg (twice daily) was cost-effective unless international normalized ratio control was excellent (time in the therapeutic range >72.6%). Neither dabigatran 110 mg nor dual therapy (aspirin and clopidogrel) was cost-effective.

Conclusions—Dabigatran 150 mg (twice daily) was cost-effective in AF populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk AF populations unless international normalized ratio control was poor. (Circulation. 2011;123:2562-2570.)

Key Words: anticoagulants ■ aspirin ■ atrial fibrillation ■ cost-benefit analysis ■ stroke ■ warfarin

Atrial fibrillation (AF) is the most commonly encountered cardiac dysrhythmia in clinical practice. The economic and mortality burden of AF is substantial. Stroke prevention with safe and effective antithrombotic therapy is a critical goal in the AF population.

Clinical Perspective on p 2570

Traditional antithrombotic therapies for AF are not ideal. Aspirin 325 mg reduces the risk of ischemic stroke by ≈22%.1 Warfarin reduces the stroke risk by 64% but increases the risk of all major bleeding by 69% compared with placebo. Therapy with warfarin is hampered by a slow onset of action, narrow therapeutic range, requirement for regular monitoring, drug and food interactions, pharmacogenetic variability, and risk of hemorrhage.2,3 As a result of these limitations, warfarin is prescribed for only two thirds of the patients with AF who are good candidates for anticoagulation.4,5

Despite the challenges with vitamin K antagonists, it is unclear whether there is a cost-effective alternative for patients with AF. Dabigatran etexilate was developed with the hope that it would be equally efficacious but safer and easier to administer than warfarin. It is the prodrug of the active compound dabigatran, which binds reversibly to thrombin.6 Active concentrations of dabigatran are achieved rapidly after oral administration, and, unlike warfarin, cytochrome P450 plays no relevant role in its metabolism.7 The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) found that dabigatran etexilate 110 mg twice daily was noninferior to and 150 mg twice daily was superior to warfarin therapy in the prevention of ischemic stroke.8 Both doses of dabigatran were superior to warfarin therapy in the prevention of intracranial or major bleeding but were associated with significantly higher rates of dyspepsia and a trend toward increased rates of myocardial infarction (MI).

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) investigators found that the combination of clopidogrel plus aspirin for stroke prophylaxis in AF reduced ischemic stroke compared with aspirin alone (relative risk [RR], 0.68),9 but was inferior to warfarin therapy.10 It is unclear whether dual antiplatelet therapy is cost-effective in the treatment of AF.

In this analysis, we compare the projected quality-adjusted survival and costs of alternative treatment strategies for AF:
dabigatran 110 or 150 mg twice daily, warfarin, dual therapy with aspirin and clopidogrel, aspirin alone, or no antithrombotic therapy.

**Methods**

**Decision Model**

The base-case model consisted of a hypothetical cohort of 70-year-old patients with AF who had a moderate risk of stroke and no contraindication to anticoagulant therapy. We used a Markov model to perform a decision analysis comparing the alternative treatment strategies and outcomes. As detailed below, drug efficacy was calculated from clinical trials with an intent-to-treat perspective. We modeled outcomes as transitions from 1 Markov health state (Figure 1, red) to another. Each month, the cohort accrued costs and quality-adjusted life-years (QALYs), depending on which health state they inhabited. The outcomes were ischemic stroke; transient ischemic attack, intracranial hemorrhage (hemorrhagic strokes, subdural or subarachnoid hemorrhage), major and minor noncerebral hemorrhage, MI, dyspepsia, and death. After an adverse event, patients entered a health state (eg, status after mild stroke) that had an increased risk for recurrence. In this manner, the transition probabilities had the markovian property of being constant except that the probability of dying increased as the patient aged. We applied utilities and cost to each outcome over its expected duration. Drug discontinuation rates (eg, 20% after 24 months of dabigatran) were based on clinical trials. For all treatments, we calculated quality-adjusted survival and net cost over a maximum of 20 years.

**Probability of Adverse Outcomes in the Decision Model**

We adjusted mortality rates in the model for age (beginning at 70 years), the presence of AF, and antithrombotic therapy. The 1-year mortality rates in our model were 4.3% for no antithrombotic therapy, 4.2% for aspirin or dual antiplatelet therapy, 4.0% for warfarin, and 3.9% for dabigatran (either dose). Rates were calibrated with mortality in RE-LY.

