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Authors

Preblick, Ronald
Kwong, W Jacqueline
White, Richard H
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RESEARCH ARTICLE

Cost-effectiveness of edoxaban for the treatment of venous thromboembolism based on the Hokusai-VTE study

Ronald Preblick[1], W. Jacqueline Kwong[1], Richard H. White[2], and Samuel Z. Goldhaber[3]

[1]*Health Economics and Outcomes Research, Daiichi Sankyo, Inc., Parsippany, NJ, USA,* [2]*Division of General Medicine, Anticoagulation Service, University of California Davis Health System, Sacramento, CA, USA, and* [3]*Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA*

Abstract

Objective: Venous thromboembolism (VTE) is associated with almost 300,000 deaths per year in the United States. Novel oral anticoagulants (NOACs) offer an alternative to warfarin-based therapy without monitoring requirements and with fewer drug and food interactions. Edoxaban, a direct Xa inhibitor, is approved by the Food and Drug Administration (FDA), based upon results of the Hokusai-VTE Phase 3 trial. The trial demonstrated that edoxaban administered once daily after initial treatment with heparin was non-inferior in reducing the risk of VTE recurrence and caused significantly less major and clinically relevant non-major (CRNM) bleeding compared to warfarin. The objective of this study was to evaluate the cost-effectiveness of edoxaban versus warfarin for the treatment of adults with VTE. *Methods*: A cost-effectiveness model was developed using patient-level data from the Hokusai-VTE trial, clinical event costs from real-world databases, and drug acquisition costs for warfarin of $0.36 and edoxaban of $9.24 per tablet. *Results*: From a U.S. health-care delivery system perspective, the incremental cost-effectiveness ratio (ICER) was $22,057 per quality adjusted life year (QALY) gained. Probabilistic sensitivity analysis showed that edoxaban had an ICER <$50,000 per QALY gained relative to warfarin in 67% of model simulations. The result was robust to variation in key model parameters including the cost and disutility of warfarin monitoring. *Conclusion*: Despite its higher drug acquisition cost, edoxaban is a cost-effective alternative to warfarin for the treatment of VTE.

Keywords

Venous thromboembolism, Edoxaban, Cost effectiveness, Warfarin, Novel oral anticoagulants

History

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Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), affects 350,000–600,000 individuals annually in the United States, with an estimated 296,370 VTE-related annual deaths.[1] PE is the third most common cause of death in patients with cardiovascular disease (following myocardial infarction and stroke).[2] As risk factors for VTE such as advanced age, immobility, surgery and obesity become increasingly prevalent in the United States, the incidence of VTE and related deaths is likely to double by the year 2050.[3,4]

The Hokusai-VTE trial, a Phase 3 clinical trial of 8240 patients, demonstrated that edoxaban administered once daily after initial treatment with heparin was non-inferior in reducing the risk of VTE recurrence and led to significantly less major and clinically relevant non-major (CRNM) bleeding compared to standard warfarin therapy.[5] As a novel oral anticoagulant (NOAC) with fewer drug and food interactions than warfarin and no requirement for routine coagulation monitoring, edoxaban can be an attractive once-daily alternative to warfarin-based therapy for the treatment of VTE.[6]

As new therapies come to market, there is a need to understand their economic value in addition to therapeutic benefits relative to standard of care. The incorporation of economic value information into treatment guidelines and performance measures has been proposed by the American Heart Association (AHA) and the American College of Cardiology (ACC) Task Force on Performance Measures and Task Force on Practice Guidelines.[7] The AHA/ACC proposal recommends the use of cost-effectiveness analysis comparing the new treatment with the relevant alternative to inform health-care decisions.[8] Based on U.S. gross domestic product (GDP) data in 2012, the AHA/ACC proposal considered interventions with cost-effectiveness analysis results expressed as an incremental cost-effectiveness ratio (ICER) of <$50,000 per quality adjusted life year (QALY) gained as high value. Interventions with an ICER between $50,000 and $150,000 per QALY gained are of intermediate value, whereas interventions with an ICER > $150,000 per QALY gained are of low value.[7]

Correspondence: W. Jacqueline Kwong, Daiichi Sankyo, Inc., 2 Hilton Court, Parsippany, NJ 07054, USA. Tel: +1-973-944-2344. Fax: +1-973-944-2031. E-mail: jkwong@dsi.com

The objective of the present analysis was to evaluate the cost-effectiveness of edoxaban versus warfarin for the treatment of adults with VTE, based on the data from the Hokusai-VTE study.

