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Background and Purpose—To estimate the cost-effectiveness of stroke prevention in patients with nonvalvular atrial fibrillation by using novel oral anticoagulants apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg compared with warfarin.

Methods—A Markov decision-analysis model was constructed using data from clinical trials to evaluate lifetime costs and quality-adjusted life-years of novel oral anticoagulants compared with warfarin. The modeled population was a hypothetical cohort of 70-year-old patients with nonvalvular atrial fibrillation, increased risk for stroke ($CHADS_2 \geq 1$), renal creatinine clearance ≥50 mL/min, and no previous contraindications to anticoagulation. The willingness-to-pay threshold was $50 000/quality-adjusted life-years gained.

Results—In the base case, warfarin had the lowest cost of $77 813 (SD, $2223), followed by rivaroxaban 20 mg ($78 738±$1852), dabigatran 150 mg ($82 719±$1959), and apixaban 5 mg ($85 326±$1512). Apixaban 5 mg had the highest quality-adjusted life-years estimate at 8.47 (SD, 0.06), followed by dabigatran 150 mg (8.41±0.07), rivaroxaban 20 mg (8.26±0.06), and warfarin (7.97±0.04). In a Monte Carlo probabilistic sensitivity analysis, apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were cost-effective in 45.1%, 40%, 14.9%, 0% of the simulations, respectively.

Conclusions—In patients with nonvalvular atrial fibrillation and an increased risk of stroke prophylaxis, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were all cost-effective alternatives to warfarin. The cost-effectiveness of novel oral anticoagulantss was dependent on therapy pricing in the United States and neurological events associated with rivaroxaban 20 mg. **(*Stroke*. 2013;44:1676-1681.)**

Key Words: anticoagulation ■ atrial fibrillation ■ cost-effectiveness ■ intracranial hemorrhage ■ Markov model ■ stroke

The rate of ischemic stroke in people with nonvalvular atrial fibrillation (NVAF) averages ≈5% per year, which is 2 to 7 times the rate of those people without NVAF.[1] An estimated 7 million Americans ≥20 years of age have had a stroke.[2] Projections estimate that by 2030, an additional 4 million people in the United States will have had a stroke, a 24% increase in prevalence from 2010.[3] Each year, ≈795 000 people in the United States experience a new or recurrent stroke.[2]

Stroke represents a substantial financial burden on the healthcare system, as well as on patients, family, and society. The lifetime cost of an ischemic stroke is estimated to be >$90 000 for an individual in 1990,[4] whereas the American Heart Association estimated that in 2008, total national direct and indirect costs of stroke in the United States exceeded $34 billion.[5] Nearly 75% of the patients who had stroke are Medicare beneficiaries, qualifying the national health insurance program as the most common payer of healthcare for patients who had stroke. The total aggregated costs for this population were $60 177 for subarachnoid hemorrhage, $50 015 for intracranial hemorrhage (ICH), and $49 996 for an ischemic stroke.[6]

Warfarin is the current standard therapy used for prolonged stroke management; however, its use is limited because of the narrow therapeutic window required, interindividual variability in dose response, and numerous drug–drug and drug–food interactions.[7] Novel oral anticoagulant (NOAC) alternatives to warfarin, apixaban, dabigatran, and rivaroxaban, have recently become accessible for patients with NVAF, and their clinical trial data have become available.[8–10] To date, published economic studies have only focused on the cost-effectiveness comparison between 2 of the 4 therapies for stroke prevention in patients in the United States with atrial fibrillation.[11–15] The primary objective of this study is to estimate the long-term cost-effectiveness of stroke prevention in patients with NVAF in the United States comparing NOACs with the standard treatment, warfarin. Furthermore, this study will provide a more comprehensive evaluation of the cost-effectiveness of available anticoagulation therapies to assist clinicians and other healthcare decision-makers to make a more informed choice regarding patient treatment.

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Methods

Decision Model

Using a Markov model, 4 treatment strategies and their associated outcomes were assessed: apixaban 5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and adjusted-dose warfarin (target international normalized ratio [INR] between 2.0 and 3.0). The baseline patient population was a hypothetical cohort of 70-year-old patients with NVAF, an increased risk for stroke ($CHADS_2$ [Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or transient ischemic attack (doubled)] ≥1, or equivalent). a renal creatinine clearance of ≥50 mL/min, and no previous contraindications to anticoagulant therapy. Therapy adherence rates were assumed to be similar across all treatments, and the efficacy was assumed to remain constant over time for all NOACs and warfarin. Patient movement between health states was modeled using 1-month cycles for 30 years or until death.