**Ischemic Stroke Risk**

Although the mortality rate increased as patients aged, the ischemic stroke rate remained constant in patients who remained free of stroke. In the base case, that stroke rate was 1.2% per year of warfarin therapy (Table 1). Dabigatran 110 mg twice daily was noninferior (RR, 1.11; 95% confidence interval, 0.89 to 1.40) and dabigatran 150 mg twice daily was superior (RR, 0.76; 95% confidence interval, 0.60 to 0.98) to warfarin therapy in the prevention of ischemic stroke. Stroke rates were 56% lower in patients treated with warfarin than with aspirin and 27% lower in those treated with aspirin and clopidogrel versus aspirin. One fourth (28%) of the neurological ischemic events were transient ischemic attacks. After an acute ischemic stroke or transient ischemic attack, the underlying stroke rate increased 2.6-fold, and patients changed to dabigatran 150 mg twice daily (regardless of initial therapy). Patients who suffered both a stroke and a major bleed were transitioned back to their initial therapy.

**Bleeding Risk**

Bleeding rates were based on clinical trials and observational data of the AF population. In RE-LY, the incident rates of major and minor bleeding were significantly lower on either dose of dabigatran compared with warfarin therapy, and the intracranial hemorrhage rates on dabigatran were less than half of that rate on warfarin therapy (Table 1). To obtain a precise estimate of the risk of major bleeding on dual antiplatelet therapy versus warfarin, we performed a traditional random-effect analysis and a network meta-analysis of AF trials. The network meta-analysis took into account results from the ACTIVE W trial, in which the RR of major bleeding on dual antiplatelet therapy versus warfarin was 1.08. In both meta-analyses, we weighed the RR of each trial by

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Representation of the decision model. The 6 treatment options are shown on the left. M represents a Markov process with 8 health states (red) and a cycle length of 1 month. Patients remain in the well state until an event (eg, a stroke) occurs. The probabilities of these events depend on the treatment. The branch from well illustrates these events. Branches from the other health states (not shown) have a similar structure. The health state TIA includes patient status after either a transient ischemic attack or a stroke that had no residual deficit. The ICH is status after an intracranial hemorrhage. MI indicates myocardial infarction.
Table 1. Model Variables: Base-Case Values and Ranges Used in Sensitivity Analysis

