Cost-Effectiveness of Oral Anticoagulants for Treatment of Atrial Fibrillation

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Background—New anticoagulants may improve health outcomes in patients with atrial fibrillation, but it is unclear whether their use is cost-effective.

Methods and Results—A Markov state transition was created to compare 4 therapies: dabigatran 150 mg BID, apixaban 5 mg BID, rivaroxaban 20 mg QD, and warfarin therapy. The population included those with newly diagnosed atrial fibrillation who were eligible for treatment with warfarin. Compared with warfarin, apixaban, rivaroxaban, and dabigatran, costs were $93,063, $111,465, and $140,557 per additional quality-adjusted life year gained, respectively. At a threshold of $100,000 per quality-adjusted life year, apixaban provided the greatest absolute benefit while still being cost-effective, although warfarin would be superior if apixaban was 2% less effective than expected. Although apixaban was the optimal strategy in our base case, in probabilistic sensitivity analysis, warfarin was optimal in an equal number of iterations at a cost-effectiveness threshold of $100,000 per quality-adjusted life year.

Conclusions—While at a standard cost-effectiveness threshold of $100,000 per quality-adjusted life year, apixaban seems to be the optimal anticoagulation strategy; this finding is sensitive to assumptions about its efficacy and cost. In sensitivity analysis, warfarin seems to be the optimal choice in an equal number of simulations. As a result, although all the novel oral anticoagulants produce greater quality-adjusted life expectancy than warfarin, they may not represent good value for money. (Circ Cardiovasc Qual Outcomes. 2013;6:724-731.)

Key Words: anticoagulants ■ atrial fibrillation ■ cost-effectiveness

Oral vitamin K antagonists such as warfarin dramatically reduce the risk of thromboembolism in patients with atrial fibrillation (AF) but are challenging to use because they interact with numerous other drugs and foods and demonstrate wide interpatient variability in metabolism. These factors have contributed to the underuse of warfarin in potentially eligible patients while making it the most commonly implicated drug in drug-related emergency hospitalizations.

Novel agents, which act by inhibiting factor Xa or thrombin and do not require routine monitoring, may provide more consistent anticoagulation and remove the inconvenience of warfarin monitoring. Two of these agents, dabigatran and rivaroxaban, are noninferior to warfarin and were approved by the US Food and Drug Administration for use in AF in October 2010 and July 2011, respectively. Apixaban seems to be superior to warfarin and was approved by the US Food and Drug Administration for use in AF in December 2012. Currently, only indirect comparisons are available to assess these drugs against one another.

The potential benefits of these novel anticoagulants come at a substantially increased cost. For example, the price of dabigatran is $8 per day. Previous economic analyses suggested that dabigatran seemed to represent relatively good value for money but contained inaccuracies in the assessment of drug costs. The trade-offs in quality and cost for rivaroxaban and apixaban compared with warfarin remain unknown. We, therefore, evaluated the comparative cost-effectiveness of all the available oral agents for stroke prophylaxis in warfarin-eligible patients with AF.

Methods

We built our model to evaluate 4 treatment strategies for anticoagulation in a cohort of 70-year-old warfarin-eligible patients with AF initiating treatment on an oral anticoagulant: (1) standard warfarin therapy managed to an international normalized ratio of 2 to 3, (2) dabigatran 150 mg BID, (3) rivaroxaban 20 mg QD, and (4) apixaban 5 mg BID. The model was built from a societal perspective and lifetime horizon to evaluate the following events: embolisms outside the central nervous system (non–central nervous system embolism), gastrointestinal infarctions, gastrointestinal bleeds, bleeds outside both gastrointestinal and nervous systems (extracranial nongastrointestinal bleed), intracranial hemorrhage, and ischemic stroke.

The method of modeling used was a Markov state transition model following highly standard and widely used guidelines from the US Panel...
WHAT IS KNOWN

- Novel oral anticoagulants (apixaban, dabigatran, and rivaroxaban) for atrial fibrillation provide marginal improvements in cardiovascular end points relative to warfarin.

