

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)¹ but are challenging to use because they interact with numerous other drugs and foods and demonstrate wide interpatient variability in metabolism.² These factors have contributed to the underuse of warfarin in potentially eligible patients^{3,4} while making it the most commonly implicated drug in drug-related emergency hospitalizations.⁵

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.^{6,7} Two of these agents, dabigatran and rivaroxaban, are noninferior to warfarin^{8,9} 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 warfarin¹⁰ 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.¹¹

The potential benefits of these novel anticoagulants come at a substantially increased cost. For example, the price of

dabigatran is ≈\$8 per day.¹² Previous economic analyses suggested that dabigatran seemed to represent relatively good value for money^{13,14} but contained inaccuracies in the assessment of drug costs.¹⁵ 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), myocardial 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 model¹⁶ following highly standard and widely used guidelines from the US Panel

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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 Medicine^{16a–16c} 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 related 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 studies^{13,14,20,21} 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),⁸ 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),⁹ 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 studies^{13,14,20,21} and the clinical literature.²³

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 (AVERROES) trials.^{24,25} Patients experiencing all other types of hemorrhagic events were assumed to temporarily discontinue anticoagulation for the next 30 days and then reinitiate their initial treatment. During this hiatus, patients experienced a loss of therapeutic protection from warfarin and had event rates comparable 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 presentations²⁷ using the previously validated time trade-off technique for utility quantification.²⁹ 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.²⁸ 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 2012.¹² 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 3 months for warfarin and every 6 months for the novel anticoagulants. Based on the analysis by Eckman et al,²⁰ international normalized ratio monitoring was assumed to require 5 visits to an anticoagulation clinic and associated laboratory fees during the first month of treatment and then 1 international normalized ratio visit for each subsequent 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.^{14,20,31} The costs of these adverse events included both professional and institutional services. Events that

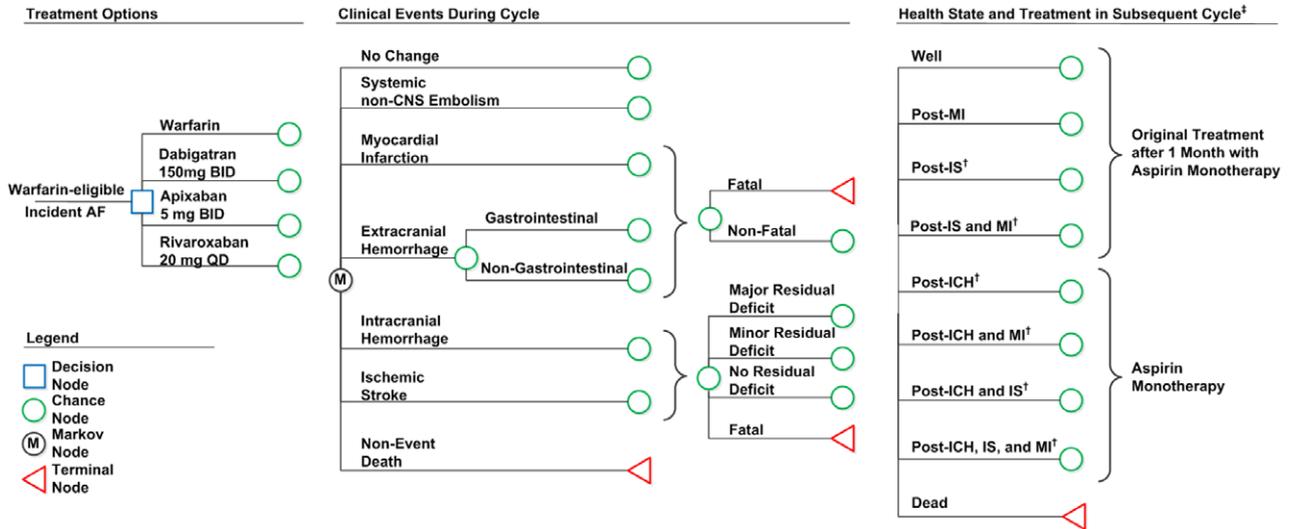


Figure 1. Model structure. In each 1-month cycle, patients may experience 1 of 7 possible clinical events, resulting in death, residual complications, or survival without deficit. Based on their health status at the end of each monthly cycle, patients begin the next cycle in 1 of 21 possible health states. ‡Complication rates are variable and modeled as a function of treatment status. †Represents a health state with 4 possible levels of residual deficit: none, minor, major, or fatal. CNS indicates central nervous system; ICH, intracranial hemorrhage; IS, ischemic stroke; and MI, myocardial infarction.

resulted in residual disability were assigned costs of chronic condition management based on the level of deficit, and a description of the method for this calculation has been described elsewhere.²⁰ All costs were expressed in 2011 dollar values and when necessary were inflated using the medical care component of the consumer price index.