Materials and methods

Overview of the model

Using a Markov state-transition model based on the data from the Hokusai-VTE study, we evaluated the cost-effectiveness of edoxaban versus warfarin for the treatment of VTE over the course of 1 year using a U.S. health-care delivery system perspective (see Figure 1 for model structure).[9] The model evaluated cohorts of VTE patients with characteristics similar to those enrolled in the Hokusai-VTE study (Table 1).

During each monthly Markov cycle, patients were at risk for any of the following five acute clinical events: (1) recurrent DVT alone, (2) recurrent PE (±DVT), (3) intracranial hemorrhage (ICH) major bleed, (4) Non-ICH major bleed and (5) CRNM bleed. In treated patients, only one VTE or bleed event per cycle was permitted. Deaths could be either related to the clinical event of interest or not related to any of these events during the modeled time frame.

The model incorporated periods where patients were on or off oral anticoagulant therapy to mimic real-life clinical practice. Guidelines from the American College of Chest Physicians recommend treatment of DVT or PE for at least 3 months; treatment may be extended in patients with higher risk of recurrence if the patient's bleeding risk is low or moderate.[10] In the Hokusai-VTE clinical trial, patients received edoxaban or warfarin for the intended treatment duration of 3, 6 and 12 months. Study investigators had the option of extending a patient's treatment on the basis of the patient's clinical status and preference.[5] In the base case cost-effectiveness analysis, all patients entered the model with an index acute VTE event

Table 1. Patient characteristics based on Hokusai-VTE trial.

Mean age (SD)	55.8 (16.2)
Male	57.2%
Female	42.8%
Index event type:	
DVT only	59.70%
PE ± DVT	40.30%
Intended treatment duration	
3 months (DVT/PE)	6.5%/4.5%
6 months (DVT/PE)	34.3%/41.3%
12 months (DVT/PE)	59.2%/54.2%
Severe PE (overall population)[a]	11.4%
Fragile[b]	17.2%
History of cancer[c]	9.40%
Age ≥ 75 years	13.40%

The model evaluated cohorts of VTE patients with characteristics similar to those in the Hokusai-VTE study [5].
[a]As indicated by NT-proBNP level of ≥500 pg/mm; 28.3% of PE population.
[b]Age ≥ 75 years, body weight ≤ 50 kg and/or CrCl 30–50 mL/min.
[c]Includes active cancer.