WHAT THE STUDY ADDS

- Provides an indirect treatment comparison of these novel anticoagulants with each other and with the common comparator of warfarin.
- Estimates the costs of treating patients with atrial fibrillation based on each of these 4 strategies.
- Based on costs and effectiveness of each of these 4 agents, this study suggests that newer agents may not be cost-effective relative to warfarin.

on Cost-Effectiveness in Health and Medicine16-16 and the Consolidated Health Economic Evaluation Reporting Standards guidelines from the International Society of Pharmacoeconomics and Outcomes Research Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force.17

Markov modeling is a stochastic modeling process that has been successfully applied to numerous healthcare decision processes and for which numerous method reviews have previously been published.16,18 Briefly, Markov modeling applies concepts from matrix algebra to simulate the transitions of a patient cohort through various health states over a series of short intervals or cycles. The model (Figure 1) simulated the progression of a theoretical cohort of 70-year-old patients with an average CHADS2 score19 of 2 as they moved in 1-month cycles through a series of health states representing thrombotic and hemorrhagic events as well as death. The likelihood of movement between these states was based on data from large-scale randomized clinical trials and other peer-reviewed literature.

The model was run separately for patients initiating each of the 4 treatments to track quality-adjusted life expectancy and costs relative to AF sequelae and treatment. The analysis was conducted for a lifetime horizon from a societal perspective such that all costs were included regardless of payer. Future costs and life-years were discounted at an annual rate of 3%. All analyses were performed using TreeAge Pro modeling software.

Model Inputs

All model parameters were drawn from the clinical literature (Table 1). When possible, data from meta-analyses were used. Previously conducted cost-effectiveness studies14,20,21 were also referenced for model validation and utility and cost data, with use of other authors’ inputs, allowing close approximation of their final result. All costs were reported in 2011 USD.

Event Rates

We estimated rates of ischemic stroke, myocardial infarction, systemic embolism, intracranial hemorrhage, and severe extracranial hemorrhage with standard warfarin dosing using a weighted average of event rates observed from the control arms of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),4 Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF),7 and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)10 trials. Mortality from other causes was calculated by applying the relative risk of death for patients with AF in the presence and absence of stroke against the rate in the general US population.22 The multiplier for this analysis was drawn from a longitudinal community-based cohort that tracked the natural history of incident cases of atrial fibrillation against age- and sex-matched controls in the same community. Patients with AF, compared with their healthy counterparts, were assumed to be at a 9.6-fold higher risk of death during the first 3 months of treatment, 4.3 for months 3 to 6, and 1.7 for all subsequent cycles.20 Patients with stroke were assigned a 1.8-fold increased risk of death because of causes not related to their AF.20 Survival curves from the model were validated against comparable previously published cost-effectiveness studies14,20,21 and the clinical literature.21

Event rates for patients treated with the novel anticoagulants were calculated by applying the hazard ratios observed in RE-LY, ROCKET-AF, and ARISTOTLE to the rates for patients treated with standard warfarin (Table 1). Although the trials differed in their eligibility criteria, none demonstrated effect modification by baseline risk of AF-associated thromboembolism; therefore, we used the overall reported hazard ratios in our analysis. Patients who experienced an intracranial hemorrhage were assumed to discontinue anticoagulation and switch to aspirin with subsequent event rates based on a weighted average of the aspirin monotherapy arm of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-A) and Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERTROES) trials.24,25 Patients experiencing all other types of hemorrhagic events were assumed to temporarily discontinue anticoagulation for the next 30 days and then reintiate their initial treatment. During this hiatus, patients experienced a loss of therapeutic protection from warfarin and the event rates compared with untreated patients. For purposes of this analysis, it was assumed based on previously conducted meta-analyses that treatment with warfarin resulted in a 64% reduction in clinical events.26

