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ORIGINAL RESEARCH

Cost-effectiveness of edoxaban versus rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in the US

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Background: Understanding the value of new anticoagulation therapies compared with existing therapies is of paramount importance in today's cost-conscious and efficiency-driven health care environment. Edoxaban and rivaroxaban for stroke prevention in nonvalvular atrial fibrillation (NVAF) patients with $CHADS_2$ scores ≥2 have been evaluated in pivotal trials versus warfarin. The relative value of edoxaban versus rivaroxaban would be of interest to health care stakeholders and patients who prefer a once-daily treatment option for long-term stroke prevention in NVAF.

Objective: To evaluate the relative cost-effectiveness of two once-daily regimens of novel oral anticoagulation therapy – edoxaban (60 mg/30 mg dose-reduced) versus rivaroxaban (20 mg/15 mg dose-reduced) – for stroke prevention in NVAF patients from a US health-plan perspective.

Materials and methods: A Markov model simulated lifetime risk and treatment of stroke, systemic embolism, major bleeding, clinically relevant nonmajor bleeding, myocardial infarction, and death in NVAF patients treated with edoxaban or rivaroxaban. Efficacy and safety data were derived from a network meta-analysis that utilized data from patients enrolled in ENGAGE AF-TIMI 48 and ROCKET-AF. Health care cost and utility data were obtained from published sources. Incremental cost-effectiveness ratios of <US$50,000, $50,000–$150,000, and >$150,000 per quality-adjusted life year (QALY) gained were used as thresholds for "highly cost-effective", "cost-effective", and "not cost-effective" treatment options, respectively, as per American Heart Association/American College of Cardiology guidelines.

Results: Edoxaban was dominant relative to rivaroxaban, such that it was associated with lower total health care costs and better effectiveness in terms of QALYs in the base-case analysis. Results were supported by probabilistic sensitivity analyses that showed edoxaban as either dominant or a highly cost-effective alternative (incremental cost-effectiveness ratio <$50,000) to rivaroxaban in 88.4% of 10,000 simulations.

Conclusion: Results of this study showed that the once-daily edoxaban (60 mg/30 mg dose-reduced) regimen is a cost-saving or highly cost-effective treatment relative to rivaroxaban (20 mg/15 mg dose-reduced) for stroke prevention in NVAF patients with $CHADS_2$ ≥2.

Keywords: edoxaban, rivaroxaban, cost-effectiveness, nonvalvular atrial fibrillation, oral anticoagulation, stroke, NOAC, SPAF, economic model, economic analysis

Introduction

Atrial fibrillation (AF) affects approximately 2.3 million people in the US, and is associated with a fivefold increase in stroke compared to patients without AF.[1–3] Oral anticoagulation with the vitamin K antagonist (VKA) warfarin has been the standard of care for stroke prevention in people with nonvalvular AF (NVAF).[4–6] However, VKAs

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have numerous limitations, including a variety of food and drug interactions, slow onset of action, high discontinuation rates, narrow therapeutic range, and variable patient dose response, which require routine laboratory monitoring.[6–8] In recent years, several non-VKA novel oral anticoagulants (NOACs; dabigatran, rivaroxaban, apixaban, and edoxaban) have been approved in the US as alternatives to warfarin for stroke prevention in NVAF patients. These newer agents do not require routine monitoring, have faster onset of action, bear fewer food and drug interactions compared to VKA therapy, and offer the promise to provide practical and more convenient oral anticoagulation (OAC) treatment.[6–8]

As new OAC therapies come to market, the need to understand their "value" is of paramount importance in today's cost-conscious health care environment. Recently, the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines proposed the inclusion of cost-effectiveness/value assessment and recommendations in practice guidelines and performance measures.[9] The cost-effectiveness of warfarin therapy compared to aspirin/no therapy for stroke-prevention NVAF anticoagulation has been well established.[10–12] Consensus has emerged from the large and ever-growing body of economic literature about the comparative costs and cost-effectiveness of anticoagulation therapies for stroke prevention in NVAF patients that NOACs are cost-effective alternatives to warfarin for stroke prevention in NVAF.[13–19] While data on the particular value of one NOAC versus another NOAC are scant, this is a subject of growing interest to health care decision makers.

Edoxaban, a factor-Xa inhibitor, was approved in 2015 by the US Food and Drug Administration as a once-daily NOAC for stroke prevention in NVAF.[20] Data from the Phase III pivotal trial ENGAGE AF-TIMI 48 have shown that a once-daily edoxaban 60 mg regimen was noninferior in the risk of stroke/systemic embolism (SE) when compared to warfarin, with significantly lower risk of major bleeding (Daiichi Sankyo, data on file, 2013).[21] Among patients with creatinine clearance ≤95 mL/min, edoxaban reduced the risk of stroke/SE by 32%, with lower risk of major bleeding by 16% relative to warfarin.[20] Although no head-to-head randomized controlled studies have evaluated the efficacy and safety of edoxaban in direct comparison with other NOACs, several network meta-analyses have been presented or published that indirectly compared the efficacy and safety of NOACs (including edoxaban).[22–28]