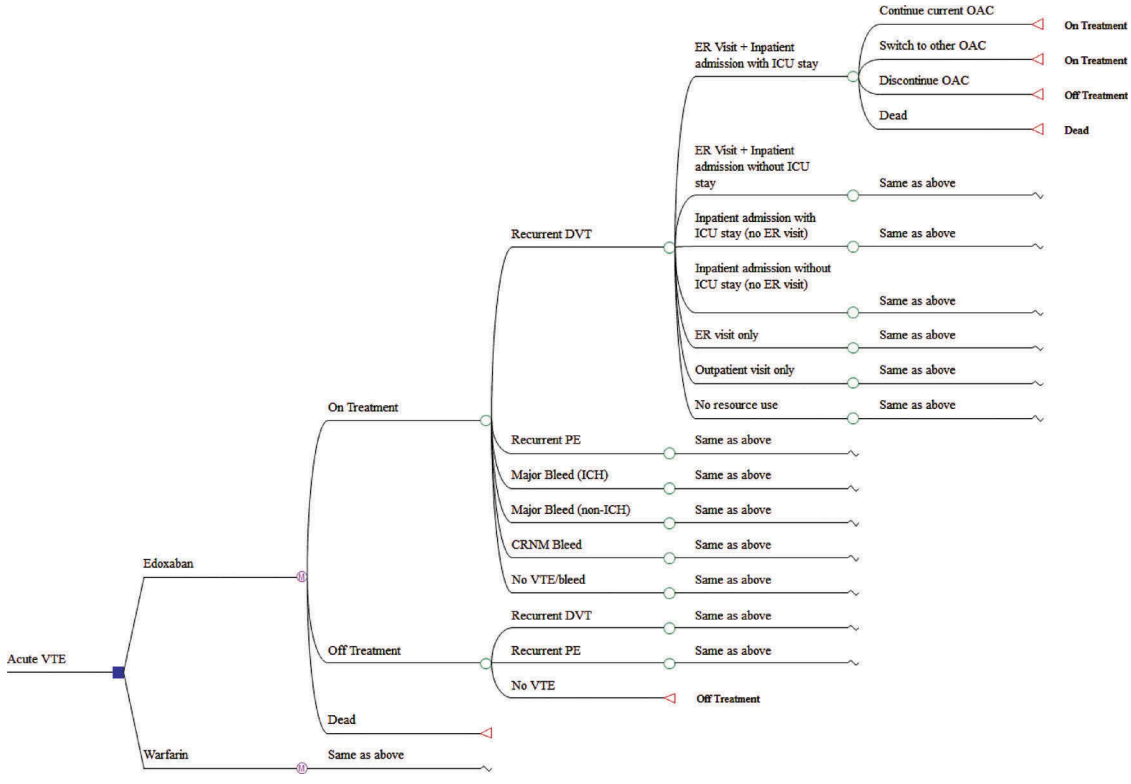

Figure 1. VTE Markov model structure.
The square at the left represents the choice between two treatment options: edoxaban or warfarin. M represents a Markov process with three health states where patients are on-treatment, off-treatment or die. While on-treatment, patients may experience one of five mutually exclusive clinical events: (1) recurrent DVT, (2) recurrent PE ± DVT, (3) ICH bleed, (4) major non-ICH bleed or (5) clinically relevant non-major bleeding that results in outpatient office visit, emergency department visit and/or inpatient admission with and without intensive care stay. Patients may remain on OAC therapy, switch to other OAC therapy or discontinue therapy after the clinical event is resolved. Patients off treatment may experience recurrent DVT or PE ± DVT.

(59.7% DVT only; 40.3% PE ± DVT) and received anticoagulant therapy for the intended treatment durations of 3, 6 and 12 months. The proportion of patients initiated treatment with the intended treatment duration of 3 months (6.5% DVT patients and 4.5% PE ± DVT patients), 6 months (34.3% DVT patients and 41.3% PE ± DVT patients) and 12 months (59.2% DVT patients and 54.2% PE ± DVT patients) were derived from the Hokusai-VTE study. At the end of each monthly cycle, patients could remain on the same treatment, switch to a different treatment, discontinue therapy or die. Patients could complete the intended course of treatment for their index VTE event or they could discontinue oral anticoagulant therapy but resume another course of therapy due to a recurrent VTE in future cycles. Switching therapies was allowed only once during the 1-year model duration. Patients who discontinued therapy due to intolerable adverse clinical events would not resume treatment but would remain in the off-treatment state until the end of the modeled time frame or die.

Risk of clinical events

The risk estimates for recurrent VTE, bleeding events and mortality while receiving edoxaban or warfarin were based on a *post hoc* analysis of patient-level efficacy and safety data from the Hokusai-VTE study.[5] The total number of each type of recurrent VTE and bleeding events was calculated separately for three time intervals: months 1–3, months 4–6 and months 7–12. Monthly event risk used in the model was then calculated as the total number of events during a time interval divided by the total number of person-months during the same time interval (Table 2). Non-VTE mortality was based on U.S. vital statistics data adjusting for patient age and sex and assumed to be the same for each cohort.[11]

Treatment discontinuation/switching

The Hokusai-VTE study collected data on mortality and whether patients remained on or discontinued study medication after experiencing an adverse event. However, the study did not collect data on oral anticoagulant (OAC) switching upon study medication discontinuation and withdrawal from the clinical study. Therefore, the model incorporated the following assumptions regarding switching of oral anticoagulant for VTE treatment that may occur in real-life clinical practice. For patients who discontinued the study drug following a recurrent VTE in the Hokusai-VTE study, it was assumed that 100% would switch to the alternative therapy in the model (i.e., either warfarin or edoxaban, depending on the therapy they were on at the time of the event). For patients who discontinued the study drug following a bleed event in the Hokusai-VTE study, it was assumed that 50% would discontinue oral anticoagulant therapy permanently, and the remaining 50% would switch to the alternative oral anticoagulant therapy (either warfarin or edoxaban) in the model. Based on these assumptions, transition probabilities for treatment discontinuation and switching subsequent to adverse clinical events were derived (Table 3).