Utilities and Costs

Patient utilities for the various health states in our model were estimated from the published literature (Table 1).27,28 Briefly, utility estimates were generated from interviews of patients with varying disease presentations29 using the previously validated time trade-off technique for utility quantification.30 In this method, patients are asked to imagine a scenario where they could trade their current state of health for a period of 10 years for a period of perfect health during a shorter period of time. The time interval given for the lowest threshold at which they would be willing to trade 10 years of current health subsequently gives an estimate of a quality-adjusted life year (QALY). The primary utility estimate used in this analysis27 is the foundation for virtually all other cost-effectiveness analyses related to AF and was cross-referenced to other estimates for disease severity for validation.29 Consistent with numerous previous cost-effectiveness analysis of interventions for AF, as well as the original utility-generating research, the effect of thromboembolic events on health-related quality of life was assumed to depend on their severity.13,14,20,21,27 Patients experiencing a stroke or systemic embolic event with no residual deficit were assumed to return to the same utility as those with AF who were healthy and on treatment.

The cost of warfarin was assumed to be $4 per month based on pricing available at numerous national pharmacies.30 The price of dabigatran and rivaroxaban, $257 and $242 per month, respectively, was set as the lowest available retail cost at US pharmacies listed on GoodRx.com in September 2012.31 Because apixaban pricing information was not available at the time of analysis, it was assumed to have the same retail price as dabigatran, which is slightly higher than that of rivaroxaban. Patients were assumed to have 1 physician office visit every month.21 The costs of clinical events were drawn from previously published cost-effectiveness analyses, the peer-reviewed literature, and the Nationwide Inpatient Sample database.14,20,21 The costs of these adverse events included both professional and institutional services. Events that
would be cost-effective at a variable willingness-to-pay threshold.

acceptable curve that shows the percent of iterations each scenario effectiveness ratio to standard warfarin and a cost-effectiveness ac-

Monte Carlo simulation in which all model parameters were var-

safety, efficacy, and cost of anticoagulation strategies.

Supplement) to determine the simultaneous effect of changes in

ducted 2-way sensitivity analyses (Figure I in the online-only Data

were simultaneously modified across the same range. We also con-

embolic events (systemic embolism, stroke, myocardial infarction)

with standard warfarin. For efficacy, the relative risks for thrombo-

of 0.5 to 1.5 to the observed hazard ratios for bleeding compared

higher than that observed in the clinical trials by applying modifier

the various strategies relative to warfarin that was 50% lower to 50%

constant (Figure 2). We evaluated a change in comparative safety of

the various strategies relative to warfarin that was 50% lower to 50%

higher than that observed in the clinical trials by applying modifier

of 0.5 to 1.5 to the observed hazard ratios for bleeding compared

standard warfarin. For efficacy, the relative risks for thrombo-

embolic events (systemic embolism, stroke, myocardial infarction) were simultaneously modified across the same range. We also con-

ducted 2-way sensitivity analyses (Figure 1 in the online-only Data

Supplement) to determine the simultaneous effect of changes in the safety, efficacy, and cost of anticoagulation strategies.

Finally, we performed a probabilistic sensitivity analysis using a Monte Carlo simulation in which all model parameters were varied simultaneously. In this analysis, the model was run using a value for each parameter drawn randomly from its assumed distribution. The process was repeated 1000x. Distributions were assigned based on the data from which the parameter estimates were derived. Beta distributions were assigned to utilities and probabilities, which were constrained to fall between 0 and 1. Rates, rate ratios, and adverse event costs were assumed to follow log-normal distributions. The rationale for choice of these types of distributions has been described elsewhere.