The objective of this study was to evaluate the relative cost-effectiveness of two once-daily NOAC-therapy options – edoxaban (60 mg/30 mg dose-reduced) versus rivaroxaban (20 mg/15 mg dose-reduced) – for stroke prevention in NVAF patients from a US health-plan perspective. We were interested in comparing edoxaban to rivaroxaban for multiple reasons. First, rivaroxaban is the most commonly prescribed NOAC in the US and dominates the NVAF stroke-prevention market.[29] Second, the pivotal trials of edoxaban – ENGAGE AF-TIMI 48 (Daiichi Sankyo, data on file, 2013)[21] and rivaroxaban ROCKET-AF[30] – were more similar in study design than the trials for other NOACs, as both studies utilized once-daily treatment and limited enrollment to patients with $CHADS_2$ scores ≥2. Finally, we believed the relative value of edoxaban versus rivaroxaban would be of interest to health care stakeholders and patients who prefer a once-daily treatment option for chronic stroke prevention in NVAF.

Materials and methods

Model design

A health-state transition (semi-Markov) model was developed using Microsoft Excel 2013. The Markov modeling approach has been used for other published economic evaluations of NOAC therapy in recent years, as reviewed and summarized in recent publications.[13,14,16,17] The economic model compared two hypothetical NVAF patient cohorts initiating treatment with either once-daily edoxaban (60 mg/30 mg dose-reduced) regimen or once-daily rivaroxaban (20 mg/15 mg dose-reduced) for stroke prevention on a chronic basis. The patient cohorts simulated in the model consisted of $CHADS_2$ score ≥2 patients (consistent with the study populations in ENGAGE AF-TIMI 48 (Daiichi Sankyo, data on file, 2013)[21] and ROCKET-AF[30]) with a starting age of 72 years (the median ages of patients in ENGAGE AF-TIMI 48 and ROCKET-AF were 72 years and 73 years, respectively). These patients transitioned between discrete health states in the model to replicate the natural course of changes in health status on a monthly basis over a remaining lifetime horizon (up to maximum age of 100 years).

A schematic presenting the model health states and transition pathways is shown in Figure 1. All patients begin in the NVAF health state. During any given model cycle, patients can either remain in their current health state, experience a clinical event, or die. Consistent with other published models evaluating OAC therapy, the following clinical events were included in the model: ischemic stroke (first and recurrent), transient ischemic attack (TIA), SE, hemorrhagic stroke (first and recurrent), other intracranial hemorrhage (ie, subdural and epidural hematoma), major gastrointestinal bleed, other major nongastrointestinal extracranial bleed, clinically

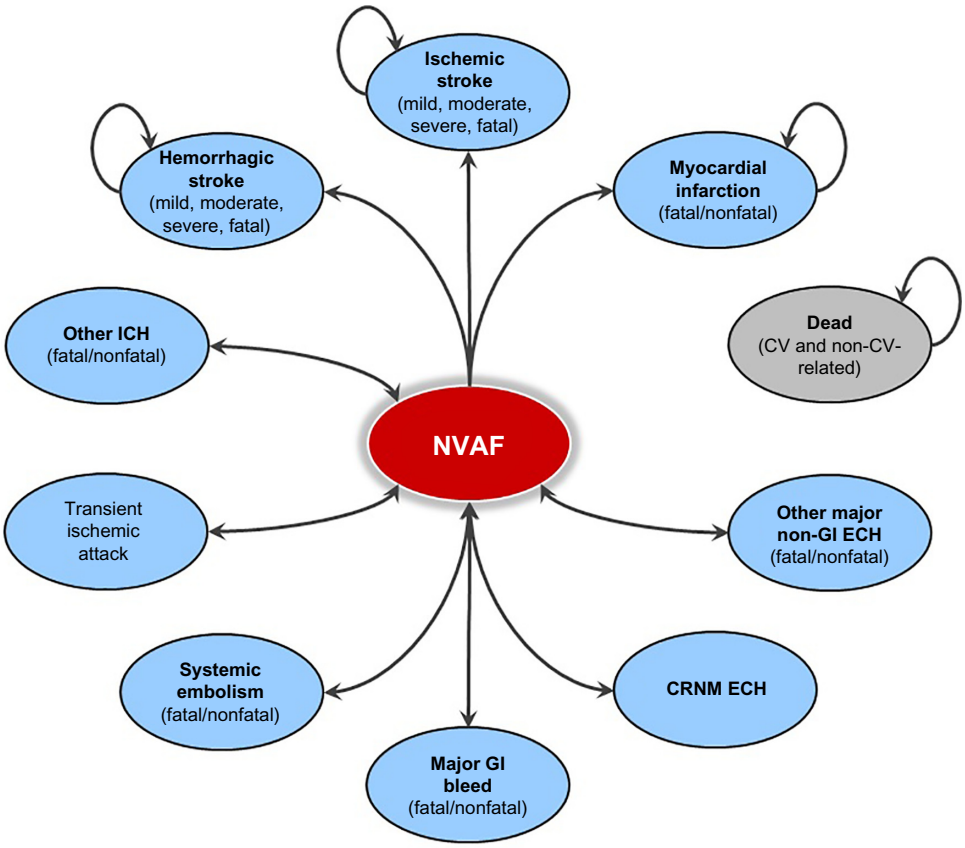

Figure 1 Health states in the economic model.
Abbreviations: CRNM, clinically relevant nonmajor; CV, cardiovascular; ECH, extracranial hemorrhage; ICH, intracranial hemorrhage; GI, gastrointestinal; NVAF, nonvalvular atrial fibrillation.