<table>
<thead>
<tr>
<th>Input Variable</th>
<th>Base Case</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of stroke on aspirin, %/y</td>
<td>2.7</td>
<td>0.8–13.7</td>
<td>8, 19</td>
</tr>
<tr>
<td>Relative risk of stroke: aspirin 325 mg and clopidogrel 75 mg vs aspirin</td>
<td>0.73</td>
<td>0.58–0.80</td>
<td>9, 20</td>
</tr>
<tr>
<td>Relative risk of stroke: warfarin vs aspirin</td>
<td>0.44</td>
<td>0.37–0.59</td>
<td>21–24</td>
</tr>
<tr>
<td>Relative risk of stroke: dabigatran 110 mg twice daily vs warfarin</td>
<td>1.11</td>
<td>0.89–1.40</td>
<td>8</td>
</tr>
<tr>
<td>Relative risk of stroke: dabigatran 150 mg twice daily vs warfarin</td>
<td>0.76</td>
<td>0.60–0.98</td>
<td>8</td>
</tr>
<tr>
<td>Percentage† of ischemic strokes with warfarin or dabigatran that were</td>
<td>8.2</td>
<td>8.2–10.1</td>
<td>8, 25–28</td>
</tr>
<tr>
<td>Fatal (within 30 d)</td>
<td>40.2</td>
<td>40.2–41.7</td>
<td>8, 25–28</td>
</tr>
<tr>
<td>Minor</td>
<td>42.5</td>
<td>34.8–42.0</td>
<td>8</td>
</tr>
<tr>
<td>No residua</td>
<td>9.1</td>
<td>9.1–13.3</td>
<td>8, 25–28</td>
</tr>
<tr>
<td><strong>Percentage† of ischemic strokes on aspirin or aspirin and clopidogrel that were</strong></td>
<td>17.9</td>
<td>10.1–17.9</td>
<td>8, 25–28</td>
</tr>
<tr>
<td>Fatal (within 30 d)</td>
<td>30</td>
<td>30.0–41.7</td>
<td>8, 25–28</td>
</tr>
<tr>
<td>Minor</td>
<td>41</td>
<td>34.8–41.0</td>
<td>8</td>
</tr>
<tr>
<td>No residua</td>
<td>11</td>
<td>11.0–13.3</td>
<td>8, 25–28</td>
</tr>
<tr>
<td><strong>Bleeding parameters</strong></td>
<td>3.36</td>
<td>1.9–10.4</td>
<td>8, 10, 21, 29</td>
</tr>
<tr>
<td>Rate of major bleeding (including ICH), %/y warfarin</td>
<td>0.64</td>
<td>0.50–0.80</td>
<td>21–23</td>
</tr>
<tr>
<td>Relative risk of major bleeding: aspirin 325 mg vs warfarin</td>
<td>1.09</td>
<td>0.83–1.45</td>
<td>10, 20, 30</td>
</tr>
<tr>
<td>Relative risk of major bleeding: aspirin and clopidogrel vs warfarin</td>
<td>0.80</td>
<td>0.69–0.93</td>
<td>8</td>
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<tr>
<td>Relative risk of major bleeding: dabigatran 110 mg twice daily vs warfarin</td>
<td>0.93</td>
<td>0.81–1.07</td>
<td>8</td>
</tr>
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<td><strong>Rate of MI</strong></td>
<td>0.53</td>
<td>0.40–0.60</td>
<td>10, 30, 31</td>
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<td>Aspirin</td>
<td>0.43</td>
<td>0.30–0.50</td>
<td>9, 10, 30</td>
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<tr>
<td>Warfarin</td>
<td>0.53</td>
<td>0.40–0.60</td>
<td>8</td>
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<tr>
<td>Dabigatran</td>
<td>0.72</td>
<td>0.60–0.80</td>
<td>8</td>
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<tr>
<td><strong>Mortality parameters</strong></td>
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<td>Age at start of 20-y interval, y</td>
<td>70</td>
<td>60–80</td>
<td>Assumption</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>50</td>
<td>0–100</td>
<td>Assumption</td>
</tr>
<tr>
<td>Relative risk of nonstroke, nonhemorrhage death</td>
<td>1.3</td>
<td>1.0–1.6</td>
<td>13, 15, 16, 32</td>
</tr>
<tr>
<td>AF</td>
<td>2.3</td>
<td>1.3–3.0</td>
<td>32, 33</td>
</tr>
<tr>
<td>AF and prior stroke</td>
<td>13</td>
<td>10.1–17.9</td>
<td>8</td>
</tr>
<tr>
<td><strong>Quality-of-life estimates (utilities)</strong></td>
<td>1.0</td>
<td>Definition</td>
<td></td>
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<tr>
<td>Healthy (ie, AF without a stroke or bleed)</td>
<td>0.998</td>
<td>0.994–1.0</td>
<td>34</td>
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<tr>
<td>Aspirin</td>
<td>0.998</td>
<td>0.994–1.0</td>
<td>Assumed equal to aspirin</td>
</tr>
<tr>
<td>Aspirin and clopidogrel</td>
<td>0.994</td>
<td>0.990–0.998</td>
<td>35</td>
</tr>
<tr>
<td><strong>Neurological event with residua‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0.75</td>
<td>0–1.0</td>
<td>34</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>0.39</td>
<td>0–1.0</td>
<td>34</td>
</tr>
<tr>
<td>Recurrent</td>
<td>0.12</td>
<td>0–0.5</td>
<td>34</td>
</tr>
<tr>
<td><strong>Temporary states</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding, other than ICH§</td>
<td>0.8</td>
<td>0.5–0.99</td>
<td>36, 37</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td></td>
<td>0.8</td>
<td>0.5–0.99</td>
</tr>
<tr>
<td>Initiating warfarin therapy§</td>
<td>0.98</td>
<td>0.9–1.0</td>
<td>Assumption</td>
</tr>
<tr>
<td>Myocardial infarction§</td>
<td>0.87</td>
<td>0.8–0.9</td>
<td>38</td>
</tr>
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</table>
the reciprocal of its variance and transformed the RR using the natural logarithm to normalize its distribution. In the network meta-analysis, we used trial and error to find the overall RR that maximized the joint probability distribution of the RR estimates from the random-effect meta-analyses that compared pairs of therapies (eg, warfarin versus dabigatran 150 mg). We modeled the conditional probability of an intracranial hemorrhage versus an extracranial major bleed to account for the greater probability of an intracranial hemorrhage with warfarin therapy.