Outcomes and Analysis

We computed incremental cost-effectiveness ratios comparing each strategy with the next least costly undominated strategy to identify the single treatment strategy that would provide the greatest improvement in health outcomes at an acceptable cost per QALY gained. We used a threshold of \$100 000 per QALY to evaluate cost-effectiveness.³²

Sensitivity Analysis

To assess the optimal treatment strategy under differing assumptions, we varied novel agent efficacy, safety, and cost, as well as patient demographics, over plausible ranges while holding all other values 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 with standard warfarin. For efficacy, the relative risks for thromboembolic events (systemic embolism, stroke, myocardial infarction) were simultaneously modified across the same range. We also conducted 2-way sensitivity analyses (Figure I 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^{33,34} 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.²⁰ Results of this analysis were reported as a predicted cost-effectiveness ratio to standard warfarin and a cost-effectiveness acceptability curve that shows the percent of iterations each scenario would be cost-effective at a variable willingness-to-pay threshold (Figure II in the online-only Data Supplement).

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

Variable	Base Case Value	Range	Reference
Normalized warfarin event rates (per year)			
Ischemic stroke	1.21%	0.85%–1.57%	8–10, 41
Systemic embolism	0.13%	0.09%–0.17%	8–10, 41
Intracranial hemorrhage	0.75%	0.53%–0.98%	8–10, 41
Extracranial hemorrhage	3.08%	2.16%–4.01%	8–10, 41
% ECH gastrointestinal	42.8%	30.0%–55.6%	8–10, 41
Myocardial infarction	0.78%	0.55%–1.02%	8–10, 41
Hazard ratio/relative risk to normalized warfarin			
Apixaban			
Ischemic stroke	0.92	0.74–1.13	10
Systemic embolism	0.87	0.44–1.75	10
Intracranial hemorrhage	0.42	0.30–0.58	10
Extracranial hemorrhage	0.79	0.68–0.93	10
% ECH gastrointestinal	0.86	0.60–1.12	10
Myocardial infarction	0.88	0.66–1.17	10
Dabigatran*			
Ischemic stroke	0.76	0.60–0.98	8, 41
Systemic embolism	0.83	0.58–1.08	8, 41
Intracranial hemorrhage	0.40	0.27–0.60	8, 41
Extracranial hemorrhage	1.07	0.92–1.25	8, 41
% ECH gastrointestinal	1.48	1.04–1.92	8, 41
Myocardial infarction	1.27	1.00–1.91	8, 41
Rivaroxaban			
Ischemic stroke	0.94	0.75–1.17	9
Systemic embolism	0.23	0.09–0.61	9
Intracranial hemorrhage	0.67	0.47–0.93	9
Extracranial hemorrhage	0.42	0.29–0.55	9
% ECH gastrointestinal	0.29	0.20–0.38	9
Myocardial infarction	0.81	0.63–1.06	9
Relative hazard for major bleeding on warfarin during initiation vs maintenance	1.90	1.33–2.47	21
Efficacy of treatment with warfarin	0.64	0.49–0.74	26
Probability of clinical severity			
Ischemic stroke			
No residual deficit	9.10%		Calculation†
Minor residual deficit	42.5%		42
Major residual deficit	40.2%		42
Fatal	8.20%		42
Intracranial hemorrhage			
No residual deficit	11.1%		Calculation†
Minor residual deficit	41.0%		43
Major residual deficit	30.0%		43
Fatal	17.9%		43

(Continued)

