Cost-Effectiveness of Apixaban Compared With Aspirin for Stroke Prevention in Atrial Fibrillation Among Patients Unsuitable for Warfarin

Soyon Lee, PharmD; Moise W. Anglade, MD; Joy Meng, BS; Kelly Hagstrom, BS; Jeffrey Kluger, MD; Craig I. Coleman, PharmD

Background—Compared with aspirin, apixaban reduces stroke risk in atrial fibrillation (AF) patients unsuitable for warfarin by 63% but does not increase major bleeding. We sought to determine the cost-effectiveness of apixaban versus aspirin.

Methods and Results—Using the Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin-K Antagonist Treatment (AVERROES) trial and other studies, we constructed a Markov model to evaluate the costs ($2011US$), quality-adjusted life-years (QALYs), and incremental cost-effectiveness of apixaban versus aspirin from the Medicare perspective. Our base-case assumed a 70-year-old AF patient cohort with a CHADS$_2$ score=2 and a lower-risk of bleeding. We used a 1-month cycle-length and ran separate base-case analyses assuming a trial-length (1-year) and a longer-term (10-year) follow-up. Total costs/patient were $3454 and $1805 for apixaban and aspirin in the trial-length and $44232 and $50066 in the 10-year model. Corresponding QALYs were 0.96 and 0.96 in the trial-length and 6.87 and 6.51 in the 10-year model, making apixaban inferior in the first model but dominant in the latter. Conclusions were sensitive to baseline stroke rate in both models, and the monthly cost of major stroke, relative risk of stroke, and prior vitamin-K antagonist use in the life-time model. Probabilistic sensitivity analysis suggested apixaban would only be a cost-effective alternative (<$50000/QALY) to aspirin 11% of the time in the trial-length model, but cost-effective or dominant 96.7% and 87.5% of iterations in the 10-year model.

Conclusions—In our trial-length model, apixaban was more costly and no more effective than aspirin; however, as follow-up was extended, apixaban became cost-effective and eventually dominant. (Circ Cardiovasc Qual Outcomes. 2012; 5:472-479.)

Key Words: anticoagulants ■ aspirin ■ atrial fibrillation ■ cost-effectiveness ■ stroke prevention

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States, affecting about 2.7 million people. It is expected that by 2050, the number of Americans with AF will exceed 12 million. Patients with AF have a 4- to 5-fold increased risk of ischemic stroke, which contributes to significant increases in morbidity and mortality. Age is another major risk factor for stroke in these patients; the percentage of strokes attributable to AF increases dramatically from 1.5% at 50 to 59 years of age to 23.5% at 80 to 89 years of age. AF is estimated to be the cause of 15% to 20% of total stroke cases in the United States, resulting in direct and indirect costs of nearly $66 billion annually.

In the Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, 5 mg twice daily of the oral factor Xa inhibitor apixaban was compared with aspirin 81 to 324 mg daily in patients with AF deemed by investigators to be unsuitable for warfarin therapy. Apixaban demonstrated superior efficacy over aspirin, reducing stroke risk by 63% ($P<0.001$). Moreover, this advantage came without a significant increase in the risk of major bleeding.

To date, no formal health economic evaluation has been undertaken to estimate the cost-effectiveness of apixaban compared with aspirin. In this analysis, we sought to estimate the quality-adjusted life-years (QALYs), costs, and cost-effectiveness of apixaban compared with aspirin in patients with AF who are unsuitable for warfarin therapy.
WHAT IS KNOWN
• Apixaban is a direct and competitive inhibitor of Factor Xa that is being evaluated as an alternative to aspirin for stroke prevention among patients with atrial fibrillation.

WHAT THE STUDY ADDS
• This analysis suggests that apixaban is not a cost-effective alternative to aspirin in patients whom warfarin is considered unsuitable in a trial-length time frame.
• Whereas modeled results suggest that apixaban may be cost-effective beyond 3 years, these results should be interpreted with caution as event rates were derived from a single randomized trial with 1-year of follow-up.