In our model, patients who suffered a major bleed while taking dabigatran, dual therapy, or warfarin switched to aspirin therapy alone. Patients who suffered a major bleed while taking aspirin discontinued all antithrombotic therapy.

Stroke and Bleeding Severity

We classified ischemic stroke into 1 of 4 categories: fatal, major neurological residua, mild neurological residua, and no residual deficit (Table 1).26,27,49 Similarly, we classified bleeding as fatal, major (including any intracranial hemorrhage), and minor (Table 1).26,28 The proportion of fatal or disabling major bleeds was 1.3 times higher with warfarin than with aspirin or dabigatran.28

Myocardial Infarction

We estimated rates of MI with dabigatran and warfarin from RE-LY.8 The RRs of MI with antiplatelet therapy were based on other large randomized trials (Table 1).10,30,31

Quality-of-Life Estimates

To calculate quality-adjusted survival, we multiplied quality-of-life estimates, known as utilities, by the probabilities of adverse events (Table 1). By definition, death (resulting from any cause) had a utility of 0. We based the utility of an ischemic or hemorrhagic stroke (including any intracranial bleed), warfarin, and aspirin on a previous survey of 69 patients with AF.34 They rated the utility of mild stroke as 0.75, moderate stroke as 0.39, and recurrent stroke as 0.12. Nonfatal extracranial major bleeds and all minor bleeds resulted in no permanent decrease in quality of life; the utility of an extracranial major bleed was 0.836,37 for 1 month and the utility of a minor bleed was 0.8 for 2 days. The utility of taking warfarin, including prothrombin time monitoring and changes in diet or lifestyle, had a mean value of 0.98. The mean utility of aspirin was 0.998.

We estimated the mean utility of dabigatran to be less than that of aspirin because it requires twice-daily dosing, but greater than warfarin because dabigatran requires no routine monitoring. We based its value of 0.994 on a previous estimate for an older thrombin inhibitor, ximelagatran.35 The estimated utility of MI was 0.87,38 but only for 30 days. The QALYs were discounted at an annual rate of 3%.55

Costs

Costs reflected the perspective of an insurance company (or Medicare) that covered inpatient and outpatient medical care and prescription costs but did not pay for indirect costs (eg, lost wages). We projected the net cost for each treatment over 20 years. Because we were interested in the incremental cost-effectiveness of one option versus the other rather than absolute costs, we excluded medical costs unrelated to antithrombotic therapy, hemorrhage, neurological ischemia, dyspepsia, or myocardial ischemia. Costs were expressed in 2010 US dollars and discounted at an annual rate of 3%.55,56