Table 3. Risks of mortality, treatment discontinuation and OAC switching following clinical events.

	Remain on therapy (%)	Switch therapy (%)	Discontinue therapy (%)	Mortality rate (%)
Recurrent DVT	34.4	65.6	0	0
Recurrent PE (±DVT)	46.4	49.3	0	4.3
Major bleed (ICH)	8.7	32.6	32.6	26.1
Major bleed (non-ICH)	37.8	28.6	28.6	5.1
CRNM bleed	80.0	10.0	10.0	0

CRNM: Clinically relevant non-major; DVT: deep vein thrombosis; ICH: intracranial hemorrhage; PE: pulmonary embolism.
Source: Derived from *post hoc* analysis of data from the Hokusai-VTE study [5] and model assumptions.

In the model, general non-compliance to therapy was assumed to be zero for all treatment options in the model. It was assumed that recurrent VTE events would result in the resetting of the 3-, 6- and 12-month intended treatment duration distribution similar to that observed for the index event in the Hokusai-VTE study. Patients who were off anticoagulation treatment were subject to a risk of recurrent VTE event based on literature (0.47% per month) [12] or death with no risk of bleeding.

Utility and disutility values

Health state utilities represent patient well-being or preference for a given health state. Utilities are measured on a scale of 0–1, where 0 represents death and 1 represents perfect health. In health economic analyses, disutilities represent the burden of undesirable clinical events and are subtracted from a patient's baseline well-being when such event is experienced. In this study, all VTE patients entering the model were

Table 2. Monthly clinical event risk while receiving treatment.

		Recurrent DVT (%)	Recurrent PE (±DVT) (%)	Major bleed (ICH) (%)	Major bleed (non-ICH) (%)	CRNM bleed (%)	No event (%)
Edoxaban							
	Months 1–3	0.15	0.22	0.02	0.36	1.75	97.50
	Months 4–6	0.06	0.03	0.01	0.07	0.90	98.93
	Months 7–12	0.02	0.02	0.02	0.03	0.56	99.34
Warfarin							
	Months 1–3	0.24	0.28	0.07	0.25	2.41	96.75
	Months 4–6	0.06	0.04	0.06	0.12	0.71	99.01
	Months 7–12	0.02	0.01	0.04	0.05	0.48	99.39

CRNM: Clinically relevant non-major; DVT: deep vein thrombosis; ICH: intracranial hemorrhage; PE: pulmonary embolism.
Source: *Post hoc* analysis of the Hokusai-VTE study [5].

assigned a baseline utility value of 0.87.[13] Disutility values for each acute event were applied within the cycle in which the event occurred. For example, a patient experiencing a CRNM bleeding event would have a disutility value of 0.09 subtracted from his/her baseline utility value. The disutility values for recurrent DVT, recurrent PE, non-ICH major bleeds and CRNM bleeds were obtained from previously published studies and VTE models [14–18] (Table 4).

Resource utilization and cost estimates

Clinical events can be managed in the inpatient or outpatient setting. Health-care resource utilization and treatment costs associated with each type of clinical event are shown in Table 5. Rates of hospitalization, emergency department (ED) visits and hospital length of stay (LOS) associated with the index VTE event, recurrent VTE events and bleeding events were derived from a *post hoc* analysis of data collected in the Hokusai-VTE trial [5] for the purpose of this model. Health-care resource utilization associated with the index event was based on a pooled analysis of both the edoxaban and the warfarin arms, while resource use associated with recurrent VTE and bleeding events was evaluated separately for edoxaban and warfarin. We separated hospital stays between general ward inpatient (GWIP) days and intensive care unit (ICU) days because hospitalization with ICU days is more resource-intensive and costly than without ICU days. Patients who were not admitted to the hospital nor had an ED visit after experiencing a clinical event were assumed to have an outpatient visit.