Methods
We constructed a Markov cohort transition state model to evaluate the incremental cost-effectiveness of apixaban compared with aspirin for stroke prevention in patients with AF not suitable for warfarin. The model included 9 permanent health states: well, reversible ischemic neurological deficit (RIND), ischemic stroke (minor or major), intracranial hemorrhage (ICH) (minor or major), ischemic stroke and ICH, myocardial infarction, and death. Two temporary health states were also included (minor bleed and nonfatal extracranial bleed). Patients were allowed to move from one health state to another, once per month (but could only experience 1 event of any kind per month-long cycle), based on defined transition probabilities. Only certain transitions were allowed as depicted by the patient cohorts receiving apixaban and aspirin separately as shown in Figure 1. The health states were equivalent for apixaban and aspirin, but the probabilities, costs, and utilities (quality-of-life) varied with treatment.

Figure 1. Simple schematic representation of the Markov model. All patients started at age 70 years in the “well” state with atrial fibrillation and then cycled between health states until death occurred or the 10-year follow-up period ended (whichever came first). Only certain transitions were allowed and patients could never transition to a more favorable health state. The length of each cycle was 1 month, and patients could only experience 1 event of any kind per cycle. Any health state could lead directly to death (not depicted). A second minor ischemic stroke resulted in a major ischemic stroke and a second major ischemic stroke resulted in death. Temporary health states (eg, minor bleed and nonfatal extracranial bleed) are not depicted in the figure. The health states were equivalent for apixaban and aspirin, but the probabilities, costs, and utilities (quality-of-life) varied with treatment.

Model Inputs
Ischemic stroke rates for those receiving aspirin were based on historical rates observed in patients with CHADS$_2$ score of 2 receiving aspirin (4.5% per year) from a large patient registry (Table 1).6 The ischemic stroke rates for those receiving apixaban were derived using the aspirin rate adjusted by the relative risk (RR) of ischemic stroke on apixaban observed in the AVERROES trial.1 We classified ischemic stroke into 1 of 4 categories: fatal, major, minor, or RIND.13 We assumed a second minor ischemic stroke resulted in a major stroke and that a second major stroke resulted in death. The rate of ischemic stroke was assumed to increase by 1.4-fold per decade of life.12

Major hemorrhage rates for those receiving aspirin were based on the rates observed in patients during the AVERROES trial.1 The major hemorrhage rates for those receiving apixaban were derived otherwise noted.1 Other sources of probabilities included published studies of anticoagulation14–17 identified through searches of Medline and the Tufts Cost-Effectiveness Analysis Registry18 and a review of previous economic models.14–17 The model simulated the progression of a hypothetical cohort of 70-year-old patients with AF, a CHADS$_2$ score of 2 (congestive heart failure, 1 point; hypertension defined as blood pressure consistently >140/90 mmHg or antihypertension medication, 1 point; age >75 years, 1 point; diabetes melitus, 1 point; previous stroke or transient ischemic attack, 2 points) and a low-risk of bleeding, who initiated pharmacological stroke prevention with either apixaban (5 mg twice daily) or aspirin (81-324 mg daily).

We conducted analyses from the Medicare perspective and costs and outcomes were discounted at 3% per annum.14 We ran separate base-case analyses assuming a trial-length (1 year) and a longer-term (10 years or death, whichever came first) follow-up of patients (commonly referred to in Markov models as the “time horizon”). The model was used to determine the mean total cost of treatment accrued by the patient cohorts receiving apixaban and aspirin separately as well as the mean number of QALYs by multiplying the percentage of the hypothetical cohorts in a given health state during a cycle by the quality-of-life associated with that state. These products were then summed over all the states and all the cycles. This allowed for the calculation of incremental cost-effectiveness ratios (ICERs) defined as the difference in mean costs between the apixaban and aspirin patients divided by the difference in mean QALYs for each treatment.18 The model was programmed in TreeAge Pro 2007 (TreeAge Software Inc, Williamstown, MA).
using the aspirin rate adjusted by the relative risk of major bleeding on apixaban observed in AVERROES. We assumed the proportion of major bleeds that were ICHs, GI bleeds, or other major bleeds, following the same pattern reported in the AVERROES trial.5 Regardless of which therapy used, ICHs were subclassified as those resulting in death, major, or some minor degree of neurological deficit.9 GI or other major hemorrhages were considered temporary health states unless they resulted in death.19 We further assumed that a major hemorrhage in patients receiving apixaban resulted in the discontinuation of therapy and patients were switched to aspirin therapy. The rate of major hemorrhage was assumed to increase by