The following health states were included in the base case: well, ischemic stroke (minor or major), ICH (minor or major), myocardial infarction (MI), and death (Figure 1). Quality-adjusted life expectancy, risk of adverse events, and net costs were quantified over a period of 30 years using a societal perspective. Cost-effective therapies were selected using a willingness-to-pay (WTP) threshold of $50 000 per quality-adjusted life-year (QALY) gained.[16] Model implementation, sensitivity analyses, and outcome calculations were performed using TreeAge Pro 2012 (Williamstown, MA).[17]

Probability and Severity of Adverse Events

The risks of adverse events for NOACs and warfarin were based on clinical trial data from Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (apixaban 5 mg twice daily); Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (dabigatran 150 mg twice

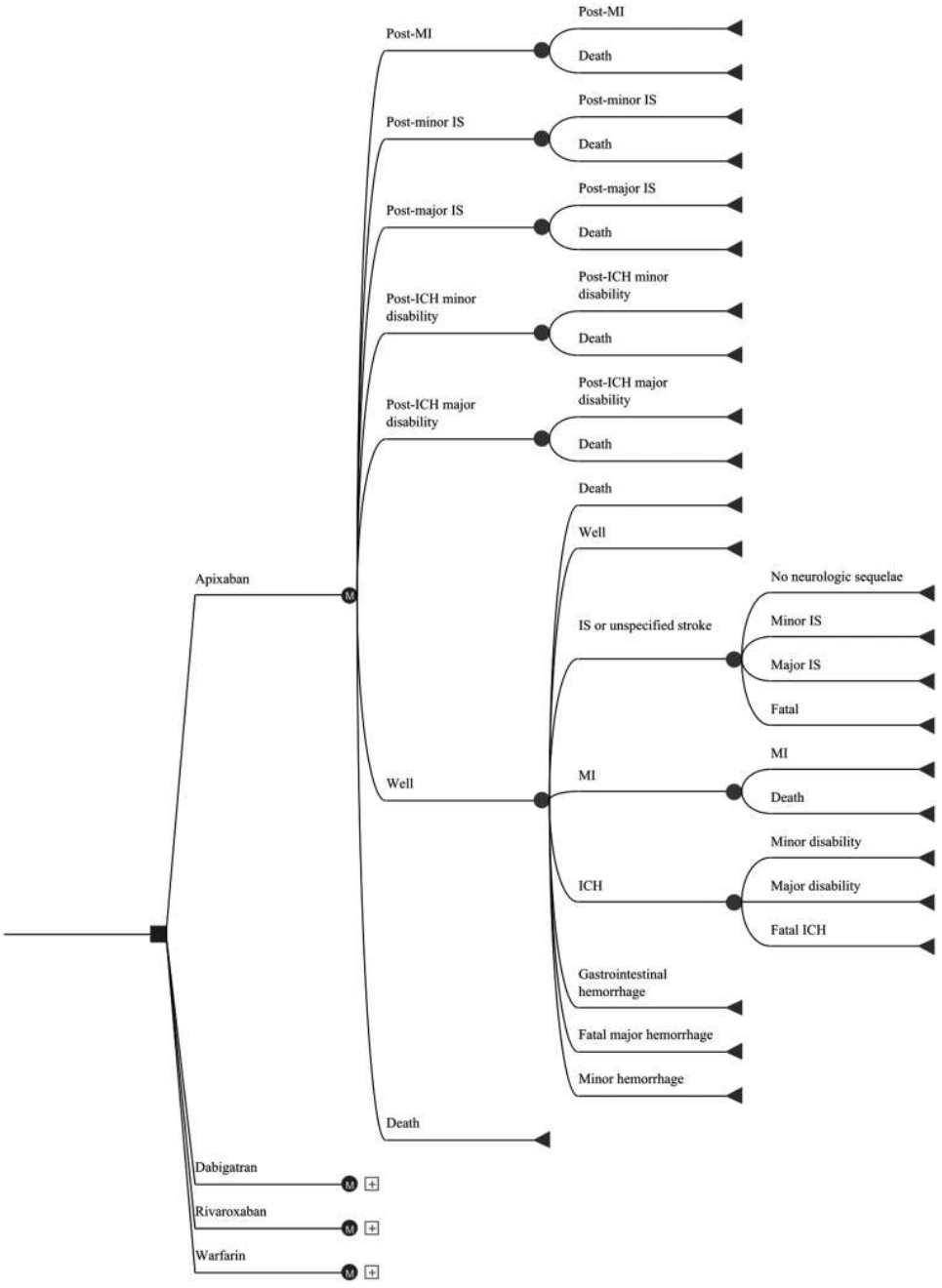

Figure 1. Schematic representation of the Markov model illustrates that all patients start at 70 years old with nonvalvular atrial fibrillation, an increased risk of stroke ($CHADS_2$ score ≥1 or equivalent), a renal creatinine clearance ≥50 mL/min, and no previous contraindications to anticoagulation therapy. Patients cycle between health states until death occurs or the 30-year model time-horizon is reached. The length of each cycle is 1 month. Depicted in the diagram is the decision node (square), chance nodes (empty circles) directed by transition probabilities, Markov nodes (circles with 'M'), and terminal nodes (triangles). Markov branches for the other 3 therapies are identical to the apixaban branch shown. ICH indicates intracranial hemorrhage; IS, ischemic stroke; and MI, myocardial infarction.

daily); and 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) (rivaroxaban 20 mg once daily).[8–10,18] Probabilities of adverse events for warfarin were calculated from pooled clinical trial results.[8–10,18]

Ischemic stroke was classified into one of the following 4 categories: fatal, major, minor, or no residual neurological sequelae.[13] The rate of stroke increased by a factor of 1.4 per decade of life (multiplicative adjustment).[12,19] After an ischemic stroke or ICH, a patient's risk of mortality increased by a factor of 3.7.[20] Hemorrhage was classified as one of the following 4 categories: fatal, ICH, gastrointestinal, or nonfatal minor extracerebral.[8–10,18] Using aggregated probabilities reported in a study by Kamel et al,[13] an ICH event was further subcategorized as minor, major, or fatal (Table in the online-only Data Supplement). The risk of MI was increased by a factor of 1.3 each decade of the patient's lifetime (multiplicative adjustment).[12] Mortality rates after an MI event increased multiplicatively by a factor of 1.051.[21]