Cost estimates for inpatient service and ED visits were derived from a retrospective analysis of VTE- and bleeding-related hospitalization and ED visits among patients admitted for VTE as identified in the 2009–2011 Premier Hospital Databases (Premier, Inc., Charlotte, NC) to represent the actual cost of care to U.S. hospitals. The Premier database contains information on more than 45 million inpatient discharges from more than 600 acute care hospitals in the United States. Cost data are reported by the hospitals, with about three-fourths of the hospitals following procedural cost accounting, and the remaining reporting costs based on the ratios of cost to charges. Cost estimates for outpatient visits in the model were obtained from a retrospective analysis of the 2009–2011 Medicare 5% institutional outpatient Standard Analytical Files.[23] All cost estimates were adjusted to 2013 USD using the medical care component of the Consumer Price Index. Estimates for post-ICH cost ($2764) were obtained from the literature.[18,24]

The two evaluated treatment options in the model were the following: (1) edoxaban (60 mg once daily) with a 5-day heparin lead-in (enoxaparin 80 mg/0.8 mL twice daily, based on the dosing of 1 mg/kg body weight and assumed 80 kg body weight) [18]; and(2) warfarin (5 mg once daily) with a 5-day heparin bridge (enoxaparin 80 mg/0.8 mL twice daily). Unit costs for edoxaban ($9.24 per day) and warfarin ($0.36 per day) were based on the wholesale acquisition cost as of January 2015.[21] Warfarin cost was based on the average cost for all strengths of generic warfarin.

Analysis

Cost-effectiveness of edoxaban relative to warfarin was assessed using the ICERs, measured as cost per QALY gained, over 1 year from a U.S. health-care delivery system perspective. One-way sensitivity analyses were performed to assess how variation around selected base case model inputs based on 95% confidence intervals, interquartile ranges

Table 4. Disutility values and one-way sensitivity analysis parameter ranges.

Input	Base case	Low	High	Base case reference	Sensitivity estimates
Disutilities[†]					
Recurrent DVT	0.19	0.06	0.45	[14]	Reported IQR
Recurrent PE (±DVT)	0.25	0.09	0.55	[14]	Reported IQR
ICH bleed, first month	0.69	0.621	0.759	[19]	Assumption: ±10%
ICH bleed, second month	0.45	0.405	0.495	[19]	Assumption: ±10%
ICH bleed, third month forward	0.39	0.351	0.429	[19]	Assumption: ±10%
Major bleed (non-ICH)	0.20	0.16	0.21	[15]	Reported utility range of 0.79–0.84
CRNM bleed	0.09	0.035	0.2125	[14]	Reported IQR
Monitoring while on warfarin therapy	0.01	0.006473574	0.015526426	[20]	Reported mean (±SD) utility of 0.989 (±0.016) with $N = 48$; approximate standard error is 0.002309
Off-treatment event rates					
Recurrent VTE, year 1 (%)	0.47	0.23	0.52	[12]	Monthly rate estimated based on annual rates ranging from 5.5–12.2%[‡]
Costs ($)					
Post ICH cost	2764	2657	2873	[18]	Lower and upper bounds provided
Edoxaban	9.64	8.67	10.59	[21]	Assumption: ±10%
Warfarin monitoring cost					
First month	106	95	117		Assumption: ±10%
Subsequent months	106	95	117		Assumption: ±10%
Other					
Index event type, % DVT alone	59.72	50.00	70.00		±10 percentage points

CRNM: Clinically relevant non-major; DVT: deep vein thrombosis; ICH: intracranial hemorrhage; IQR: interquartile range; PE: pulmonary embolism; SD: standard deviation.

[†]Base case disutility values are obtained from published literature. Disutility values represent the burden of undesirable clinical events and are subtracted from a patient's baseline well-being when such an event is experienced.

[‡]Source: Boutitie et al. [22].

Table 5. Health-care resource utilization and costs.

	Percent of patients						
	OP	ED	GWIP	ED + GWIP	GWIP + ICU	ED + GWIP + ICU	Average LOS (days)
Index event							
DVT alone	26.3	12.5	41.2	18.2	0.8	0.9	8.79
PE ± DVT	4.0	5.0	30.1	44.7	4.6	11.7	8.23
Acute events: edoxaban							
Recurrent DVT	51.7	8.3	21.7	15.0	3.3	0.0	8.96
Recurrent PE (±DVT)	4.1	8.2	24.5	38.8	10.2	14.3	8.66
Major bleed (ICH)	25.0	0.0	12.5	25.0	12.5	25.0	9.00
Major bleed (non-ICH)	18.2	7.3	34.6	12.7	14.6	12.7	9.73
CRNM bleed	73.6	5.3	11.9	6.9	1.9	0.5	7.88
Acute events: warfarin							
Recurrent DVT	40.6	10.1	31.9	13.0	1.5	2.9	18.21
Recurrent PE (±DVT)	16.0	2.0	24.0	38.0	8.0	12.0	13.53
Major bleed (ICH)	0.0	4.5	22.7	36.4	4.5	31.8	12.44
Major bleed (non-ICH)	30.2	7.6	26.4	13.2	9.4	13.2	16.72
CRNM bleed	77.3	5.0	10.3	6.2	0.5	0.7	9.76
Cost per day or per visit ($)*							
Index event							
DVT alone	304	1071	1362	1609	3024	2470	
PE ± DVT	149	2367	1644	1879	2104	2245	
Acute events							
Recurrent DVT	248	1380	1808	1824	3990	3189	
Recurrent PE (±DVT)	187	2048	1634	2000	1971	2797	
Major bleed (ICH)	784	2004	4230	2008	3282	3500	
Major bleed (non-ICH)	396	2849	1726	2191	2607	2996	
CRNM bleed	374	741	2267	2006	2803	2807	