### Table 1. Base–Case Model Variables and Ranges Used in Sensitivity Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-Case, Likeliest in PSA</th>
<th>Range, Minimum, Maximum in PSA References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td></td>
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<tr>
<td>Aspirin, monthly, $</td>
<td>0.60</td>
<td>0.15–6.60</td>
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<tr>
<td>Apixaban, monthly, $</td>
<td>205</td>
<td>125–243</td>
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<tr>
<td>Event cost of minor stroke, $</td>
<td>9619</td>
<td>4500–18000</td>
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<tr>
<td>Monthly cost of minor stroke, $</td>
<td>2578</td>
<td>1000–4500</td>
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<tr>
<td>Event cost of major stroke, $</td>
<td>14283</td>
<td>11000–27500</td>
</tr>
<tr>
<td>Monthly cost of major stroke, $</td>
<td>5616</td>
<td>2200–9500</td>
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<tr>
<td>Event cost of RIND, $</td>
<td>6340</td>
<td>3500–13000</td>
</tr>
<tr>
<td>Event cost of ICH, $</td>
<td>40237</td>
<td>11000–27500</td>
</tr>
<tr>
<td>Monthly cost of stroke and ICH, $</td>
<td>7525</td>
<td>3500–15000</td>
</tr>
<tr>
<td>Event cost of GI bleed, $</td>
<td>5633</td>
<td>2000–9000</td>
</tr>
<tr>
<td>Event cost of other major bleed, $</td>
<td>5633</td>
<td>2000–9000</td>
</tr>
<tr>
<td>Event cost of MI, $</td>
<td>19669</td>
<td>16500–24000</td>
</tr>
<tr>
<td>Monthly cost of MI, $</td>
<td>318</td>
<td>125–650</td>
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<tr>
<td>Event cost of minor bleed, $</td>
<td>41</td>
<td>0–200</td>
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<tr>
<td>Event cost of nonevent death, $</td>
<td>6000</td>
<td>3500–7500</td>
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<tr>
<td>Annual discount rate, %</td>
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<td>Utility</td>
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<tr>
<td>Healthy on aspirin</td>
<td>0.998</td>
<td>0.994–1.0</td>
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<tr>
<td>Healthy on apixaban</td>
<td>0.994</td>
<td>0.975–1.0</td>
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<tr>
<td>Major neurological event</td>
<td>0.39</td>
<td>0–1.0</td>
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<tr>
<td>Minor neurological event</td>
<td>0.76</td>
<td>0–1.0</td>
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<tr>
<td>Major bleed, 2 wk</td>
<td>0.84</td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>Minor bleed, 2 d</td>
<td>0.84</td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>MI</td>
<td>0.86</td>
<td>0.50–1.0</td>
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<tr>
<td>Probabilities</td>
<td></td>
<td></td>
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<tr>
<td>Baseline rate of stroke on aspirin, %/y, (CHADS2 score)</td>
<td>4.5 (2)</td>
<td>0.8–13.7 (0–6)</td>
</tr>
<tr>
<td>RR of stroke per decade of life</td>
<td>1.4</td>
<td>NA</td>
</tr>
<tr>
<td>RR of stroke on apixaban</td>
<td>0.37</td>
<td>0.25–0.55</td>
</tr>
<tr>
<td>Percentage of strokes with apixaban or aspirin that were</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal, %</td>
<td>17.9</td>
<td>10.1–17.9</td>
</tr>
<tr>
<td>Major, %</td>
<td>30.0</td>
<td>30.0–41.7</td>
</tr>
<tr>
<td>Minor, %</td>
<td>41.0</td>
<td>34.8–41.0</td>
</tr>
<tr>
<td>No residual deficit, %</td>
<td>11.0</td>
<td>11.0–13.3</td>
</tr>
</tbody>
</table>