A relatively common side effect of using dabigatran 150 mg is dyspepsia. As reported in the RE-LY trial, 11.3% of patients receiving dabigatran 150 mg experienced a dyspepsia event.[9] The associated cost and utility decrement with dyspepsia were included for patients with the side effect.[22,23]

Mortality rates for the baseline population were initially adjusted in the model for age (starting at 70 years).[24] A patient's mortality risk was adjusted for age and postevent mortality risks (MI, ischemic stroke, and ICH) throughout the course of the patient's lifetime and disease progression.[20,21,24]

Utilities

The baseline patient utility value was adjusted for age, atrial fibrillation, and anticoagulation treatment.[25,26] Subsequent disutilities for ischemic stroke, neurological events (ischemic stroke or ICH) with residua, MI, gastrointestinal hemorrhage, minor hemorrhage (1 week after the event), and dyspepsia were estimated using pooled nationally representative Medical Expenditure Panel Survey data, as well as derived from published population-specific articles (Table in the online-only Data Supplement).[25–29]

Costs

One-time event costs for ischemic stroke, ICH, MI, GI hemorrhage, and dyspepsia were estimated from 2009 mean costs published online by the Agency for Healthcare Research and Quality from Healthcare Cost and Utilization Project data under relevant primary *International Classification of Diseases Ninth Revision* codes and diagnosis-related group codes for Medicare remuneration.[22] Cost of a minor hemorrhage was based on payment for an expanded problem–focused physician visit for an established patient (Current Procedural Terminology code 99213).[30] Costs of INR testing (Current Procedural Terminology code 85610) and physician visits (Current Procedural Terminology codes 99211 and 99212) were estimated using Medicare reimbursement values.[30] Mean prescription drug costs for dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were estimated using wholesale acquisition costs listed in the Medi-Span drug database. The US Food and Drug Administration recently approved apixaban 5 mg for use in the United States; however, the cost is not yet available to include in this analysis. The listed price for apixaban 5 mg in the United Kingdom reported in the National Institutes for Health and Clinical Evidence costing statement was used (£3.43 per day) and converted to US dollars.[31]