Results

Base Case Analysis

For a cohort of 70-year-old AF patients with an average CHADS2 of 2 initiating warfarin, we estimated a quality-adjusted life expectancy of 5.87 years and total discounted lifetime healthcare cost of $49,638 for expenditures related to the consequences of AF and their treatment (Table 2). All the novel agents produced greater quality-adjusted life expectancy than warfarin but at a much greater cost. Compared with warfarin, dabigatran, rivaroxaban, and apixaban cost $140,557, $111,465, and $93,062 per additional QALY gained, respectively. When rank-ordered by costs to determine the optimal treatment strategy, apixaban seemed optimal because dabigatran was eliminated by simple dominance (because it was more costly and less effective than apixaban), and rivaroxaban was eliminated by extended dominance (because it was less effective [ie, had a higher incremental cost-effectiveness ratio] than apixaban).

One-Way Sensitivity Analysis

Although apixaban was the optimal strategy at a conventional cost-effectiveness threshold of $100,000 per QALY gained, this finding was sensitive to assumptions about treatment efficacy, risks, patient demographics, and drug costs (Figure 2). For example, if apixaban was less effective (ie, had a relative effect on thrombotic events that was 2% less favorable than found in ARISTOTLE) or less safe (ie, had a relative effect on bleeding that was 10% less favorable than found in ARISTOTLE), warfarin would become the optimal strategy.

The model was more robust to modifications in values for dabigatran and rivaroxaban. Apixaban would remain the optimal treatment as long as dabigatran and rivaroxaban were not substantially more effective than observed in the trials of these drugs. For example, rivaroxaban and dabigatran did not become the optimal strategies until their efficacy was increased by 8% and 18%, respectively. Similarly, apixaban would
Table 1. Base Case Assumptions and Ranges for Sensitivity Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized warfarin event rates (per year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.21%</td>
<td>0.85%–1.57%</td>
<td>8–10, 41</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.13%</td>
<td>0.09%–0.17%</td>
<td>8–10, 41</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.75%</td>
<td>0.53%–0.98%</td>
<td>8–10, 41</td>
</tr>
<tr>
<td>Extracranial hemorrhage</td>
<td>3.08%</td>
<td>2.16%–4.01%</td>
<td>8–10, 41</td>
</tr>
<tr>
<td>% ECH gastrointestinal</td>
<td>42.8%</td>
<td>30.0%–55.6%</td>
<td>8–10, 41</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.78%</td>
<td>0.55%–1.02%</td>
<td>8–10, 41</td>
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Hazard ratio/relative risk to normalized warfarin

Apixaban

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.92</td>
<td>0.74–1.13</td>
<td>10</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.87</td>
<td>0.44–1.75</td>
<td>10</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.42</td>
<td>0.30–0.58</td>
<td>10</td>
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<tr>
<td>Extracranial hemorrhage</td>
<td>0.79</td>
<td>0.68–0.93</td>
<td>10</td>
</tr>
<tr>
<td>% ECH gastrointestinal</td>
<td>0.86</td>
<td>0.60–1.12</td>
<td>10</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.88</td>
<td>0.66–1.17</td>
<td>10</td>
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</table>

Dabigatran*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.76</td>
<td>0.60–0.98</td>
<td>8, 41</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.83</td>
<td>0.58–1.08</td>
<td>8, 41</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.40</td>
<td>0.27–0.60</td>
<td>8, 41</td>
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<tr>
<td>Extracranial hemorrhage</td>
<td>1.07</td>
<td>0.92–1.25</td>
<td>8, 41</td>
</tr>
<tr>
<td>% ECH gastrointestinal</td>
<td>1.48</td>
<td>1.04–1.92</td>
<td>8, 41</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.27</td>
<td>1.00–1.91</td>
<td>8, 41</td>
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Rivaroxaban

<table>
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<tr>
<td>Ischemic stroke</td>
<td>0.94</td>
<td>0.75–1.17</td>
<td>9</td>
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<tr>
<td>Systemic embolism</td>
<td>0.23</td>
<td>0.09–0.61</td>
<td>9</td>
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<tr>
<td>Intracranial hemorrhage</td>
<td>0.67</td>
<td>0.47–0.93</td>
<td>9</td>
</tr>
<tr>
<td>Extracranial hemorrhage</td>
<td>0.42</td>
<td>0.29–0.55</td>
<td>9</td>
</tr>
<tr>
<td>% ECH gastrointestinal</td>
<td>0.29</td>
<td>0.20–0.38</td>
<td>9</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.81</td>
<td>0.63–1.06</td>
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Relative hazard for major bleeding on warfarin during initiation vs maintenance