### Table 1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-Case, Likeliest in PSA</th>
<th>Range, Minimum, Maximum in PSA References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline rate of hemorrhage on aspirin, %/y</td>
<td>1.2</td>
<td>0.9–1.7</td>
</tr>
<tr>
<td>RR of hemorrhage per decade of life</td>
<td>1.97</td>
<td>NA</td>
</tr>
<tr>
<td>RR of hemorrhage on apixaban</td>
<td>1.13</td>
<td>0.74–1.75</td>
</tr>
<tr>
<td>Percentage of hemorrhage that are ICH, %</td>
<td>28.9</td>
<td>20.3–39.4</td>
</tr>
<tr>
<td>Percentage of ICH with apixaban or aspirin that were</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal, %</td>
<td>36.4</td>
<td>28.3–45.2</td>
</tr>
<tr>
<td>Major, %</td>
<td>14.1</td>
<td>9.0–21.4</td>
</tr>
<tr>
<td>Minor, %</td>
<td>49.5</td>
<td>NA</td>
</tr>
<tr>
<td>Percentage of hemorrhage that are GI bleeds, %</td>
<td>31.3</td>
<td>22.4–41.9</td>
</tr>
<tr>
<td>Proportion of GI bleeds that are fatal, %</td>
<td>7.2</td>
<td>0–10.0</td>
</tr>
<tr>
<td>Proportion of hemorrhage that are other major bleeds, %</td>
<td>39.8</td>
<td>NA</td>
</tr>
<tr>
<td>Proportion of other major bleeds that are fatal, %</td>
<td>2.1</td>
<td>0–4.0</td>
</tr>
<tr>
<td>Rate of minor bleeding on aspirin, %/year</td>
<td>5.0</td>
<td>4.3–5.8</td>
</tr>
<tr>
<td>RR of minor bleeding on apixaban</td>
<td>1.24</td>
<td>1.00–1.53</td>
</tr>
<tr>
<td>Baseline rate of MI on aspirin, %/y</td>
<td>0.9</td>
<td>0.6–1.3</td>
</tr>
<tr>
<td>RR of MI per decade of life</td>
<td>1.3</td>
<td>NA</td>
</tr>
<tr>
<td>RR of MI on apixaban</td>
<td>1.0</td>
<td>0.86–1.48</td>
</tr>
<tr>
<td>Percentage of MI that are fatal, %</td>
<td>16.6</td>
<td>15.8–17.4</td>
</tr>
<tr>
<td>RR of nonevent death with NVAF</td>
<td>1.3</td>
<td>1.0–1.9</td>
</tr>
<tr>
<td>RR of nonevent death with NVAF and stroke</td>
<td>2.3</td>
<td>1.3–3.0</td>
</tr>
</tbody>
</table>

PSA indicates probabilistic sensitivity analysis; RIND, reversible ischemic neurological; ICH, intracranial bleed; GI, gastrointestinal bleed; MI, myocardial infarction; NVAF, nonvalvular atrial fibrillation, deficit; RR, relative risk; NA, not applicable; and $, amount in 2011 US dollars.
1.97-fold per decade of life. Minor hemorrhage rates for those receiving aspirin and apixaban were based on the rates observed in patients during the AVERROES trial.6

We derived rates of MI with aspirin from the AVERROES trial.3 Of note, our base-case analysis assumed that relative risk of MI would be the same between the 2 strategies since this end point was not found to be statistically significant in the AVERROES trial. Based on a recent observational study, we estimated that MI would be fatal in 16.6% of patients whom experience them.21 We further assumed that the risk of MI would increase by 1.3-fold per decade of life.15,19

Similar to previous Markov models of stroke prevention in AF,8,14–17 we used age-adjusted mortality rates for nonevent (nonischemic stroke or major hemorrhage) death derived from published US Census Bureau estimates22 to extrapolate the results of AVERROES to a patient’s lifetime.3 To do so, we multiplied these mortality rates by a factor of 1.3 to reflect mortality rates in patients with AF.21,67 We further assumed the risk of nonevent death was 2.3 times higher in patients with AF and who developed a stroke.11

QALYs were calculated by multiplying the time spent in a given state (in life-years) by the utility score (a health status value from 0 [death] to 1 [perfect health]) associated with that state.18 The utility weights of neurological events (both ischemic stroke or ICH and MI) were derived from the published literature.13–16 The utility of aspirin was estimated to be 0.998,13–15,17 We estimated the utility of apixaban at a value of 0.994, assuming there was additional disutility with apixaban due to increased rates of minor bleeding compared with aspirin.14 The disutilities associated with the bleeding health states, including major extracranial (2 weeks) and minor bleeding (2 days), were assumed to be 0.16 and 0.16, respectively.8