<table>
<thead>
<tr>
<th>Input Variable</th>
<th>Base Case</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual cost of prophylaxis, $ per year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>10</td>
<td>5–50</td>
<td>35</td>
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<tr>
<td>Aspirin and clopidogrel</td>
<td>1857</td>
<td>365–3650</td>
<td>39</td>
</tr>
<tr>
<td>Warfarin (not including INR monitoring)</td>
<td>180</td>
<td>60–360</td>
<td>35</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>3240</td>
<td>2500–4000</td>
<td>35</td>
</tr>
<tr>
<td>Cost of INR + minimal established patient visit, $</td>
<td>26</td>
<td>10–50</td>
<td>35</td>
</tr>
<tr>
<td>Short-term (1-time) cost of neurological event, $</td>
<td>14680</td>
<td>6000–25 000</td>
<td>40–43</td>
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<tr>
<td>Moderate to severe ischemic neurological event</td>
<td>9200</td>
<td>3500–15 000</td>
<td>40–43</td>
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<tr>
<td>Minor ischemic neurological event</td>
<td>7500</td>
<td>3000–12 000</td>
<td>40–43</td>
</tr>
<tr>
<td>ICH</td>
<td>38500</td>
<td>15 000–60 000</td>
<td>40–43</td>
</tr>
<tr>
<td>Long-term (monthly) cost of event, $</td>
<td>5400</td>
<td>2000–8000</td>
<td>40–43</td>
</tr>
<tr>
<td>Moderate to severe ischemic neurological event</td>
<td>2470</td>
<td>1000–4000</td>
<td>40–43</td>
</tr>
<tr>
<td>Minor ischemic neurological event</td>
<td>5700</td>
<td>2000–9000</td>
<td>40–43</td>
</tr>
<tr>
<td>ICH</td>
<td>7200</td>
<td>3000–12 000</td>
<td>40–43</td>
</tr>
<tr>
<td>Ischemic neurological event and ICH</td>
<td>4400</td>
<td>1500–6000</td>
<td>40</td>
</tr>
<tr>
<td>Cost of nonstroke, nonhemorrhage death</td>
<td>69</td>
<td>0–200</td>
<td>44</td>
</tr>
<tr>
<td>MI</td>
<td>17 000</td>
<td>5000–50 000</td>
<td>45</td>
</tr>
</tbody>
</table>

ICH indicates intracranial hemorrhage; MI, myocardial infarction; AF, atrial fibrillation; and INR, international normalized ratio.

*Rate of stroke increased by a factor of 1.4 per decade of life, compounded monthly.14
†Percentages may not sum to 100% because of rounding.
‡Residua occur after either an ischemic stroke or an ICH. ICH includes hemorrhagic strokes and subdural hematomas.
§This quality of life applied only for 1 month.
||This quality of life applied only for 2 days.
Cost of Adverse Events

Cost of a minor hemorrhage was based on remuneration for an expanded problem-focused physician visit (99213). The cost of a major extracranial hemorrhage was based on Medicare remuneration for the diagnosis-related group associated with gastrointestinal hemorrhage. Costs for adverse events were estimated by using the median value or geometric mean of published studies, HCUPnet, and Medicare remuneration (adjusted for medical inflation).

Drug Costs

We calculated $545 as the annual cost of warfarin therapy by combining its prescription cost with Medicare reimbursement for 14 international normalized ratio (INR) tests and minimal established patient office visits (CPT 99211 or 99212) per year (Table 1).

Sensitivity Analyses

We performed sensitivity analyses of the variables in the decision model over their plausible ranges (Table 1 and Figure 2). We used 2 validated prediction rules, CHADS2 and HEMORR2HAGES, to quantify rates of stroke and hemorrhage. CHADS2 is a clinical prediction rule in which stroke rate depends on following risk factors: congestive heart failure, hypertension, age <75 years, diabetes mellitus, and a history of stroke or transient ischemic attack (which is assigned 2 points rather than 1). HEMORR2HAGES is a clinical prediction rule in which hemorrhage rate depends on the presence of hepatic or renal disease, ethanol abuse, malignancy, age <75 years, reduced platelet count, prior bleed (which is assigned 2 points rather than 1), uncontrolled hypertension, anemia, genetic factors, excessive fall risk, and stroke. We calculated cost-effectiveness ratios of dabigatran across combinations of stroke and hemorrhage risk (Figure 3) using SMLTREE.

Results

Base-Case Analysis

Under base-case conditions (a typical participant in RE-LY), warfarin cost approximately $12,000 per QALY compared with aspirin. Dabigatran 150 mg twice daily was associated with the greatest quality-adjusted survival (8.65 QALYs), followed by dabigatran 110 mg twice daily (8.54 QALYs), warfarin (8.40 QALYs), aspirin and clopidogrel (8.32 QALYs), and aspirin (8.17 QALYs). Dabigatran 150 mg (twice daily) cost $86,000 per QALY; dabigatran 110 mg (twice daily) and dual therapy (aspirin and clopidogrel) were even more expensive per QALY (Table 2).

Sensitivity Analyses

We examined how each variable affected quality-adjusted survival and cost for all plausible values (Table 1). The most influential variables (Figure 2) were stroke and hemorrhage rates, cost of dabigatran, and time in the INR range. Sensitivity analyses of other variables in the model did not affect our overall findings. For example, when the time horizon was extended from 20 to 40 years, dabigatran 150 mg cost $84,000 per QALY versus warfarin.