relevant nonmajor extracranial bleed, myocardial infarction (MI), event-related death, and death from other causes. Also consistent with other models,[31,32] both ischemic stroke and hemorrhagic stroke were modeled as closed health states, such that after experiencing the first stroke patients would transition to a post-stroke state where they could experience only stroke recurrence or die. Nonfatal stroke events were stratified by severity: mild stroke (modified Rankin score 0–2), moderate stroke (modified Rankin score 3–4), and severe stroke (modified Rankin score 5). Patients experiencing an MI entered a post-MI health state where they were allowed to experience other clinical events, including subsequent MI. The post-stroke and post-MI states were included to account for residual deficits as a result of these events. All other clinical events were modeled as transient health states, such that patients who survived an event would return to the NVAF "well" state without any residual deficit. All clinical events have the potential of being fatal, except TIA and clinically relevant nonmajor bleeds. Institutional Review Board (IRB) approval was not required for this economic model using simulated cohorts of patients.

Clinical event risks and health state-transition probabilities

Warfarin served as the reference treatment in the Markov model, and its transition probabilities were based on the warfarin event rates stratified by $CHADS_2$ score (as per the format of the data from the overall population in ENGAGE AF-TIMI 48 (Daiichi Sankyo, data on file, 2013)[21] and reflecting differing underlying risk of thrombotic events) and consolidated into a single value weighted by $CHADS_2$-score distribution (Table 1). The rationale for this was supported by the data from the pivotal trials of edoxaban (Daiichi Sankyo, data on file, 2013)[21] and rivaroxaban,[30] which showed that their relative efficacy versus warfarin did not differ by $CHADS_2$ score, so there was no need to stratify the thrombotic event risks by $CHADS_2$ score (Table 1). Consistent with the approach taken by other published cost-effectiveness analyses, the risk of ischemic stroke, TIA, MI, and bleeding events (including hemorrhagic stroke) in our model increased with age, using factors of 1.40,[33–36] 1.73,[37] 1.30,[31,32,34,38,39] and 1.97,[31,32,34,36,40] respectively, for each decade increase in age. The distribution of stroke severity was based on data from ENGAGE AF-TIMI 48 (Daiichi Sankyo, data on file, 2013).[21]

Table 1 Patient characteristics, clinical event rates, and stroke-severity distribution

Patient characteristics[a]	
Starting age (years)	72
$CHADS_2$ distribution	
0	0
1	0
2	46.81%
3	30.58%
4	15.57%
5	5.81%
6	1.23%

Clinical event rates								
	Warfarin (rate per 100 person-years by $CHADS_2$ score)[a]					**Hazard ratio in reference to warfarin**		
	$CHADS_2$ =2	**$CHADS_2$ =3**	**$CHADS_2$ =4**	**$CHADS_2$ =5**	**$CHADS_2$ =6**	**Edoxaban**[b]	**Rivaroxaban**[b]	**Second-line aspirin therapy**[c]
Ischemic stroke	0.49	0.94	1.87	2.02	2.45	0.99	1.05	1.62
Hemorrhagic stroke	0.41	0.59	0.57	0.47	0	0.59	0.68	0.84
TIA	0.42	0.31	0.71	0.59	1.25	1.07	1.05	1.56
Other ICH	0.18	0.39	0.79	0.35	1.83	0.47	0.62	0.51
MI	0.45	0.74	0.93	1.19	3.10	0.91	0.87	1.42
SE	0.04	0.11	0.13	0.24	0	0.61	1.08	1.77
Major GI bleed	0.92	1.37	1.91	1.18	2.47	1.24	1.44	1.14
Major non-GI ECH	1.30	1.28	1.42	1.66	4.95	0.62	1.03	1.14
CRNM ECH	9.42	10.28	11.27	11.71	16.63	0.84	1.05	1.04

Stroke-severity distribution[a]		
	Ischemic stroke	**Hemorrhagic stroke**
Mild	58.6%	32.8%
Moderate	20.4%	16.4%
Severe	7.3%	6.7%
Fatal	13.7%	44%

Notes: [a]Daiichi Sankyo, data on file, 2013; γ-distribution for all values used in the probabilistic sensitivity analysis (limit values available from the authors upon request). [b]Fernandez et al;[22] lognormal distribution for all values used in the probabilistic sensitivity analysis (limit values available from the authors upon request). [c]Adapted with permission from Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost*. 2011;105(5):908–919;[41] data from Hart et al;[42] lognormal distribution for all values used in the probabilistic sensitivity analysis (limit values available from the authors upon request).

Abbreviations: CRNM, clinically relevant nonmajor; ECH, extracranial hemorrhage; GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischemic attack.