The monthly cost of aspirin was derived from the wholesale acquisition cost (WAC) and the cost of apixaban was assumed to be $205.24 At the time of this analysis, the pricing for apixaban had not been established, as apixaban was not approved in the United States. Therefore, we estimated the drug cost of apixaban to be similar to the drug cost of rivaroxaban or dabigatran, similar, branded oral anticoagulants. The cost of complications and adverse events was based on values from the Agency of Healthcare Research and Quality’s (AHRQ) Healthcare Cost and Utilization Project (HCUP) (using the most current data set, 2008)26 and previously published estimates.27–30 Both 1-time costs (transition rewards) and monthly costs were incorporated into the model. The cost of a major extracranial hemorrhage was estimated by the diagnosis-related group (DRG)-related cost of a gastrointestinal bleed (DRG: 378), since it is typically the most commonly reported major bleed observed in anticoagulation trials.11 The cost of minor hemorrhage was valued as an outpatient visit (Current Procedural Terminology code: 99212).32 All costs were inflated to 2011 US dollars using the Consumer Price Index for Medical Care.31

Sensitivity Analyses

We performed 1-way sensitivity analyses for the trial-length and lifetime models by varying each included variable separately across a priori determined plausible ranges. For the longer-term model, we also conducted analyses to further assess the impact of time horizon (years 2-10), prior vitamin K antagonist use, and vitamin K antagonist refusal as a reason for inclusion into AVERROES on our model’s results. For the latter 2 analyses, subgroup-specific efficacy and safety data from AVERROES were used.3 Finally, we conducted probabilistic sensitivity analysis (PSA) for the trial-length and lifetime models separately by randomly sampling a distribution of all variables from the abovementioned plausible ranges and simulating outcomes 10000 times. For all variables, we assumed a triangle distribution (defined by a likeliest, low and high value), since the true nature of variance for these variables is not well understood and the triangle distribution (when used appropriately) does not violate the requirements of any variable (ie, costs cannot be less than $0 and probabilities and utilities must lie between 0 and 1). Ranges used in sensitivity analyses were taken directly from published literature whenever available.

Results

Under base-case conditions, total costs per patient were $3454 and $1805 for apixaban and aspirin, respectively, in the trial-length model and $44232 and $50066 in the 10-year model. Corresponding QALYs were 0.96 and 0.96 in the trial-length model and 6.87 and 6.51 in the 10-year model, making apixaban an inferior strategy (more costly but no more effective) in the trial-length model, but a dominant one (less costly and more effective) in the 10-year model.

Sensitivity Analyses

In 1-way sensitivity analyses, the results were most sensitive to changes in the model’s time horizon, the baseline rate of stroke on aspirin based on CHADS2 score, the monthly cost of major stroke, and the effect of apixaban on ischemic stroke. Using a trial-length time horizon of 1 year resulted in apixaban being dominated by aspirin (more costly and no more effective). As time horizon of the model was extended, the ICER for apixaban became more favorable, eventually falling below the $50000 per QALY (becoming cost-effective) sometime between years 3 and 3.5 (ICER at 3.5 years=$45240 per QALY) and dominant (more efficacious and less costly) by year 6. In both the trial-length and 10-year models, results were sensitive to changes in the baseline risk of stroke as depicted by CHADS2 scores (Figure 2). In the trial-length model, apixaban was not cost-effective/dominated by aspirin in patients with a CHADS2 score of ≤4. At higher

Figure 2. Incremental cost-effectiveness ratios (ICERs) for apixaban compared with aspirin for the trial-length and 10-year models as baseline rate of stroke on aspirin (CHADS2 score) is varied. This figure depicts the effect of varying baseline stroke rates on the ICER. Apixaban becomes a cost-effective therapy (ICER <$50 000 per quality-adjusted life-year [QALY]) compared with aspirin in the trial-length model when baseline stroke risk on aspirin exceeds 11.4% per year. In the 10-year model, the ICERs for apixaban compared with aspirin remained less than $320675 per QALY for the full range of stroke rates on aspirin. At the highest baseline rate of stroke, apixaban dominates aspirin providing better outcome at lower cost. As the baseline rate of stroke on aspirin decreases below 3.2% per year, apixaban costs more than aspirin and the incremental effectiveness is reduced, leading to a substantial increase in the ICER. Horizontal dotted line demarcates the $50000 per QALY threshold. The following symbols represent a different CHADS2 score with corresponding baseline rate of stroke on aspirin; dash indicates 0 (0.8%/y) in patients taking aspirin only; diamond, 1 (2.2%/y); shaded circle, 2 (4.5%/y); square, 3 (6.6%/y); triangle, 4 (10.9%/y); nonshaded circle, 5 (12.3%/y); and X, 6 (13.7%/y).
previously receiving a vitamin K antagonist, apixaban was
to the base-case; however, in the subgroup of patients not
K antagonist prior to enrollment in A VERROES was simi-
The ICER for patients who had previously used a vitamin
0.55) (Figure 4). Starting at RR higher than 0.526, apixa-
emic stroke, the ICERs for apixaban compared with aspirin
remained cost-effective with the highest ICER being $7808
month for major stroke, apixaban was no longer dominant but remained
cost-effective. The results of the trial-length model were not
sensitive to variation in the monthly cost of major stroke (not
depicted).