Long-term costs were calculated using the study by Leibson et al[32] who evaluated the use of acute care services 12 months after an ischemic stroke or ICH. A study conducted by Jonas et al[33] eliciting patient time requirements for warfarin anticoagulation therapy was used to estimate the economic cost of patient time. An equivalent study has not been conducted for NOACs, and therefore, the estimate of clinic visits alone (excluding anticoagulation-related activities) was used for patients modeled to receive apixaban 5 mg, dabigatran 150 mg, or rivaroxaban 20 mg. The medical care component of the US Bureau of Labor Statistics' Consumer Price Index was used for cost inflation. All costs were expressed in 2012 US dollars.

Costs and QALYs were implemented in each cycle according to the health state the patient occupied. The costs and QALYs accrued for each Markov state were weighted according to the amount of time a person spent in the health state. After completing the model simulations, a summed amount was calculated for each treatment. A discount rate of 3% per year was applied for both costs and QALYs.[34]

Sensitivity Analyses

Multiple sensitivity analyses of the model variables were performed. First, a series of univariate sensitivity analyses were conducted to assess the relative impact of each model parameter as well as key model assumptions (Figure 2). Parameters and model assumptions were varied over plausible ranges to identify influential model variables (Table in the online-only Data Supplement). Second, a Monte Carlo probabilistic sensitivity analysis was performed incorporating first- and second-order uncertainty (intraindividual and parameter uncertainty, respectively). The gamma distribution was used for costs, whereas a beta distribution was used for transition probabilities and utilities.[35]

Results

Base Case

In the base case, quality-adjusted life expectancy for apixaban 5 mg was the highest of the anticoagulants, with a value of 8.47 (SD, 0.06; Table), whereas warfarin had the lowest QALY estimate (7.97±0.04). Compared with warfarin, apixaban 5 mg provided an additional 0.5 QALYs at a cost of $7513, resulting in an incremental cost-effectiveness ratio (ICER) of $15 026 per QALY gained, well below the threshold of $50 000 per QALY gained.

One-Way Sensitivity Analyses

One-way sensitivity analyses were conducted for costs, utilities, probabilities, age, and the discount rate to determine influential variables with the most impact on the results of the model. A tornado diagram illustrating the cost variables in descending order of influence is shown in Figure 2. Costs with the most influence on total costs estimated from the model were costs of therapy for apixaban, dabigatran, and rivaroxaban, as well as cost of dyspepsia adverse event for patients receiving dabigatran 150 mg. Probabilities contributing the most leverage to model results were age-associated probabilities of ischemic stroke, ICH, and MI, as well as the probability of either an ICH or ischemic stroke for patients receiving rivaroxaban 20 mg. Varying all of these variables over plausible ranges simultaneously did not substantially influence the ICER values of the NOACs compared with warfarin from the base case, nor did the values exceed $50 000 per QALY gained (Table).

Probabilistic Sensitivity Analyses

Mean costs and QALYs derived from the probabilistic sensitivity analysis are presented in the Table. Using a WTP threshold of $50 000 per QALY gained, apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were cost-effective in 45.1%, 40%, 14.9%, 0% of the simulations, respectively (Figure 3). Increasing the WTP threshold to $100 000 per QALY gained yielded a greater difference in the probability of cost-effectiveness among the anticoagulant therapies, where apixaban 5 mg was cost-effective in 60.7% of the iterations, dabigatran 150 mg in