CRNM: Clinically relevant non-major; DVT: deep vein thrombosis; ED: emergency department; GWIP: general ward inpatient; ICH: intracranial hemorrhage; ICU: intensive care unit; IP: inpatient; LOS: length of stay; OP: outpatient; PE: pulmonary embolism.
*Costs of inpatient treated VTE include first 7 days of medication costs.
Sources: Resource use data are from a *post hoc* analysis of the Hokusai-VTE study [5]; cost data are from an analysis of the Premier Hospital Database 2009–2011.

(IQRs), where applicable, or assumption may affect study results (see Table 4). In addition, probabilistic sensitivity analysis (PSA) where acute event rates, resource utilization, inpatient LOS and disutility associated with warfarin monitoring were simultaneously varied for 1000 iterations was performed. Per AHA/ACC guidance, a threshold of <$50k, $50–$150k and >$150k was utilized as the therapy providing high, intermediate and low economic value, respectively.[7] It should be noted that while the $50,000 threshold is often used, greater thresholds may be considered.[16,25,26]

Results

Base case analysis

The Markov model estimated that in cohorts of 100,000 patients over 1 year, patients treated with edoxaban had fewer recurrent VTE events (4197 vs. 4779), fewer major bleed events (1617 vs. 1763) and fewer CRNM bleeds (9721 vs. 10,804), compared to patients treated with warfarin. Although patients treated with edoxaban had identical life expectancy (0.978) as patients treated with warfarin, patients treated with edoxaban had higher QALYs (0.849 vs. 0.837). While edoxaban costs were higher ($2760 for edoxaban vs. $490 for warfarin; difference = $2270 per patient) than the costs of warfarin, lower VTE- and bleeding-related costs among edoxaban patients led to similar total health-care costs ($14,384 for edoxaban vs. $14,127 for warfarin; difference = $257 per patient), resulting an ICER of $22,057 per QALY gained (see Table 6).

Table 6. Model results.

Output		Warfarin	Edoxaban
Acute and chronic events			
	N events: recurrent VTE	4779	4197
	N events: major bleed	1763	1617
	N events: CRNM bleed	10,804	9721
Life years			
	Total LYs	97,787	97,844
	Total QALYs	83,744	84,909
Per patient costs ($)			
	VTE related	11,222	10,775
	Bleeding related	1484	833
	Pharmacy	490	2760
	Warfarin monitoring	932	17
Total costs (per patient) ($)		14,127	14,384
ICER, per QALY gained (vs. warfarin) ($)		n/a	22,057

CRNM: Clinically relevant non-major; ICER: incremental cost-effective ratio; LY: life year; *N*: number; QALY: quality-adjusted life year; VTE: venous thromboembolism.
Individual cost and QALY estimates have been rounded for reporting purposes; however, the ICER is based on the full precision estimates generated in the model.