CHADS\textsubscript{2} scores (5 or 6), the cost per QALY of apixaban fell
below $50000 per QALY. In the 10-year model, apixaban
was a dominant economic alternative to aspirin in patients
with a moderate-to-high risk of stroke (CHADS\textsubscript{2} score \geq 2).
For patients with a minimal risk of stroke (CHADS\textsubscript{2} score of
1), apixaban was no longer dominant but was cost-effective,
with an ICER of $29547 per QALY saved. Apixaban was not
cost-effective with an ICER of $320675 for patients with a
CHADS\textsubscript{2} score of 0. The cost-effectiveness of apixaban was
somewhat sensitive to the monthly cost of major stroke in
the life-time model. Starting at a cost less than $3368 per
month for major stroke, apixaban was no longer dominant but remained
cost-effective with the highest ICER being $7808
per QALY (Figure 3). For the effect of apixaban on ischemic
stroke, the ICERs for apixaban compared with aspirin
remained less than $4104 per QALY for the full range (0.25-
0.55) (Figure 4). Starting at RR higher than 0.526, apixa-
ban was no longer dominant but remained cost-effective.
The ICER for patients who had previously used a vitamin
K antagonist prior to enrollment in AVERROES was simi-
lar to the base-case; however, in the subgroup of patients not
previously receiving a vitamin K antagonist, apixaban was
cost-effective (ICER=$20482 per QALY) and not dominant
(Table 2). Patient refusal as a reason for inclusion in AVER-
ROES did not alter our model’s conclusions. Other variables
in the models did not affect the cost-effectiveness of apixaban
compared with aspirin.

PSA suggested that apixaban would only be cost-effective
alternative to aspirin (at a willingness-to-pay (WTP) thresh-
hold of $50000/QALY) in 11% of 10000 iterations in the
trial-length model but would be cost-effective or dominate
aspirin in 96.7% and 87.5% of iterations in the 10-year model
(Figure 5).

Discussion
Our model suggests that apixaban is not a cost-effective
alternative to aspirin in patients whom warfarin is con-
sidered unsuitable when evaluated using a trial-length
time horizon but may be at least cost-effective when the
model’s time horizon is extended beyond 3 years. In our
trial-length base case analysis, the use of apixaban was not
associated with any additional QALYs but was associated
with an additional treatment cost of $1649. However, in the
10-year model, apixaban yielded an additional 0.36 QALYs
at a savings of $5834 in costs compared with aspirin for
patients with AF and a CHADS\textsubscript{2} score of 2. Apixaban’s
superior efficacy in preventing ischemic stroke, without
increasing major bleeding risk compared with aspirin,
probably explains our finding that apixaban is economically
dominant in the 10-year model despite prices significantly
higher than aspirin. Upon one-way sensitivity analysis, a
reduction in the baseline stroke rate/CHADS\textsubscript{2} score had a
significant effect on the cost-effectiveness of apixaban in
both model durations.

Many of the transition probabilities used in the Markov
model were extrapolated from a single randomized
controlled trial, AVERROES.\textsuperscript{5} The AVERROES trial design
was a multicenter, double-blind, double-dummy, randomized
study that used intention-to-treat analysis, but the study was
stopped early and had a mean follow-up of about 1 year.\textsuperscript{5}
Thus, 1-year study data had to be extrapolated to a longer
time horizon when making the 10-year estimations, and,
in doing so, we assumed the benefits and harms associated
with apixaban would remain constant throughout the entire
duration of follow-up. It is possible that rates of adverse
events for apixaban or aspirin may vary with a longer follow-
up period. Thus, such assumptions would clearly decrease
the internal validity of our analysis. Moreover, while our
10-year model concluded apixaban was economically domi-
nant, it is important to note that economic dominance was
not achieved until the model simulated AF patients’ costs and outcomes for 6 years. Consequently, decision-makers should review our results with caution as they do not, like in most Markov models, provide the full picture regarding the cost-effectiveness of a new intervention.