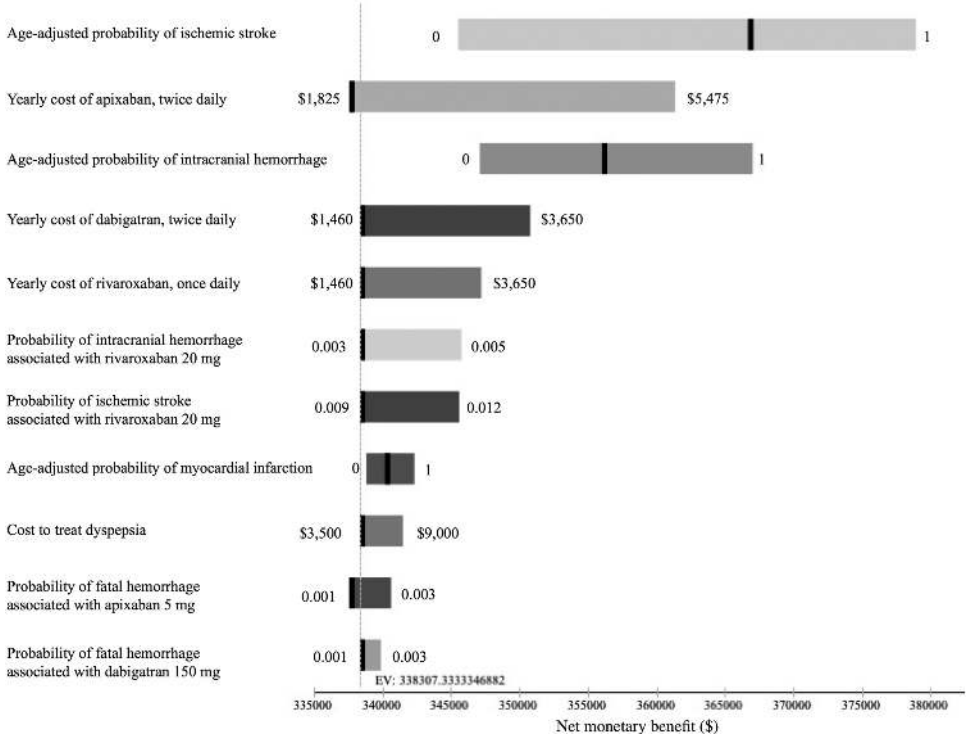

Figure 2. Each horizontal bar in the tornado diagram represents net monetary benefit values expected from a range of values evaluated for each variable. The vertical black line represents a change in the preferred treatment for a given variable being analyzed.

34.9%, rivaroxaban 20 mg in 4.4%, and warfarin was cost-effective in 0% of the iterations.

Discussion

This study used published clinical trial data to build a decision model, and results indicated that for patients ≥70 years of age with an increased risk for stroke ($CHADS_2$ ≥1), normal renal functionality, and no previous contraindications to anticoagulant therapy, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg may be cost-effective substitutes for warfarin in the prevention of stroke prophylaxis. Apixaban 5 mg was the most cost-effective anticoagulant among the 3 NOACs in 45.1% of the iterations conducted in a probabilistic sensitivity analysis (WTP threshold was $50 000 per QALY gained).

Published economic literature to date has solely focused on the comparison of 2 treatments: warfarin compared with one of the NOACs. The results from this study may be interpreted in light of previous analyses conducted from a US perspective. In their original study, Freeman et al[36] reported a baseline ICER of $45 372 per QALY gained for dabigatran 150 mg compared with warfarin. Newly released information prompted the authors to repeat the analysis, incorporating the US cost of dabigatran 150 mg and follow-up RE-LY trial results, which yielded a reduced ICER value of $12 386 per QALY gained.[36] In a similar study conducted by Kamel et al,[13] the authors found the ICER between dabigatran 150 mg and warfarin was $25 000 per QALY gained. The adjusted ICER value reported by Freeman et al and study results from Kamel et al indicate dabigatran is a cost-effective alternative to warfarin, which is a similar finding to this study.

Alternatively, Shah and Gage's model of dabigatran versus warfarin yielded an ICER estimate of $86 000 per QALY