Table 1. Continued

Variable	Base Case Value	Range	Reference
Fatality			
Extracranial hemorrhage			
Gastrointestinal	7.20%		31
Nongastrointestinal	2.10%		31
Myocardial infarction	16.6%		44
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
Costs (2012 USD)			
Drugs (monthly)			
Aspirin	\$5.32	\$3–\$15	46
Post-MI drugs	\$37.65	\$20–\$60	20
Dabigatran 150 mg BID	\$257	\$177.01–\$328.73	12
Apixaban 5 mg BID	\$257	\$177.01–\$328.73	Assumption
Rivaroxaban 20 mg QD	\$242	\$177.01–\$328.73	12
Warfarin	\$4.00	\$3–\$20	47
Laboratory and medical monitoring (1 time)			
INR laboratory test (CPT code 85610)	\$5.82	\$3–\$15	21
Anticoagulation clinic visit (CPT code 99211)	\$19.71	\$10–\$40	21
Physician office visit (CPT code 99212)	\$41.25	\$20–\$75	21
Acute clinical events (1 time)			
Extracranial hemorrhage			
Gastrointestinal bleed	\$10 937	\$7655–\$14 217	20
Nongastrointestinal bleed	\$10 208	\$7145–\$13 270	20
Intracranial hemorrhage			
Major residual deficit	\$35 319	\$24 723–\$45 915	20
Minor residual deficit	\$27 317	\$19 122–\$35 512	20
No residual deficit	\$19 315	\$13 520–\$25 109	Assumption
Ischemic stroke			
Major residual deficit	\$26 394	\$18 476–\$34 312	20
Minor residual deficit	\$20 544	\$14 381–\$26 707	20
No residual deficit	\$17 635	\$12 344–\$22 925	Assumption
Systemic embolism	\$19 833	\$13 883–\$25 782	31
Myocardial infarction	\$17 930	\$12 551–\$23 309	14
Death	\$11 054	\$7737–\$14 369	20
Chronic conditions (annual)			
Major residual deficit	\$16 757	\$11 729–\$21 784	20
Minor residual deficit	\$5384	\$3769–\$6999	20

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.

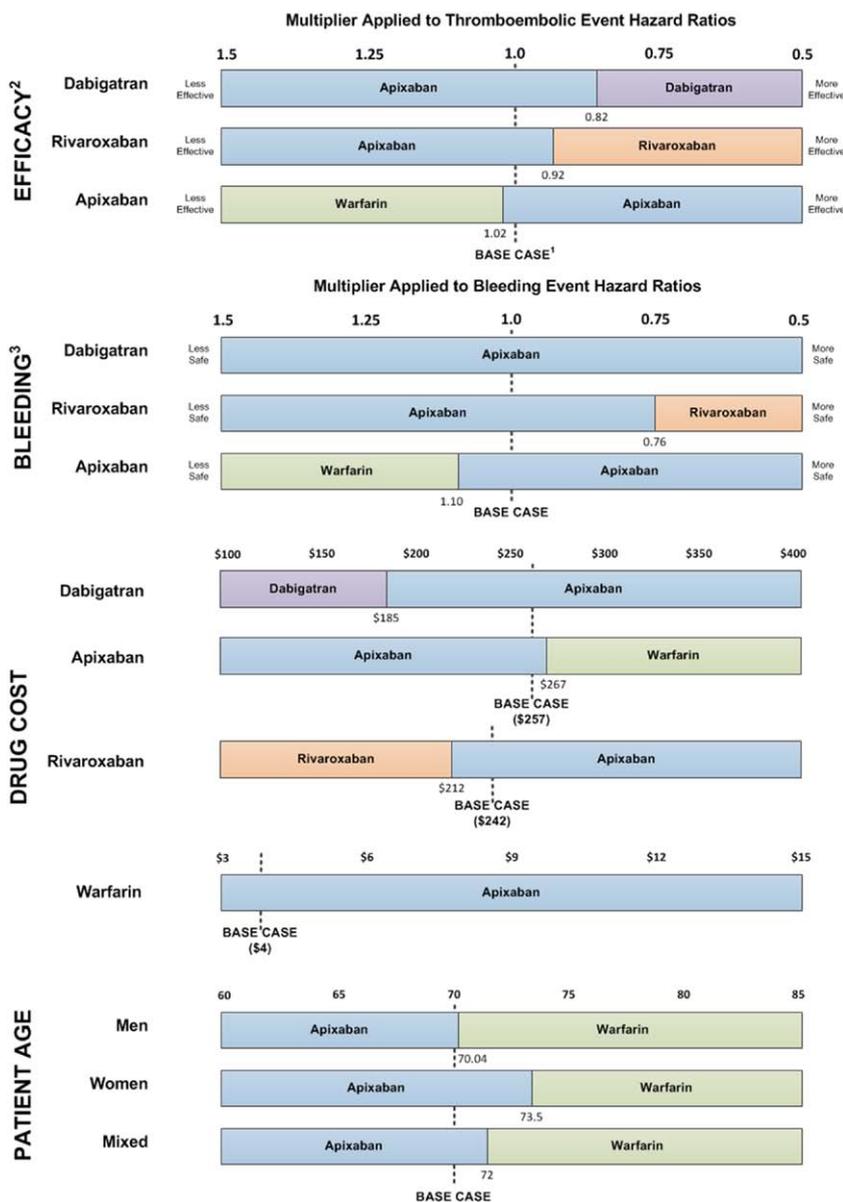


Figure 2. One-way sensitivity analyses on efficacy, safety, and cost identifying the threshold at which the various strategies become optimal.¹ Base case represents the value used in the model for initial results before sensitivity analysis. Threshold analysis evaluates the variable value at which a strategy becomes cost-effective. This analysis assumes a \$100,000 per quality-adjusted life year cost-effectiveness threshold.² Efficacy represents a modifier applied to the hazard ratios of ischemic stroke, systemic embolism, and myocardial infarction of novel agents relative to warfarin.³ Bleeding represents a modifier applied to the hazard ratios of intra- and extracranial hemorrhages of novel agents relative to warfarin.