Event rates for patients receiving edoxaban or rivaroxaban were calculated based on risk ratios relative to warfarin obtained from a network meta-analysis of data from Phase III pivotal trials where rivaroxaban and edoxaban were compared to warfarin (Table 1).[22] Patients either continue OAC therapy or discontinue OAC therapy temporarily or permanently at any time. Patients who discontinue edoxaban and rivaroxaban were assumed in the model to receive aspirin therapy. Event rates for second-line aspirin therapy were obtained from a published NOAC cost-effectiveness modeling study that used data from a meta-analysis of clinical trials (Table 1).[41,42] The risk of recurrent ischemic or hemorrhagic stroke was independent of treatment, and was set to 2.7% for both the edoxaban- and rivaroxaban-treatment arms to be consistent with other recently published OAC-therapy economic evaluations.[31,32,43]

Mortality

Case-fatality rates for modeled clinical events are presented in Table 2. Cardiovascular mortality outside clinical events explicitly represented in the model was separately accounted for using a cardiovascular mortality risk-ratio estimate of 0.87 for both edoxaban versus warfarin and for rivaroxaban versus warfarin, as estimated from the network meta-analysis.[22] In addition to event-related mortality, allowance was made in the model for patients to die from other causes. This underlying mortality risk unrelated to clinical events was based on age-specific US life tables.[44] A multiplier of 1.34 was applied to the general mortality rate to account for the increased mortality risk for NVAF patients relative to the general population.[31,32] In addition, mortality risk for patients who survived clinical events was further increased according to the mortality-risk multipliers presented in Table 2.

Table 2 Mortality estimates for model inputs

Fatality rates for clinical events (other than ischemic stroke and hemorrhagic stroke)[a]		
	Fatality rate	**Sources**
Other ICH	13%	Lip et al,[31] Dorian et al[32]
MI	13.1%	Lip et al,[31] Dorian et al[32]
SE	9.4%	Lip et al,[31] Dorian et al[32]
Major GI bleed	2%	Lip et al,[31] Dorian et al[32]
Major non-GI ECH	2%	Lip et al,[31] Dorian et al[32]
Mortality risk multipliers for chronic health states[b]		
	Multiplier	**Sources**
NVAF	1.34	Lip et al,[31] Dorian et al[32]
Ischemic stroke		
Mild	3.18	Lip et al,[31] Dorian et al[32]
Moderate	5.84	Lip et al,[31] Dorian et al[32]
Severe	15.75	Lip et al,[31] Dorian et al[32]
Hemorrhagic stroke		
Mild	3.18	Lip et al,[31] Dorian et al[32]
Moderate	5.84	Lip et al,[31] Dorian et al[32]
Severe	15.75	Lip et al,[31] Dorian et al[32]
MI	3.36	Lip et al,[31] Dorian et al[32]
SE	1.34	Assumed to be same as NVAF

Notes: [a]Triangular distribution for all values used in the probabilistic sensitivity analysis (limit values available from the authors upon request); [b]lognormal distribution for all values used in the probabilistic sensitivity analysis (limit values available from the authors upon request).
Abbreviations: ECH, extracranial hemorrhage; GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; NVAF, nonvalvular atrial fibrillation; SE, systemic embolism.

Treatment discontinuation

All patients were assumed to discontinue NOAC therapy temporarily for the model cycle (1 month) after an acute clinical event occurred. In addition, patients could continue OAC therapy, or discontinue OAC therapy temporarily or permanently in future model cycles subsequent to clinical events. Assumptions about permanent discontinuation of OAC therapy following clinical events mirrored those used in other published economic evaluations.[31,32] All patients discontinue NOAC therapy permanently following hemorrhagic stroke or MI, which is consistent with assumptions used in other models.[31,32] Fifty-six percent of patients discontinue NOAC therapy permanently and 44% temporarily stop therapy for 1 month after intracranial hemorrhage (other ICH).[31,32] Following a major extracranial hemorrhage, 25% of patients will discontinue NOAC therapy permanently, and 75% will stop therapy temporarily for 1 month.[31,32] Patients who discontinue NOAC therapy permanently were assumed to receive aspirin.[31,32] In addition, the model assumed an annual permanent treatment discontinuation rate of 5% unrelated to clinical events to account for medication nonadherence.

Utilities and disutilities

NVAF patients entered the model with a baseline utility of 0.836, consistent with baseline utility for patients enrolled in ENGAGE-AF TIMI 48 assessed by the EQ-5D™, a standardized instrument for use as a measure of health outcome.[45] Disutility associated with all clinical events was applied for the full 1-month cycle in which an acute clinical event occurred; otherwise, disutility associated with chronic health states was applied across the full duration of time in which a patient remained in a particular chronic health state (Table 3).

Costs

The wholesale acquisition cost of edoxaban (US$9.24 per day for both 60 mg and 30 mg) and rivaroxaban ($10.49 per