Efficacy of treatment with warfarin

Probability of clinical severity

Ischemic stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No residual deficit</td>
<td>9.10%</td>
<td>Calculation†</td>
<td></td>
</tr>
<tr>
<td>Minor residual deficit</td>
<td>42.5%</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Major residual deficit</td>
<td>40.2%</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>8.20%</td>
<td>42</td>
<td></td>
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</tbody>
</table>

Intracranial hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>No residual deficit</td>
<td>11.1%</td>
<td>Calculation†</td>
<td></td>
</tr>
<tr>
<td>Minor residual deficit</td>
<td>41.0%</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Major residual deficit</td>
<td>30.0%</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>17.9%</td>
<td>43</td>
<td></td>
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</table>

Costs (2012 USD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Drugs (monthly)</td>
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<tr>
<td>Aspirin</td>
<td>$5.32</td>
<td>$3–$15</td>
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<td>Post-MI drugs</td>
<td>$37.65</td>
<td>$20–$60</td>
<td>20</td>
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<tr>
<td>Dabigatran 150 mg BID</td>
<td>$257</td>
<td>$177.01–$328.73</td>
<td>12</td>
</tr>
<tr>
<td>Apixaban 5 mg BID</td>
<td>$257</td>
<td>$177.01–$328.73</td>
<td>Assumption</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD</td>
<td>$242</td>
<td>$177.01–$328.73</td>
<td>12</td>
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<tr>
<td>Warfarin</td>
<td>$4.00</td>
<td>$3–$20</td>
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Laboratory and medical monitoring (1 time)

<table>
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<th>Variable</th>
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<tbody>
<tr>
<td>INR laboratory test</td>
<td>$5.82</td>
<td>$3–$15</td>
<td>21</td>
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<tr>
<td>Anticoagulation clinic visit</td>
<td>$19.71</td>
<td>$10–$40</td>
<td>21</td>
</tr>
<tr>
<td>Physician office visit</td>
<td>$41.25</td>
<td>$20–$75</td>
<td>21</td>
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</table>

Acute clinical events (1 time)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracranial hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>$10,937</td>
<td>$7655–$14,217</td>
<td>20</td>
</tr>
<tr>
<td>Nongastrointestinal bleed</td>
<td>$10,208</td>
<td>$7145–$13,270</td>
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Chronic conditions (annual)

<table>
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<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major residual deficit</td>
<td>$35,319</td>
<td>$24,723–$45,915</td>
<td>20</td>
</tr>
<tr>
<td>Minor residual deficit</td>
<td>$27,317</td>
<td>$19,122–$35,512</td>
<td>20</td>
</tr>
<tr>
<td>No residual deficit</td>
<td>$19,315</td>
<td>$13,520–$25,109</td>
<td>Assumption</td>
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Ischemic stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major residual deficit</td>
<td>$26,394</td>
<td>$18,476–$34,312</td>
<td>20</td>
</tr>
<tr>
<td>Minor residual deficit</td>
<td>$20,544</td>
<td>$14,381–$26,707</td>
<td>20</td>
</tr>
<tr>
<td>No residual deficit</td>
<td>$17,635</td>
<td>$12,344–$22,925</td>
<td>Assumption</td>
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CPT indicates current procedural terminology; ECH, extracranial hemorrhage; and INR, international normalized ratio.

*Values for dabigatran are presented as relative risk.

†This value represents remainder of those without greater severity events.