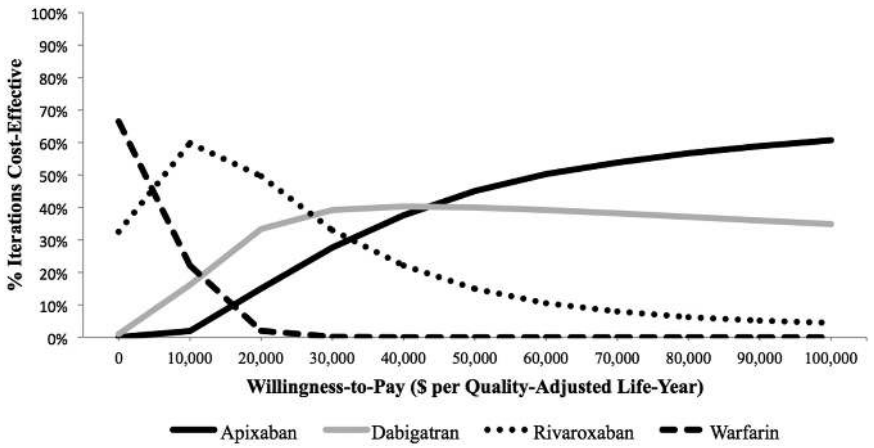

Figure 3. This cost-effectiveness acceptability curve illustrates the probability that a treatment will be cost-effective (percentage of iterations for which the treatment was cost-effective is indicated along the *y* axis) at varying willingness-to-pay thresholds (shown along the *x* axis as the amount, in dollars, a decision maker is willing to pay to achieve an additional quality-adjusted life-year) for a patient.

Table. Projected Costs, QALYs, and ICERs for Patients With Nonvalvular Atrial Fibrillation Receiving Anticoagulation Therapy

	Base Case			Probabilistic Sensitivity Analysis		
	Total Cost	QALY	ICER	Total Cost (SD)	QALY (SD)	ICER
Warfarin	$77 813	7.97	…*	$77 772 ($2223)	7.97 (0.04)	…*
Rivaroxaban, 20 mg	$78 738	8.26	$3190/QALY	$78 719 ($1852)	8.26 (0.06)	$3266/QALY
Dabigatran, 150 mg	$82 719	8.41	$11 150/QALY	$82 705 ($1959)	8.41 (0.07)	$11 211/QALY
Apixaban, 5 mg	$85 326	8.47	$15 026/QALY	$85 337 ($1512)	8.47 (0.06)	$15 130/QALY

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; and SD, standard deviation.
*Warfarin is the reference therapy for the ICER calculation.

gained, a much higher value than those ICERs estimated in this study and in previously discussed studies.[11] The authors attributed the high ICER value to variations in INR management achieved for patients receiving warfarin. Dabigatran has been found in some studies to be a cost-effective alternative to warfarin when INR control was poor, patients were at a high risk of stroke or ICH, and patients were older.[11,13] Although INR control is a determinant of the cost-effectiveness of dabigatran in studies conducted in the United States and United Kingdom, INR management in real-world populations varies, and the time in therapeutic range for patients receiving warfarin is highly variable.[11–13,37] A number of studies have estimated that patients spend from 41% to 72% of their time in the recommended INR range for warfarin.[38–40] Clinical trials for NOACs report time in therapeutic range values within this range, and therefore, INR was not incorporated as a model parameter in this study.[8–10] It is recommended that future studies monitor NOACs in community practices to identify differences in clinical effectiveness compared with warfarin and the time in therapeutic range that patients are able to maintain in the real-world setting.

In contrast to dabigatran, limited cost-effectiveness studies are available for apixaban and rivaroxaban. Lee et al[14] evaluated the cost-effectiveness of rivaroxaban compared with warfarin and reported that the ICER for rivaroxaban was $27 498 per QALY gained. Rivaroxaban was deemed cost-effective in >80% of the Monte Carlo simulations in probabilistic sensitivity analyses using threshold values of $50 000 and $100 000 per QALY gained.[14] Kamel et al[15] conducted a cost-effectiveness analysis of a subgroup from the ARISTOTLE trial, which included patients with a previous stroke or transient ischemic attack. The authors reported ICER of apixaban as $11 400 per QALY gained, concluding it was a cost-effective alternative to warfarin in >60% of the Monte Carlo simulations using a threshold of $50 000 per QALY gained and 81% of the simulations using $100 000 per QALY gained.[15] Similar to dabigatran, both of these studies reported NOACs to be cost-effective compared with warfarin.

Model structure and inputs used in this study are broadly similar to other published analyses; however, several differences exist that may contribute to differences in analysis results. First, dyspepsia was explicitly modeled (probability, utility, and associated costs) as a side effect for patients receiving dabigatran 150 mg in this analysis, but this approach has not always been included.[12,13] Second, mortality adjustments after MI, ischemic stroke, or ICH were integrated as model parameters. Finally, other studies did not explicitly incorporate the cost associated with patients' time for anticoagulation therapy or required visits for INR management.[11–13]