Table 3 Health state utilities and disutilities

	Utility/disutility value[a]	**Sources**
NVAF	0.836	Magnuson et al[45]
Ischemic stroke (acute and chronic)		
Mild	–0.209	Canestaro et al,[73] Sullivan et al[74]
Moderate	–0.2926	Canestaro et al,[73] Sullivan et al[74]
Severe	–0.51	Canestaro et al,[73] Sullivan et al[74]
Hemorrhagic stroke (acute and chronic)		
Mild	–0.209	Canestaro et al,[73] Sullivan et al[74]
Moderate	–0.2926	Canestaro et al,[73] Sullivan et al[74]
Severe	–0.51	Canestaro et al,[73] Sullivan et al[74]
TIA	–0.013	Freeman et al,[39] Coyle et al[64]
Other ICH	–0.1511	Lip et al,[31] Dorian et al,[32] Sullivan et al[75]
MI (acute and chronic)	–0.1087	Canestaro et al[73]
SE (acute and chronic)	–0.1087	Assumed equal to MI
Major GI bleed	–0.1511	Lip et al,[31] Dorian et al,[32] Sullivan et al[75]
Major non-GI ECH	–0.1511	Lip et al,[31] Dorian et al,[32] Sullivan et al[75]
CRNM ECH	–0.0582	Lip et al,[31] Dorian et al,[32] Sullivan et al[75]
NOAC or aspirin use	–0.002	Lip et al,[31] Dorian et al[32]

Notes: [a]Triangular distribution for all values used in the probabilistic sensitivity analysis, except for chronic MI and CRNM ECH, where normal distribution was used (limit values available from the authors upon request).
Abbreviations: CRNM, clinically relevant nonmajor; ECH, extracranial hemorrhage; GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; NOAC, novel oral anticoagulant; NVAF, nonvalvular atrial fibrillation; SE, systemic embolism; TIA, transient ischemic attack.

Table 4 Cost inputs

Drug costs (2015 US$)			
	Monthly cost		**Sources**
Edoxaban 60 mg, 30 mg	$277.20		First Databank[46]
Rivaroxaban 20 mg, 15 mg	$314.70		First Databank[46]
Aspirin	$2.00		Assumption
Clinical event costs (2014 US$)			
	Acute cost (per episode)[a]	**Monthly maintenance cost[b]**	**Sources**
Ischemic stroke			
Mild	$18,836	$943	Canestaro et al,[73] Eckman et al,[76] Vilain et al[77]
Moderate	$21,943	$2,575	Canestaro et al,[73] Eckman et al,[76] You[78]
Severe	$28,192	$5,593	Canestaro et al,[73] Eckman et al,[76] You[78]
Fatal	$28,192	–	Canestaro et al,[73] Eckman et al[76]
Hemorrhagic stroke			
Mild	$20,631	$943	Canestaro et al,[73] Eckman et al,[76] Vilain et al[77]
Moderate	$29,178	$2,575	Canestaro et al,[73] Eckman et al,[76] You[78]
Severe	$37,725	$5,912	Canestaro et al,[73] Eckman et al,[76] You[78]
Fatal	$37,725		Canestaro et al,[73] Eckman et al[76]
TIA	$3,788	–	Computed as per 2011 CMS Medicare and Medicaid reimbursement rate for MS-DRG 69, inflated to 2014 US$, and multiplied by 1.2 to account for physician fees
Other ICH	$21,964	–	Canestaro et al,[73] Eckman et al[76]
MI	$19,151	$313	Freeman et al,[39] Canestaro et al,[73] Harrington et al[57]
SE	$21,184	–	Canestaro et al,[73] Eckman et al[76]
Major GI bleed	$7,979	–	Agency for Healthcare Research and Quality[47] (computed from all-age mean cost for DRG 378)
Major non-GI ECH	$12,064	–	Canestaro et al,[73] Eckman et al[76]
CRNM ECH	$1,016	–	Magnuson et al[45]

Notes: [a]Lognormal distribution for all values used in the probabilistic sensitivity analysis, except for major non-GI ECH, where triangular distribution was used (limit values available from the authors upon request); [b]triangular distribution for all values used in the probabilistic sensitivity analysis (limit values available from the authors upon request).

Abbreviations: CRNM, clinically relevant nonmajor; DRG, diagnosis-related group; ECH, extracranial hemorrhage; GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; MS, Medicare severity; SE, systemic embolism; TIA, transient ischemic attack; CMS, Centers for Medicare & Medicaid Services.

day for both 20 mg and 15 mg) were used in the analysis.[46] Health care expenditures associated with each health state in the model were derived from published literature, diagnosis-related group data from the Healthcare Cost and Utilization Project,[47] and from Centers for Medicare & Medicaid Services (CMS) fee schedules, adjusted where necessary to 2014 levels using the "Medical care" component of the US Consumer Price Index (Table 4). Future costs and life years (LYs) and quality-adjusted LYs (QALYs) were discounted by 3% annually after the first year, as recommended by pharmacoeconomic guidelines published by the Academy of Managed Care Pharmacy.[48]

Analyses

The cost-effectiveness of edoxaban relative to rivaroxaban was assessed using an incremental cost-effectiveness ratio (ICER), which is calculated as the incremental cost per QALY gained. ICERs of <$50,000, $50,000–$150,000, and >$150,000 per QALY gained were proposed as thresholds for "high value/highly cost-effective", "intermediate value/cost-effective", and "low value/not cost-effective" treatment options, respectively, as per the American Heart Association/American College of Cardiology statement on cost/value methodology in clinical practice guidelines and performance measures.[9]

Probabilistic sensitivity analysis, which allows all model parameters to be varied simultaneously, was conducted to test the robustness of model parameter values and their impact on the ICERs. Second-order Monte Carlo simulation with 10,000 iterations where the value of each model parameter was randomly sampled from the probability distribution (either normal, γ-, lognormal, or triangular distribution, as uniquely determined for each type of model parameter) of base-case value was performed. Results were depicted on a cost-effectiveness plane and transformed into a cost-effectiveness acceptability curve. In addition, a series of one-way sensitivity analyses was performed to determine the independent impact of key model parameters on model

results. The mean starting age of the cohort was varied from 60 years to 80 years. The acquisition cost of edoxaban was varied ±13.5% to match the acquisition cost of rivaroxaban on the upper end of the bound, while all clinical event costs were varied ±10% and all utility decrements varied ±25%, as is typically done in modeling sensitivity analyses. An additional one-way sensitivity analysis was performed where clinical events were varied from the lower and upper bounds of their 95% confidence intervals.