Table 1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Fatality</td>
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<tr>
<td>Extracranial hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>7.20%</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Nongastrointestinal</td>
<td>2.10%</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16.6%</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

Quality-of-life estimates (utilities)

Healthy with atrial fibrillation 0.82 27
Myocardial infarction 0.87 45

Chronic vascular condition

Minor residual deficit 0.75 27
Major residual deficit 0.39 27

Utility of drug therapy

Nonwarfarin regimen 0.998 27
Warfarin Regimen 0.987 27

CPT indicates current procedural terminology; ECH, extracranial hemorrhage; and INR, international normalized ratio.

*Values for dabigatran are presented as relative risk.

†This value represents remainder of those without greater severity events.
remain optimal even if the relative safety of dabigatran and rivaroxaban was to increase by >50% and 26%, respectively.

Our final result was also sensitive to assumptions about the cost of drugs. Modifications to the monthly cost of the novel agents had significant effects on the optimal choice of therapy, with rivaroxaban becoming optimal with a drop in price of $30 (from $242 to $212) and dabigatran becoming optimal with a drop of $72 (from $257 to $185).

Two-Way Sensitivity Analysis
Figure IA in the online-only Data Supplement represents the effect of simultaneously varying the efficacy of either rivaroxaban or dabigatran against apixaban. The 3 strategies of warfarin, apixaban, and rivaroxaban would become equivalent if the efficacy of apixaban were 3% less than assumed and if the efficacy of rivaroxaban were 5% greater than assumed. As found in 1-way analyses, slightly larger simultaneous changes in bleeding risks would need to be observed for rivaroxaban or warfarin to become an optimal strategy (Figure IB in the online-only Data Supplement). For example, it would take a 10% increase and a 16% decrease in the bleeding risk of apixaban and rivaroxaban, respectively, for the 3 strategies described above to become equivalent in net monetary benefit.

The effect of drug costs on the optimal treatment strategy is presented in Figure IC in the online-only Data Supplement. For the 3 strategies of warfarin, apixaban, and rivaroxaban to be equivalent, there would have to be a simultaneous $9 increase and a $14 decrease in the monthly prices of apixaban and rivaroxaban, respectively.

Probabilistic Sensitivity Analysis
Figure 3 presents the results of our probabilistic sensitivity analysis. The results of this analysis show a slightly higher cost-effectiveness ratio relative to warfarin and a wide range of possible outcomes in the 95% confidence interval for each point estimate. The percentage of model simulations for which each of the evaluated strategies was optimal at increasing
cost-effectiveness thresholds is presented in Figure II in the online-only Data Supplement. At a cost-effectiveness threshold of $100,000 per QALY, an equivalent number of simulations (39.8%) suggested that apixaban and warfarin were the optimal approach. That is, although apixaban seems optimal (offering the greatest absolute health benefit while still being cost-effective at $100,000 per QALY) in our base case, it seems virtually indistinguishable from warfarin in the probabilistic analysis. Dabigatran and rivaroxaban were the optimal strategy in a minority of simulations and were virtually indistinguishable across the entire willingness-to-pay range evaluated.

**Discussion**

This cost-effectiveness analysis found that all of the currently available novel oral anticoagulation agents produced greater quality-adjusted life expectancy than warfarin. At a conventional cost-effectiveness threshold of $100,000 per QALY, apixaban provided the greatest value for the money. However, this finding was sensitive to assumptions about the efficacy and cost of the approaches we evaluated, and, in probabilistic analysis, apixaban was indistinguishable from warfarin. As a result, our analysis suggests that there is still substantial uncertainty about whether the novel agents are cost-effective. These comparisons will be clarified further as experience is gained with the real-world use and outcomes of these drugs, as opposed to the randomized trial data on which our analyses are based.