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

Table 2. Base Case Results

Strategy	Cost, \$	Effectiveness, QALY	Cost-Effectiveness, \$/QALY	Cost-Effectiveness Ratio to Warfarin, $\Delta\$/\Delta\text{QALY}$	Incremental Cost-Effectiveness, $\Delta\$/\Delta\text{QALY}$
Warfarin	\$49 638	5.87	\$8450	Reference	Reference
Rivaroxaban	\$84 192	6.18	\$13 618	\$111 465	Ext Dom*
Apixaban	\$87 794	6.28	\$13 989	\$93 063	\$93 063
Dabigatran	\$88 994	6.15	\$14 473	\$140 557	Abs Dom†

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

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,^{13,14,35-38} none have evaluated the new agents apixaban and rivaroxaban. In analyses by Freeman et al¹⁴ and Shah and Gage,¹³ dabigatran 150 mg BID cost \$45 372 and \$86 000 per QALY gained, respectively,

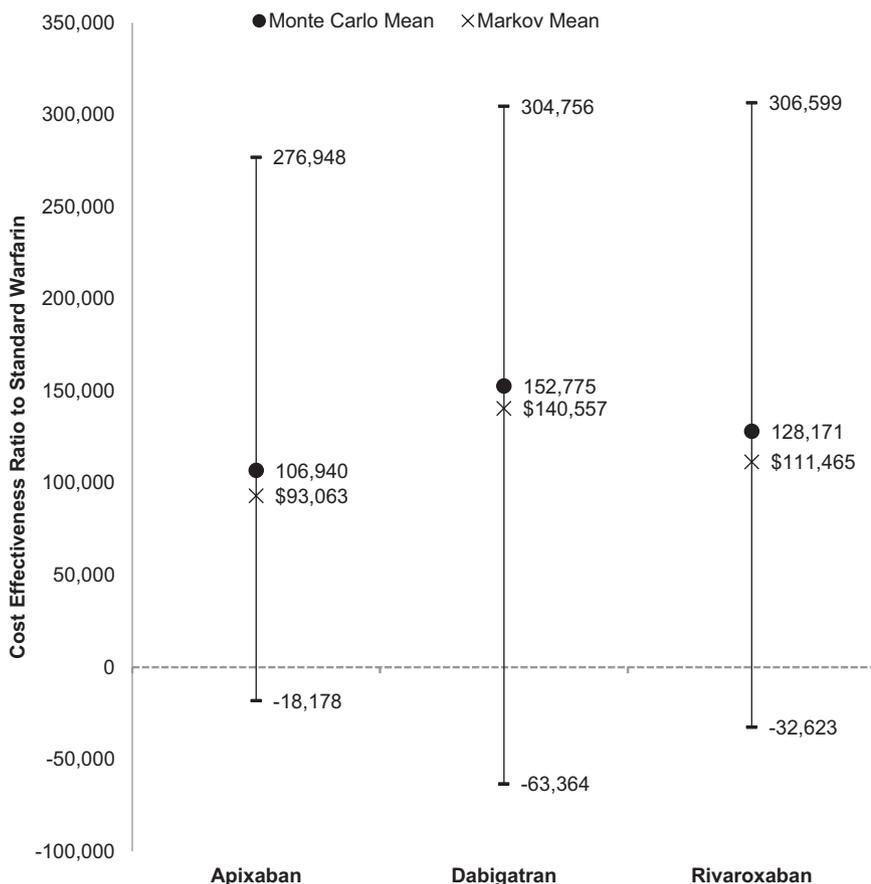


Figure 3. Probabilistic sensitivity analysis. Graph represents the result of a probabilistic sensitivity analysis using a Monte Carlo simulation. Point estimates show the predicted cost-effectiveness ratio to standard warfarin for novel strategy of anticoagulation in both our Markov and Monte Carlo models. 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.^{15,30} We also used a more accurate cost for dabigatran than was possible in the analysis by Freeman et al,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,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 \$140557 to \$110768 per QALY, giving it greater absolute improvement than rivaroxaban but not proving to be cost-effective at a \$100000 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,³⁹ 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 CHADS₂ 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.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 2012.¹² 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 \$100000 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.

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