A notable limitation inherent in this study is the need to extract model parameter values from a variety of different sources. Treatment efficacy and adverse events for apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were based on one large clinical trial for each therapy (ARISTOTLE, RE-LY, and ROCKET-AF, respectively). Differences among trial designs, outcome definitions, and patient populations spotlight the challenges with cross-trial comparisons. In addition, it should be kept in mind that use of therapies in actual practice may result in different outcomes from clinical trials because different dosing regimens, monitoring, comorbidities, and inclusion/exclusion criteria may be used in actual practice compared with published clinical trials.[8–10,18] Real-world evaluations of therapy effectiveness should also assess therapy compliance, which was not reported in the clinical trials, to provide essential data for future economic evaluations to incorporate adherence as a model parameter. Furthermore, important information about different subgroups was not available for each drug, including $CHADS_2$ stroke risk score and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) hemorrhage risk score. Conducting head-to-head studies in real-world community practices will also allow for an assessment of the effectiveness of NOACs compared with the already established warfarin. Other sources were used to collect values for costs, utilities, and other adverse events (ie, stroke severity and disability after stroke), which potentially introduce bias into the analysis. Although cost estimates did not directly incorporate discounts, a range of costs was assessed in the probabilistic sensitivity analysis.

Conclusions

The NOACs evaluated in this study were more cost-effective compared with warfarin treatment for stroke prevention in patients with NVAF. Of the 3 NOACs, apixaban 5 mg was the preferred anticoagulant for this population because it was most likely to be the cost-effective treatment option at all WTP thresholds >$40 000 per QALY gained. As additional data emerge from studies evaluating the efficacy in subgroups, side effect profile, and generalizability of NOACs, future analyses will perform a more inclusive evaluation of the cost-effectiveness of NOACs. Important subgroups to integrate into future cost-effectiveness models include strata of $CHADS_2$ stroke risk score, HAS-BLED hemorrhage risk score, renal impairment, and age. Meanwhile, healthcare providers already encounter choices between NOACs and

warfarin in clinical practice for this high-risk population. The findings provided from this study, in combination with results of previously conducted analyses, provide an estimation of the implications of clinician decisions. NOACs are adequate cost-effective alternatives to warfarin for the prevention of stroke prophylaxis in patients with NVAF.

Disclosures

None.

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ONLINE SUPPLEMENT

1. Supplemental Table S1
2. Supplemental References

Supplementary Table S1. Decision model inputs: event probabilities, utilities, and costs.

Annual event probabilities			
	Base-Case	**Range**	**References**
Stroke			
IS			
Apixaban, 5 mg	0.0088	(0.008 -0.010)	1
Dabigatran, 150 mg	0.0091	(0.008 -0.010)	2,3
Rivaroxaban, 20 mg*	0.0110	(0.009 -0.012)	4
Warfarin†	0.0110	(0.009 -0.012)	1-4
Severity of IS, all therapies			
Non-disabling	0.091		5
Minor	0.415		5
Major	0.392		5
Fatal	0.102		5
Hemorrhage			
ICH			
Apixaban, 5 mg	0.0029	(0.002 - 0.004)	1
Dabigatran, 150 mg	0.0031	(0.002 - 0.004)	3
Rivaroxaban, 20 mg*	0.0039	(0.003 - 0.005)	4
Warfarin†	0.0066	(0.006 - 0.008)	1,3,4
ICH severity, all therapies			
Minor	0.17		5
Major	0.41		5
Fatal (within 30 days)	0.42		5
GI hemorrhage			
Apixaban, 5 mg	0.0058	(0.005 - 0.007)	1
Dabigatran, 150 mg	0.0154	(0.005 - 0.025)	3
Rivaroxaban, 20 mg	0.0156	(0.005 - 0.025)	4
Warfarin†	0.0089	(0.008 - 0.010)	1,3,4
Minor hemorrhage			
Apixaban, 5 mg	0.0914	(0.08 - 0.10)	1
Dabigatran, 150 mg	0.1368	(0.12 - 0.15)	2,3
Rivaroxaban, 20 mg	0.7994	(0.07 - 0.09)	4
Warfarin†	0.1118	(0.10 - 0.12)	1-4
Fatal hemorrhage			
Apixaban, 5 mg	0.0018	(0.001 - 0.003)	1
Dabigatran, 150 mg‡	0.0019	(0.001 - 0.003)	1,4
Rivaroxaban, 20 mg	0.0019	(0.001 - 0.003)	4
Warfarin‡	0.0034	(0.002 - 0.005)	1,4
Myocardial Infarction			
Apixaban, 5 mg	0.0049	(0.004 - 0.006)	1
Dabigatran, 150 mg	0.0080	(0.007 - 0.009)	3
Rivaroxaban, 20 mg	0.0071	(0.006 - 0.008)	4
Warfarin†	0.0068	(0.006 - 0.008)	1,3,4
QALY estimates (utilities)			
Atrial Fibrillation (ICD-9 427)	0.81	(0.70-0.90)	6
Decrement for age	-0.0003	(-0.0002 - -0.0001)	6
Decrement for anticoagulation	-0.0105	(-0.011 - 0.009)	7
Decrement for ischemic stroke (CCC 109)	-0.1393	(-0.150 - 0.120)	8
Neurological event (IS and ICH) with residua			
Minor	-0.2916	(-0.30 - -0.28)	9
Major	-0.4455	(-0.46 - -0.43)	9
Decrement for MI (ICD-9 410)	-0.1351	(-0.145 - 0.120)	6