Although there have been previous cost-effectiveness analyses comparing warfarin with dabigatran, rivaroxaban,

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost, $</th>
<th>Effectiveness, QALY</th>
<th>Cost-Effectiveness, $/QALY</th>
<th>Cost-Effectiveness Ratio to Warfarin, Δ$/ΔQALY</th>
<th>Incremental Cost-Effectiveness, Δ$/Δ QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>$49,638</td>
<td>5.87</td>
<td>$8,450</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Rivaroxaban</td>
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<td>6.18</td>
<td>$13,618</td>
<td>$111,465</td>
<td>Ext Dom*</td>
</tr>
<tr>
<td>Apixaban</td>
<td>$87,794</td>
<td>6.28</td>
<td>$13,989</td>
<td>$93,063</td>
<td>$93,063</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>$88,994</td>
<td>6.15</td>
<td>$14,473</td>
<td>$140,557</td>
<td>Abs Dom†</td>
</tr>
</tbody>
</table>

QALY indicates quality-adjusted life year.
* Ruled out by extended dominance.
† Ruled out by simple dominance.

**Figure 3.** Probabilistic sensitivity analysis. Graph represents the result of a probabilistic sensitivity analysis using a Monte Carlo simulation. Point estimates show the predicted cost-effectiveness ratio to standard warfarin for novel strategy of anticoagulation in both our Markov and Monte Carlo models. Lines extend to the upper and lower bounds of a 95% confidence interval for the results of our Monte Carlo analysis.
relative to standard warfarin therapy. Our results differ in large part because of assumptions about the monthly cost of warfarin, which we assumed to be $4 rather than ≈$30.\textsuperscript{15,30} We also used a more accurate cost for dabigatran than was possible in the analysis by Freeman et al.,\textsuperscript{14} which was written before the drug came to market in the United States. We also assumed that healthy patients living with AF had less than perfect health-related quality of life,\textsuperscript{2,27} which affected the absolute results for our model but not the relative cost-effectiveness of the strategies we evaluated.

Because the magnitude of the protective effect of dabigatran on stroke and bleeding observed in RE-LY was larger than that for the other strategies, we anticipated that this agent would have been relatively cost-effective. However, dabigatran was also associated with a higher hazard of myocardial infarction, which counterbalanced its potential benefits. As a result, in our probabilistic analysis, dabigatran was optimal in few scenarios and only when simultaneously making favorable assumptions about its efficacy, safety, and cost and unfavorable assumptions about the other treatment arms. When the potential increased risk of myocardial infarction from dabigatran was removed from our model (ie, its hazard ratio was set to 1), the cost-effectiveness ratio relative to warfarin improved from $140,557 to $110,768 per QALY, giving it greater absolute improvement than rivaroxaban but not proving to be cost-effective at a $100,000 per QALY threshold or providing greater absolute health improvement or cost-effectiveness than apixaban.

Several limitations of our analysis should be acknowledged. Although clinical trials have compared warfarin with the agents we evaluated, head-to-head trials of these drugs do not currently exist. The trials on which our analysis was based did have important differences in design (RE-LY was not double-blinded), populations included (ROCKET-AF was restricted to higher risk populations, and the warfarin group had less adequate control than in other studies), and how optimally warfarin was managed in the control arm. Thus, our assumptions about their relative efficacy and safety, especially for a lifetime horizon, may have been incorrect. Recent analysis, however, suggests similar effect for apixaban at varying ranges of international normalized ratio control for warfarin,\textsuperscript{29} lending credibility to our choice of a standardized warfarin comparator for all agents and supporting the comparability of the different trials. Furthermore, our analysis facilitates comparisons between the agents by evaluating a hypothetical cohort of 70-year-old patients with an average CHADS\textsubscript{2} score of 2, thereby making it more feasible to indirectly compare these trials. Furthermore, the event rates observed in actual practice may differ from those in highly monitored trials; however, this is likely to be the case for all drugs we evaluated, including standard warfarin.\textsuperscript{40} Monthly prices set for dabigatran and rivaroxaban were $257 and $242, respectively, based on the lowest available retail cost at US pharmacies listed on GoodRx.com in September 2012.\textsuperscript{12} More recently, prices for these agents have risen to $275, which may result in a greater advantage for warfarin in our probabilistic sensitivity analyses.