Defining whether an intervention is cost-effective or not must be viewed in context of the WTP threshold used. While $50,000 per QALY is the most common WTP threshold (52%) in US economic analyses—regardless of disease state or intervention evaluated—followed by $100,000 per QALY (11%), these values are arbitrary and much debated. The use of $50,000 as a WTP threshold has been widely used due to its convenience as a round number despite its theoretical justification. The conclusions of our cost-effectiveness analyses and sensitivity analyses may be interpreted differently, depending on which WTP threshold is considered acceptable by a decision-maker. Our PSA of the 10-year model suggested apixaban would theoretically be at least cost-effective in virtually all patients (>99%) at a WTP of $100,000 per QALY.

As new antithrombotic choices for stroke prevention become available, healthcare decision-makers will need to make difficult choices. Historically aspirin has been used in patients who are not candidates for warfarin, despite its inferior efficacy in reducing stroke. At present, only 2 pharmacological strategies, including dual antiplatelet therapy with clopidogrel and aspirin and apixaban, have been directly compared with aspirin in a randomized trial to reduce stroke in patients unable to take warfarin. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) trial, clopidogrel plus aspirin reduced the risk of stroke by 28% but increased the risk of major hemorrhage by 57% compared with aspirin alone. Based on the trial data, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) suggests patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or physician’s assessment of the patient’s ability to safely sustain anticoagulation, might consider taking clopidogrel plus aspirin (class IIb, level of evidence: B). However, a recent decision analysis by Shah et al suggests the addition of clopidogrel to aspirin is not cost-effective (ICER of $99,000 per QALY in 2010 US dollars) versus aspirin alone for patients with a low-to-moderate risk of stroke (CHADS2 score of 1-2; 2.7% year) and no contraindication to anticoagulation therapy. Although no direct comparison trial data are available between dabigatran and aspirin, the same decision analysis showed that dabigatran 150 mg twice daily was cost-effective at an ICER of $50,000 per QALY compared with aspirin therapy alone using a life-time time horizon. Based on apixaban’s superior stroke reducing efficacy, similar rate of major bleeding and economic dominance compared with aspirin, it appears to be a highly attractive alternative (if approved) in patients with AF who deemed unsuitable for warfarin.

Our model has some additional limitations that must be considered when interpreting its results. First, as in any cost-effectiveness analysis, special attention should be paid to the choice of a comparator. In our study, the comparison was made to aspirin. In the AVERROES trial, two of the major reasons

Table 2. Effect of Prior Vitamin K Antagonist Use and Refusal of Vitamin K Antagonist Use on the Incremental Cost-Effectiveness Ratio

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Prior VKA Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>50 066</td>
<td></td>
<td>6.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>37 915</td>
<td>Cost-saving</td>
<td>6.97</td>
<td>0.46</td>
<td>Dominant</td>
</tr>
<tr>
<td>No prior VKA Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>50 066</td>
<td></td>
<td>6.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>53 952</td>
<td>3892</td>
<td>6.70</td>
<td>0.19</td>
<td>20482</td>
</tr>
<tr>
<td>Patient refused VKA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>50 066</td>
<td></td>
<td>6.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>42 013</td>
<td>Cost-saving</td>
<td>6.90</td>
<td>0.39</td>
<td>Dominant</td>
</tr>
<tr>
<td>No refusal of VKA</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>50 066</td>
<td></td>
<td>6.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>46 364</td>
<td>Cost-saving</td>
<td>6.83</td>
<td>0.32</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

QALY indicates quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; VKA, vitamin K antagonist; and $, amount in 2011 US dollars.
for not being on warfarin were the physician’s determination that international normalized range levels could not or was not likely to be measured at requested intervals (43%) and patient refusal to take warfarin (37%). A final limitation arises from the assumption in the model that patients who discontinue apixaban because of major bleeds were not allowed to switch to another agent other than aspirin. As agents such as dabigatran and rivaroxaban are new to the market, it is unclear what clinicians will do in such a situation, but these agents might be considered an alternative therapy in these patients. However, in the absence of clinical trial data evaluating dabigatran and rivaroxaban in this way, we refrained from making such assumptions in our model.

Conclusions

Our trial-length model found apixaban to be more costly and less effective than aspirin; however, as the time horizon was extended apixaban became cost-effective and eventually economically dominant.

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References


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