Sensitivity Analyses

One-way sensitivity analyses showed that the cost-effectiveness analysis results were most sensitive to the disutility associated with warfarin monitoring and the cost of warfarin monitoring (Figure 2). As disutility and costs of warfarin monitoring increased, the ICER for edoxaban relative to warfarin was reduced, making it more cost-effective. When switching OAC therapy was not allowed in the model

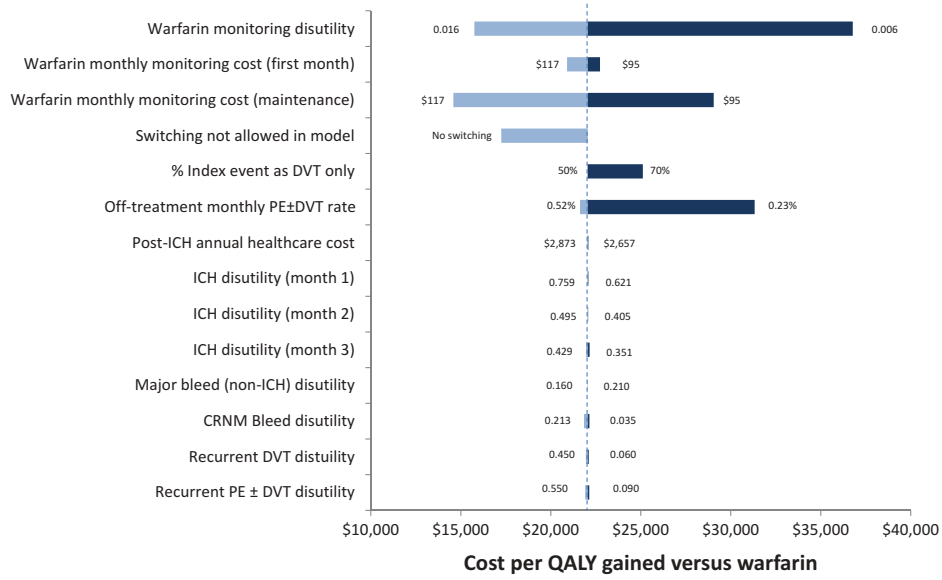

Figure 2. Tornado diagram for one-way sensitivity analyses.
Horizontal bars show the range of incremental cost-effectiveness ratios obtained when setting a specific parameter to values shown while keeping other parameters in the model the same as the base case. Dotted line represents base case ICER result of $22,057 per QALY gained.

such that patients could only remain on, or discontinue, their initial OAC therapy, the ICER of edoxaban relative to warfarin was reduced to $17,250 per QALY gained, making it more cost-effective. The ICER relative to warfarin also increased slightly to $25,115 per QALY gained when the proportion of patients with DVT without PE was increased from 50% to 70%. As expected, the model was sensitive to the cost of edoxaban; decreasing the base case edoxaban price by 10% to $8.32 per day yielded a lower ICER of $1974 per QALY gained. Increasing base case edoxaban price by 10% to $10.16 per day increased ICER to $42,140 per QALY gained. The model result was sensitive to treatment duration. When all patients in the model were assigned an intended treatment duration of 3 months or 6 months, edoxaban dominated warfarin, yielding more QALYs (ΔQALY = +0.010 for 3 months; +0.012 for 6 months) at lower cost (Δ cost per patient = −$829 for 3 months; −$343 for 6 months) than warfarin. However, when all patients were assigned intended treatment duration of 12 months, ICER of edoxaban relative to warfarin increased to $70,108 per QALY gained. When hospital LOS estimates for clinical events were set to be equal between edoxaban and warfarin using hospital LOS data from the Medicare 5% sample (see Table 7), ICER was increased to $72,002 per QALY gained. ICER results were not sensitive to the disutility associated with other events (e.g., recurrent DVT, bleeding), and other parameters/scenarios.

In the PSA, when key model parameters including warfarin disutility values, event rates and health-care resource use were randomly sampled from their respective distributions simultaneously, 67% of the simulations resulted in an ICER of ≤$50,000, 82% in ≤$100,000 and 88% in ≤$150,000 (Figure 3). Edoxaban was dominant to warfarin (lower costs and higher QALYs vs. warfarin) in 33.9% of simulations and dominated by warfarin (higher costs and lower QALYs vs. warfarin) in zero simulations.

Table 7. Medicare 5% sample (2009–2011) LOS data.

Hospitalization for event	Mean LOS in days
Index DVT	6.21
Index PE	7.55
Recurrent DVT	8.17
Recurrent PE	8.31
Major bleed (ICH)	13.45
Major bleed (non-ICH)	9.02
CRNM bleed	8.90

CRNM: Clinically relevant non-major; DVT: deep vein thrombosis; ICH: intracranial hemorrhage; LOS: length of stay; PE: pulmonary embolism.

