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 CHADS2 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; 00:00-00.)

Key Words: anticoagulants ▪ aspirin ▪ atrial fibrillation ▪ cost-effectiveness ▪ stroke prevention
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 (MI), 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 Figure 1, 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.

The model simulated the progression of a hypothetical cohort of 70-year-old patients with AF, a CHADS2 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 mellitus, 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. 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.

The model was programmed in TreeAge Pro 2007 (TreeAge Software Inc, Williamstown, MA).

Model Inputs

Ischemic stroke rates for those receiving aspirin were based on historical rates observed in patients with a CHADS2 score of 2 receiving aspirin (4.5% per year) from a large patient registry (Table 1). 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. We classified ischemic stroke into 1 of 4 categories: fatal, major, minor, or RIND. We assumed a second minor ischemic stroke resulted in a major 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.
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.4 Regardless of which therapy used, ICHs were subclassified as those resulting in death, major, or some minor degree of neurological deficit.3 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

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<td>RR of nonevent death with NVAF</td>
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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. We derived rates of MI with aspirin from the AVERROES trial. 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. We further assumed that the risk of MI would increase by 1.3-fold per decade of life.

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

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. The utility weights of neurological events (both ischemic stroke or ICH) and MI were derived from the published literature. The utility of aspirin was estimated to be 0.998. 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. 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.

The monthly cost of aspirin was derived from the wholesale acquisition cost (WAC) and the cost of apixaban was assumed to be $205. 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 for Healthcare Research and Quality’s (AHRQ) Healthcare Cost and Utilization Project (HCUP) (using the most current data set, 2008) and previously published estimates. 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. The cost of minor hemorrhage was valued as an outpatient visit (Current Procedural Terminology code: 99212). All costs were inflated to 2011 US dollars using the Consumer Price Index for Medical Care.

**Sensitivity Analyses**

We performed 1-way sensitivity analyses for the trial-length and lifetime models by varying each included variable separately across a plausible range 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 $44 232 and $50 066 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 $50 000 per QALY (becoming cost-effective) sometime between years 3 and 3.5 (ICER at 3.5 years=$45 240 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
The ICER for patients who had previously used a vitamin K antagonist, 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).

Many of the transition probabilities used in the Markov model were extrapolated from a single randomized controlled trial, AVERROES. 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. 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 dominant, it is important to note that economic dominance was somewhat sensitive to the monthly cost of major stroke (not depicted).
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.34–37 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.35 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.38 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).39 However, a recent decision analysis by Shah et al40 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 $59,000 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. 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.38 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).39 However, a recent decision analysis by Shah et al40 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 $59,000 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 $59,000 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.

Figure 5. Probabilistic sensitivity analysis results. The graph is based on 10,000 Monte Carlo simulations of the model, drawing parameters for each input simultaneously from probability distributions. Apixaban is only cost-effective at a willingness-to-pay threshold of $500,000/quality-adjusted life-year (QALY) in 10.9% of iterations in the trial-length model but is cost-effective or dominant in 96.7% and 87.5% of iterations in the 10-year model. Vertical dotted line demarcates the $50,000 per QALY threshold.

| Table 2. Effect of Prior Vitamin K Antagonist Use and Refusal of Vitamin K Antagonist Use on the Incremental Cost-Effectiveness Ratio |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Prior VKA Use                   |                 |                 |                 |                 |                 |
| Aspirin                         | 50,066          |                 | 6.51            |                 |                 |
| Apixaban                        | 37,915          | Cost-saving     | 6.97            | 0.46            | Dominant        |
| No prior VKA use                |                 |                 |                 |                 |                 |
| Aspirin                         | 50,066          |                 | 6.51            |                 |                 |
| Apixaban                        | 53,952          | 3,892           | 6.70            | 0.19            | 20,482          |
| Patient refused VKA             |                 |                 |                 |                 |                 |
| Aspirin                         | 50,066          |                 | 6.51            |                 |                 |
| Apixaban                        | 42,013          | Cost-saving     | 6.90            | 0.39            | Dominant        |
| No refusal of VKA               |                 |                 |                 |                 |                 |
| Aspirin                         | 50,066          |                 | 6.51            |                 |                 |
| Apixaban                        | 46,364          | Cost-saving     | 6.83            | 0.32            | Dominant        |

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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