In conclusion, while at a standard cost-effectiveness threshold of $100,000 per QALY, apixaban seems to be the optimal anticoagulation strategy; this finding is sensitive to assumptions about its efficacy and cost. Interestingly, apixaban was indistinguishable from warfarin in our probabilistic analysis, suggesting that while efficacious and comparatively safe, this agent may not represent good value for the money. Furthermore, it seems unlikely that rivaroxaban or dabigatran would be cost-effective at their currently assumed prices.

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Disclosures

None.

References


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Appendix Figure 1A: Two-way Sensitivity of Efficacy on the Optimal Treatment Strategy at a Cost-Effectiveness Threshold of $100 000 per QALY

Efficacy risk is modified by adjusting the hazard ratio of ischemic stroke, systemic embolism, and MI novel agents relative to warfarin by the value indicated on the graph. Red solid line represents the threshold under which different scenarios become optimal. Black dashed lines represent intercepts of values of interest (Base case values, 1-way sensitivity threshold values, etc.).
Appendix Figure 1B: Two-way Sensitivity of Bleeding Risk on the Optimal Treatment Strategy at a Cost-Effectiveness Threshold of $100 000 per QALY

Bleeding risk is modified by adjusting the hazard ratio of both ICH and ECH for novel agents relative to warfarin by the value indicated. Red solid line represents the threshold under which different scenarios become optimal at a $100K per QALY threshold. Black dashed lines represent the intercepts of the values of interest (Base case values, 1-way sensitivity threshold values, etc.).
Appendix Figure 1C: Two-way Sensitivity of Drug Pricing on the Optimal Treatment Strategy at a Cost-Effectiveness Threshold of $100 000 per QALY

QALY is defined as quality adjusted life year, a standard measure of clinical effectiveness used in health economics. Graph represents a two-way sensitivity analysis of optimal strategy at a $100K/QALY willingness to pay and variable drug pricing for apixaban and rivaroxaban. The red solid line represents the threshold under which different scenarios become cost effective. The black dashed lines represent intercepts of values of interest (Base case values, 1-way sensitivity threshold values, etc.).
Appendix Figure 2: Cost-Effectiveness Acceptability Curve Demonstrating the Optimal Choices at Various Willingness-to-Pay Thresholds.

Plot represents the result of a probabilistic sensitivity analysis using a Monte Carlo simulation. Trend lines show the percent of iterations at which each strategy would be optimal at various willingness-to-pay thresholds. The vertical intersect on the graph shows the $100K per QALY threshold.
Appendix Figure 3: Tornado Plot: ICER of Novel Agents versus Warfarin

- Apixaban vs. Warfarin
  - Apixaban Cost
  - Patient Age
  - MI Hazard Ratio A vs. W
  - Ischemic Stroke Hazard Ratio A vs. W
  - Utility: Healthy with AF
  - ICH Hazard Ratio A vs. W
  - Cost of INR Monitoring Visit
  - Discount Rate
  - Cost of Doctors Office Visit
  - ECH Hazard Ratio A vs. W

- Rivaroxaban vs. Warfarin
  - Cost of Rivaroxaban
  - Ischemic Stroke Hazard Ratio R vs. W
  - Patient Age
  - ICH Hazard Ratio R vs. W
  - MI Hazard Ratio R vs. W
  - Utility: Healthy with AF
  - Cost of INR Monitoring Visit
  - Discount Rate
  - Cost of Doctors Office Visit
  - Cost of INR Test

- Dabigatran vs. Warfarin
  - MI Hazard Ratio D vs. W
  - Dabigatran Cost
  - Ischemic Stroke Hazard Ratio D vs. W
  - Patient Age
  - ICH Hazard Ratio D vs. W
  - Utility: Healthy with AF
  - Cost of INR Monitoring Visit
  - ECH Hazard Ratio D vs. W
  - Discount Rate
  - GI Bleed Hazard Ratio D vs. W