Results

Base-case analysis

In the base-case analysis, while the estimated lifetime mean number of thrombotic events per patient was similar between treatment groups, the mean number of hemorrhagic events was lower for edoxaban relative to rivaroxaban (Table 5). These findings resulted in a numerically higher mean number of QALYs for edoxaban (7.299 versus 7.238), and lower mean total health care cost for edoxaban than rivaroxaban ($45,358 versus $49,472 per patient) (Table 5). Therefore, edoxaban was economically dominant over rivaroxaban in the base-case analysis. Across both therapies, about 24% of total health care cost was attributable to acute events, 31%

Table 5 Analysis results

Variable	Edoxaban	Rivaroxaban
Number of events (per cohort of 100 patients)		
Ischemic stroke	17.3	17.6
Recurrent ischemic stroke	2.1	2.1
Hemorrhagic stroke	4.0	4.4
Recurrent hemorrhagic stroke	0.4	0.4
TIA	6.8	6.7
Other ICH	2.4	2.9
MI	8.5	8.3
SE	1.6	1.9
Major GI bleed	20.0	24.6
Major non-GI ECH	10.6	18.9
CRNM ECH	130.1	153.4
Event-related death	6.8	7.3
Non-event-related death	93.2	92.7
Health outcomes (per cohort of 100 patients)[a]		
LYs	899.2	892.8
QALYs	729.9	723.8
Costs (per cohort of 100 patients), US$[a]		
Acute events	1,055,006	1,219,727
Chronic health states	1,456,128	1,499,310
Drug treatment	2,024,687	2,228,136
Total	4,535,821	4,947,173
Base-case cost-effectiveness analysis (per cohort of 100 patients)[a]		
ΔCost (edoxaban vs rivaroxaban)	–$411,352	
ΔQALYs (edoxaban vs rivaroxaban)	6.1	
ICER	Edoxaban dominant[b]	

Notes: [a]Discounted at 3% per annum; [b]edoxaban confers greater effectiveness at lower cost, as indicated by the positive ΔQALY and negative Δcost values versus rivaroxaban.

Abbreviations: CRNM, clinically relevant nonmajor; ECH, extracranial hemorrhage; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio; ICH, intracranial hemorrhage; MI, myocardial infarction; QALYs, quality-adjusted life years; SE, systemic embolism; TIA, transient ischemic attack; LYs, life years.

Table 6 Results of one-way sensitivity analyses

Analysis variables	ΔCost and ΔQALYs versus rivaroxaban	
	Low value	High value
Base-case analysis (edoxaban vs rivaroxaban)	Edoxaban dominant[a] ΔCost = –US$4,114 ΔQALYs = +0.061	
Acquisition cost of edoxaban ±13.5%	Edoxaban dominant ΔCost = –$6,845 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$1,382 ΔQALYs = +0.061
Mean starting age of cohort (60 years/ 80 years)	Edoxaban dominant ΔCost = –$4,945 ΔQALYs = +0.067	Edoxaban dominant ΔCost = –$3,481 ΔQALYs = +0.049
Cost of ischemic stroke ±10%	Edoxaban dominant ΔCost = –$4,085 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,142 ΔQALYs = +0.061
Cost of hemorrhagic stroke ±10%	Edoxaban dominant ΔCost = –$4,072 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,155 ΔQALYs = +0.061
Cost of SE ±10%	Edoxaban dominant ΔCost = –$4,108 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,119 ΔQALYs = +0.061
Cost of major GI bleed±10%	Edoxaban dominant ΔCost = –$4,083 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,144 ΔQALYs = +0.061
Cost of non-GI ECH ±10%	Edoxaban dominant ΔCost = –$4,032 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,195 ΔQALYs = +0.061
Cost of CRNM ECH ±10%	Edoxaban dominant ΔCost = –$4,094 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,133 ΔQALYs = +0.061
Utility decrement of ischemic stroke ±25%	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.061
Utility decrement of hemorrhagic stroke ±25%	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.059	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.062
Utility decrement of SE ±25%	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.061	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.061
Utility decrement of major GI bleed ±25%	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.060	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.061
Utility decrement of non-GI ECH ±25%	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.060	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.061
Utility decrement of CRNM ECH ±25%	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.060	Edoxaban dominant ΔCost = –$4,114 ΔQALYs = +0.061

Note: [a]Edoxaban confers greater effectiveness at lower cost, as indicated by the positive ΔQALY and negative Δcost values versus rivaroxaban.