Ischemic Stroke

For patients with an average risk of major hemorrhage (<3%/y), cost-effectiveness varied with stroke risk (Figure 3A). For patients with the lowest stroke rate (CHADS2 of 0), aspirin was cost-effective. For patients at moderate risk of stroke (CHADS2 of 1 or 2), warfarin was cost-effective. Dabigatran 150 mg (twice daily) was cost-effective for patients with a CHADS2 of 2 if the risk of hemorrhage was >6%/y or at lower hemorrhage rates if it cost less than $2500/y; otherwise, warfarin was cost-effective (two-toned area in Figure 3A). For high-risk patients (CHADS2 of >3), dabigatran 150 mg (twice daily) was cost-effective at any hemorrhage rate (provided it cost less than $3500/y). Neither dabigatran 110 mg (twice daily) nor dual therapy (aspirin and clopidogrel) was cost-effective.

Major Bleeds

Compared with stroke rate, major bleeding rate had less effect on cost-effectiveness. For example, dabigatran 150 mg (twice daily) was cost-effective therapy at a CHADS2 score of >3 regardless of hemorrhage risk (Figure 3A). It was also cost-effective at a CHADS2 score of 2 if the risk of major bleeding was high (ie, HEMORR2HAGES score >3). Aspirin was the only cost-effective therapy at a CHADS2 of 0 unless the risk of major bleeding was high (HEMORR2HAGES score >2), in which case no antithrombotic therapy was cost-effective. Warfarin was cost-effective at moderate stroke and low major bleeding rates.
Because dabigatran 150 mg was more effective than dabigatran 110 mg,\(^8\) the lower dose was not cost-effective at hemorrhage rates encountered in clinical practice. Even if aspirin and clopidogrel therapy did not increase the risk of hemorrhage compared with warfarin, their cost per QALY exceeded $50 000 for all scenarios.

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>43 700</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>NA</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>NA</td>
<td>NA</td>
</tr>
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</table>

QALY indicates quality-adjusted life-year; NA, not applicable.

Costs
The costs and utilities of adverse events, including major and minor stroke, major and minor hemorrhage, transient ischemic attack, and MI, did not significantly affect our findings. The cost-effectiveness of warfarin did not significantly change in the plausible price range (Table 1). However, the cost-effectiveness of dabigatran 150 mg was sensitive to its price: If dabigatran 150 mg costs less than $1800/y, it was always more cost-effective than warfarin (regardless of stroke and hemorrhage rates).

Two- and 3-Way Sensitivity Analyses of Rates of Adverse Events and International Normalized Ratio Control
Two-way sensitivity analyses of stroke and hemorrhage risk confirmed that low stroke rates favored aspirin therapy, moderate rates favor warfarin, and high stroke and/or hemorrhage rates favored dabigatran 150 mg (twice daily).

Cost-effectiveness of dabigatran was markedly sensitive to INR control. In a secondary analysis of RE-LY,\(^9\) dabigatran 150 mg was much more effective (RR for nonhemorrhagic
stroke, 0.54) and safer (RR for major bleed, 0.71) than warfarin managed at medical centers where the INR control was in the lowest quartile (<57.1% time in the therapeutic range). In such settings, we found that dabigatran would be cost-effective for all patients with a CHADS2 score of ≥2 (Figure 3B). In contrast, dabigatran 150 mg had no advantage (RR for major bleed, 1.16; RR for stroke, 1.21) to warfarin managed at medical centers where the INR control was in the highest quartile (>72.6% time in the therapeutic range). For these centers, dabigatran was not cost-effective (Figure 3C).

Discussion

For patients with AF who had an average risk of major hemorrhage (≈3%/y), the most cost-effective therapy depended on stroke risk. For patients with the lowest stroke rate (CHADS2 score of 0), only aspirin was cost-effective (ie, a cost of less than $50,000 per QALY gained). For patients at moderate risk of stroke (CHADS2 of 1 or 2), warfarin was cost-effective. For higher-risk patients (CHADS2 of ≥3), dabigatran 150 mg (twice daily) was cost-effective. Dabigatran 150 mg (twice daily) was cost-effective for patients with a CHADS2 of 2 only if they were at a high risk of major hemorrhage (>6%/y) or would have poor INR control with warfarin.