Supplementary Table S1 (continued). Decision model inputs: event probabilities, utilities, and costs.			
Decrement for GI hemorrhage	-0.0486	(-0.060 - 0.030)	10
Decrement for minor hemorrhage (1 week)	-0.0031	(-0.004 - 0.002)	11
Decrement for dyspepsia§	-0.0032	(-0.004 - 0.002)	10
Costs			
One-time events costs			
IS, no residua (ICD-9 434.91, DRG 66)	$9,503.39	($4,000 - $16,000)	12
Minor IS (ICD-9 434.91, DRG 65)	$10,669.51	($4,000 - $16,000)	12
Major IS (ICD-9 434.91, DRG 64)	$13,337.50	($10,000 - $25,000)	12
ICH (ICD-9 430-432)	$20,790.34	($15,000 - $65,000)	12
MI (ICD-9 410.71)	$20,323.17	($10,000 - $45,000)	12
GI hemorrhage (ICD-9 578.9)	$10,201.12	($5,000 - $15,000)	12
Dyspepsia[4] (ICD-9 536.8)	$6,648.00	($3,500 - $9,000)	12
Minor hemorrhage (CPT 99213)	$83.94	($0 - $200)	13, 14
Death	$10,000.00	($0 - $20,000)	5, 14
Long-term event costs, yearly			
Minor ischemic stroke	$20,880.24	($12,000 - $48,000)	15
Major ischemic stroke	$64,629.36	($24,000 - $102,000)	15
ICH	$96,926.04	($24,000 - $120,000)	15
MI	$3,638.40	($1,568.28 - $7,267.68)	16
Therapy costs, yearly			
Apixaban 5 mg	$3,920.10	($1,825 - $5,475)	17
Dabigatran 150 mg	$2,664.50	($1,460 - $3,650)	18
Rivaroxaban 20 mg	$2,660.85	($1,460 - $3,650)	18
Warfarin	$164.25	($109.90 - $730)	18
Warfarin associated costs, yearly			
INR testing (monthly) (CPT 85610)	$83.80	($27.93 - $167.60)	13
Minimal established visits (monthly) (CPT 99211, 99212)	$408.00	($136 - $816)	13
Economic value of patient time for INR test	$1,750.92	($583.64 - $1,750.92)	19
Non-warfarin associated costs, yearly			
Minimal established visit (every 3 months) (CPT 99211, 99212)	$136.00	($68 - $408)	13
Economic value of patient time for visit	$229.36	($114.68 - $688)	19
Cost and utility discounting rate, %	3	(0 - 5)	20

CPT = Current Procedural Terminology; DRG = Diagnostic Related Group; ICH = intracranial hemorrhage; INR = International Normalized Ratio; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year

* Summed ischemic and unspecified strokes for rivaroxaban 20 mg, once daily.

† Warfarin event rates were pooled warfarin events from ARISTOTLE, RE-LY, and ROCKET-AF.

‡ Fatal hemorrhage was not reported in the dabigatran trial (RE-LY). A weighted average was calculated using ARISTOTLE (apixaban 5 mg) and ROCKET-AF (rivaroxaban 20 mg).

§ Dyspepsia events and costs only for patients receiving dabigatran 150 mg, twice daily.

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