Abbreviations: CRNM, clinically relevant nonmajor; ECH, extracranial hemorrhage; GI, gastrointestinal; QALYs, quality-adjusted life years; SE, systemic embolism.

was attributable to time spent in chronic health states, and the remaining 45% of total costs came from the OAC drugs themselves.

Sensitivity analyses

In one-way sensitivity analyses, when the acquisition cost of edoxaban was increased by 13.5% to the same level as rivaroxaban, at $10.49 per day, edoxaban remained dominant over rivaroxaban, with cost savings of $1,382 per patient (mean per patient cost of $48,090 edoxaban versus $49,472 rivaroxaban) and higher QALYs (7.299 versus 7.238) (Table 6). The cost-effectiveness of edoxaban relative to rivaroxaban was not sensitive to age. Edoxaban remained the economically dominant therapy versus rivaroxaban when cost parameters were varied ±10% from their base values and utilities were varied ±25% from their base values. Although not reported in Table 6, edoxaban also remained the economically dominant therapy versus rivaroxaban when risks of clinical events were varied from the lower and upper bounds of their 95% confidence intervals.

In the Monte Carlo probabilistic sensitivity analysis with 10,000 model iterations, in which all model parameters were randomly sampled from their distributions, edoxaban yielded an ICER <$50,000 per QALY gained in 88.4% of the 10,000 simulations (Figure 2).

Discussion

This study assessed the cost-effectiveness of edoxaban versus rivaroxaban as treatment for stroke prevention among patients with NVAF from a US health-plan perspective. Our analysis found that edoxaban was associated with greater quality-adjusted life expectancy at lower total health care costs than rivaroxaban. This finding of economic dominance was robust under a series of one-way sensitivity analysis where event-treatment cost and health state-utility estimates were varied. The cost-effectiveness of edoxaban relative to rivaroxaban for stroke prevention was further supported by probabilistic sensitivity analysis where all model parameters were randomly sampled from their distribution, and ICER estimates fell below $50,000 per QALY gained in 88.4% of model simulations. These results were primarily driven by the lower number of nonintracranial major and clinically relevant nonmajor bleeding events in the edoxaban cohort, resulting in lower bleeding-related health care cost and bleeding-related quality-of-life impairment and mortality.

As new OAC therapies come to market, the need to understand their value compared with existing therapies is of paramount importance in today's cost-conscious and efficiency-driven health care environment. There have been numerous published cost-effectiveness analyses comparing edoxaban and rivaroxaban with warfarin.[34,45,49–59] These studies have consistently showed that edoxaban and rivaroxaban are cost-effective relative to warfarin. However, few studies have set out to assess the particular value or cost-effectiveness of one NOAC versus another NOAC, and where such analyses have been conducted (albeit using an indirect comparison approach), there has been substantial inconsistency and contradiction between their findings.[13,17]

Edwards et al[60] found rivaroxaban to be economically dominant over dabigatran in the UK setting, but Kansal et al[58] found dabigatran to dominate rivaroxaban in the Canadian setting. In the Canadian model by Wells et al,[61] rivaroxaban

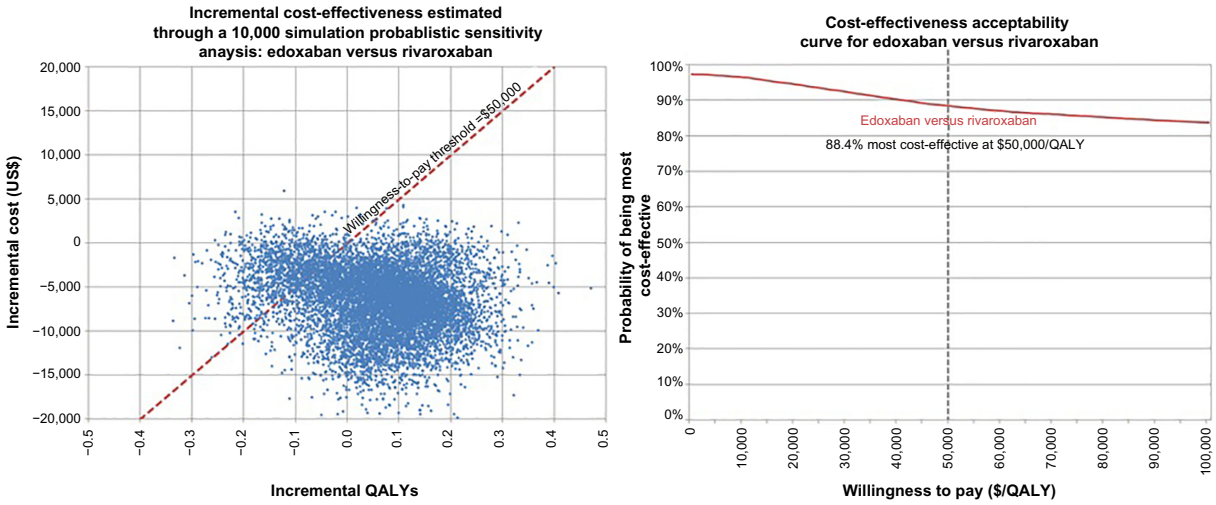

Figure 2 Results of the probabilistic sensitivity analysis.
Abbreviation: QALYs, quality-adjusted life years.