Because of the greater efficacy of dabigatran 150 mg, dabigatran 110 mg (also twice daily) was not cost-effective for any realistic rate of stroke and hemorrhage. Likewise, dual therapy (aspirin and clopidogrel) was never cost-effective. Because we did not consider patients with renal or liver disease (RE-LY excluded these populations) or nonagenarians, we cannot say whether dabigatran 110 mg or dual antiplatelet therapy might be cost-effective for them.

The decision analysis by Freeman et al also found that dabigatran 110 mg would not be cost-effective but that dabigatran 150 mg twice daily would be cost-effective for many patients with AF. In the base case, they estimated a cost-effectiveness of $45,372 per QALY gained with dabigatran 150 mg, whereas we calculated a cost-effectiveness of $86,000 per QALY. There are several minor differences that may explain this: We explicitly modeled dyspepsia, calibrated our mortality rates to those of RE-LY, and stratified our results by INR control and CHADS2 and HEMORR2HAGES scores. Despite these differences, both models found that dabigatran 150 mg would be cost-effective for patients with a CHADS2 score of ≥3 (unless INR control was excellent) and for patients with a CHADS2 of 2 and 2 high risk of hemorrhage.

In situations in which hemorrhage risk determines the most cost-effective therapy, testing for genetic polymorphisms that affect warfarin metabolism could guide therapy. For example, patients with polymorphisms in CYP2C9 have slowed metabolism of S-warfarin and triple the risk of hemorrhage after warfarin initiation. If a patient with a CHADS2 score of 2 and moderate risk of hemorrhage is found to be a slow metabolizer of warfarin, then the hemorrhage risk is greater and dabigatran could become cost-effective. However, if genotyping continues to cost more than $200, it is unlikely to be cost-effective for AF populations.

Our study has potential limitations. First, the efficacies of dabigatran are based on a single trial (RE-LY) with a median follow-up of 2 years. Rates of adverse events on dabigatran or warfarin may vary over the long term. The average age in RE-LY was 71 years, and extrapolating results to octogenarians may be inaccurate. Second, in RE-LY, warfarin administration was not blinded. Although adverse events were adjudicated blindly, lack of a blinding treatment arm would tend to exaggerate the benefits of dabigatran.

The relative benefits of dabigatran depended on how well warfarin therapy was managed. The percentage of time in which the INR was therapeutic in RE-LY averaged 64%, but varied widely. For patients already taking warfarin who have excellent INR control, dabigatran 150 mg (twice daily) was not cost-effective (Figure 3C). In contrast, for patients whose INR control was poor, dabigatran 150 mg was widely cost-effective (Figure 3B). In summary, the benefits of dabigatran outweigh costs in AF patients at moderate to high risk of stroke and/or hemorrhage unless their INR control with warfarin therapy would be excellent.

Clinicians may be tempted to prescribe dabigatran even when it would not be cost-effective. Such practice would increase costs with modest health benefits. In RE-LY, dabigatran caused more dyspepsia and possibly more MIs than warfarin, so prescribing dabigatran when not indicated could even worsen health. Whether these adverse events are frequent and disabling enough to decrease long-term compliance with dabigatran is unknown, but because dabigatran has a 12- to 17-hour half-life, lapses of dabigatran therapy could be more problematic than lapses of warfarin.

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Disclosures

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References


CLINICAL PERSPECTIVE

Each year, in the United States alone, atrial fibrillation causes >50 000 strokes and $12 billion in medical expenditure. Thus, safe and cost-effective stroke prevention is critical to the atrial fibrillation population. Dabigatran etexilate was developed with the hope that it would be as effective as warfarin, but safer and easier to administer. The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) found that dabigatran 150 mg twice daily was superior to warfarin in the prevention of ischemic stroke. On the basis of results from RE-LY, the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE), and other trials, we developed a decision-analysis model to compare the cost and quality-adjusted survival of various antithrombotic therapies. Dabigatran 150 mg (twice daily) was cost-effective in atrial fibrillation populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk atrial fibrillation populations unless international normalized ratio control was poor.