was dominated by apixaban, yet apixaban is either a dominant strategy or a dominated strategy compared with dabigatran, depending on the dose of dabigatran evaluated. In the UK model by Lip et al,[31] apixaban was cost-effective relative to both rivaroxaban and dabigatran, with ICERs well below the commonly assumed threshold of £20,000 per QALY gained. Similarly, Lanitis et al[62] reported that in the French setting, apixaban dominates both rivaroxaban and dabigatran, with rivaroxaban either dominating or having favorable ICERs compared with dabigatran. By contrast, the UK model by Zheng et al[63] showed dabigatran to be economically dominant over both rivaroxaban and apixaban, while Coyle et al[64] found both apixaban and dabigatran dominating rivaroxaban in the Canadian setting. None of these studies were from the perspective of US health care payers. In consideration of the fact that rivaroxaban is the most commonly prescribed NOAC in the US, the relative value of edoxaban relative to rivaroxaban is an important consideration for clinicians and payers. To the best of our knowledge, this is the first study formally to evaluate the cost-effectiveness of edoxaban relative to rivaroxaban.

In the absence of head-to-head comparative trials, cost-effectiveness analysis comparing one NOAC to another requires reliance on clinical data derived from network meta-analysis that indirectly compares one treatment versus another. Several researchers have conducted network meta-analyses of pivotal trial data to assess the relative efficacy and safety of edoxaban versus other NOACs. While these studies differ in methodology and the inclusion of data from patients with $CHADS_2$ scores of 1, they consistently showed rivaroxaban 20 mg was associated with a higher risk of major bleeding and the composite of major and clinically relevant major bleeding, than edoxaban 60 mg. To be consistent with the study population in ENGAGE AF-TIMI 48 and ROCKET-AF (both studies enrolled patients with $CHADS_2$ scores $\geq$2), we purposefully chose to use data from a network meta-analysis of data from patients with $CHADS_2$ scores $\geq$2, which showed that among patients with NVAF and $CHADS_2$ scores $\geq$2, edoxaban (60 mg/30 mg dose-reduced) had similar efficacy to rivaroxaban for the risk of stroke and SE (relative risk 0.90, 95% confidence interval 0.70–1.16 for composite of stroke/SE) and substantially lower risk of major bleeding compared with rivaroxaban (relative risk 0.76, 95% confidence interval 0.52–1.10).[22] In other indirect comparisons analyses, Skjøth et al[25] and Fu et al[26] drew similar conclusions that edoxaban has similar efficacy to rivaroxaban for the risk of stroke and SE, but substantially lower risk of major bleeding.

Limitations

The economic model we developed for this study has several potential limitations. First, many of the model's data inputs were derived from a network meta-analysis of clinical trial data. Indirect treatment comparisons through network meta-analysis of clinical trials has its own inherent limitations. Although we used data from an analysis of patients with $CHADS_2$ scores $\geq$2 as an attempt to minimize biases, the comparison did not control for all differences in patient baseline characteristics, such as warfarin time in therapeutic range. The relative efficacy of an NOAC to warfarin depends on the quality of warfarin control. The amount of time warfarin patients spent in the target therapeutic range was higher in ENGAGE AF-TIMI 48 (median 68.4%) than ROCKET-AF (median 58%). This variation would be expected to favor the rivaroxaban-versus-warfarin comparison rather than the edoxaban-versus-warfarin comparison, thus leading to a conservative estimate for the cost-effectiveness of edoxaban.

Another potential study limitation comes from the fact that participants in clinical trials are likely to have received closer management and had better adherence to therapy than patients who would be treated in a nontrial, real-world population. Therefore, the efficacy, safety, and tolerability observed from clinical trials may be better than what would occur in actual clinical practice.

We also note that many data parameters required for an economic model that would include dabigatran and apixaban, the other two NOACs marketed in the US, were not available in the published literature for the subgroup of patients with $CHADS_2$ scores $\geq$2, as the pivotal trials of these agents included patients with $CHADS_2$ scores $\geq$1. Other researchers who have attempted indirectly to compare apixaban and dabigatran to rivaroxaban have also acknowledged the challenges for adequately controlling the heterogeneity in patient baseline characteristics and study design.[13,31,65–72] For similar reasons, we were unable to pursue analysis for apixaban and dabigatran. The comparative effectiveness of edoxaban relative to all marketed NOACs should be addressed in future observational studies in the real-world setting. Finally our model and analyses were based on costs and resource-use data specific for the US, and thus results are not necessarily generalizable to other countries, due to differences in health care practices and financing.

Conclusion

Our cost-effectiveness analysis over a remaining lifetime horizon provides a comprehensive assessment of the health care resources, mortality risk, and quality-of-life impairment

incurred in NVAF patients receiving lifetime once-daily OAC therapy for stroke prevention. Our base-case analysis findings, along with the results of sensitivity analyses, suggest that edoxaban is an economically attractive alternative to rivaroxaban for stroke prevention in NVAF patients. In an era of evidence-based medicine, comparative effectiveness and economics research can inform health care stakeholders in their resource-allocation decisions. Future research is warranted to evaluate further the economic implications of edoxaban therapy in the real-world setting.

Disclosure

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