Discussion

This is the first known head-to-head cost-effectiveness analysis of edoxaban and warfarin for the treatment of VTE using patient-level clinical and resource data captured in the Hokusai-VTE trial. The results demonstrate that over a 1-year time horizon, edoxaban had fewer recurrent VTE events and bleed events, but higher overall costs, compared to warfarin. However, from a U.S. health delivery system perspective, the ICER was just $22,057 per QALY gained, which is well below the $50,000 per QALY gained threshold for highly cost-effective according to AHA/ACC guidance.[7]

The strengths of this analysis are that we utilized patient-level data to the greatest extent possible, including resource use data, and we matched Hokusai-VTE cohort study characteristics to our model. While such an approach increases the internal validity of our results, there are limitations. The generalizability of our cost-effectiveness results depends on how well the Hokusai-VTE clinical trial population mimics VTE patients requiring OAC treatment in the real-world setting. The Hokusai-VTE study enrolled VTE patients with a wide range of disease characteristics, including patients with severe pulmonary embolism and unprovoked VTE who required OAC treatment for at least 3–12 months. This broad spectrum of patient risk profiles, along with flexible

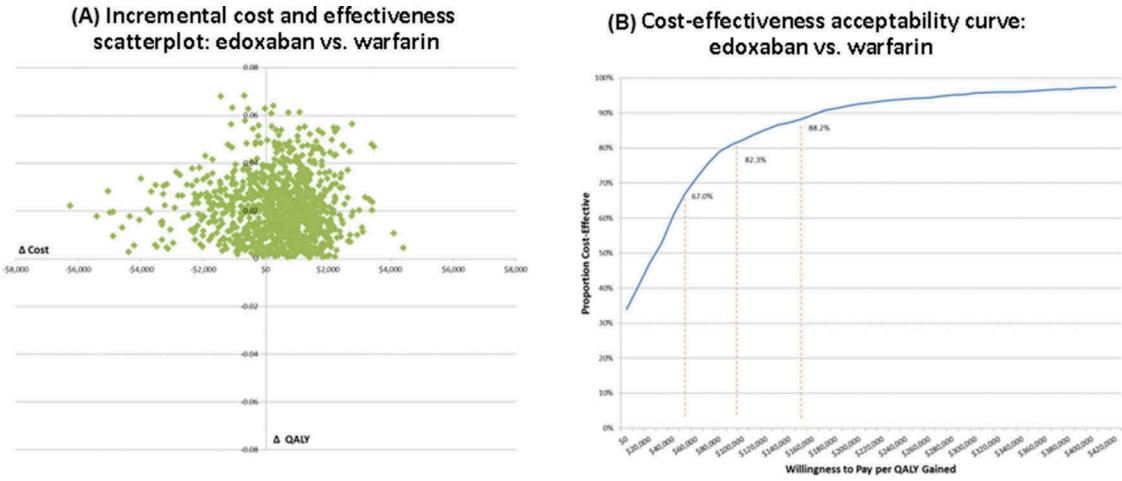

Figure 3. Probabilistic sensitivity analysis results.
The results of probabilistic sensitivity analysis where model parameters were simultaneously varied for 1000 iterations based on their distributions. (**A**) Incremental cost and QALY difference pairs of 1000 iterations are shown. Positive values are in favor of edoxaban versus warfarin. (**B**) Line showing the proportion of simulations where ICER value falls below willingness to pay thresholds. About 67% of simulations yield ICER below the $50,000 per QALY gained threshold.

treatment durations of 3–12 months, reflects the heterogeneous VTE population in clinical practice and enhances the generalizability of the results of this Phase 3 trial to clinical practice.

However, patients participating in clinical trials are likely to receive closer management and are more adherent to therapy than patients in real-world situations. Maintaining adherence with warfarin therapy has been shown to be challenging among VTE patients in clinical practice. Studies have shown that one in four patients would not fill prescriptions for the recommended length of treatment [27] and 77% of patients at high risk of VTE recurrence would be non-compliant with warfarin therapy.[28] In the Hokusai-VTE clinical trial, adherence to edoxaban treatment was 80% or more in 99% of the patients randomized to edoxaban treatment.[5] Patients receiving warfarin in the Hokusai-VTE clinical trial had international normalized ratio (INR) in the therapeutic range for 63.5% of the time,[5] which is much higher than the average time in therapeutic range of 55% observed among U. S. patients receiving warfarin anticoagulation in clinical practice.[29] Therefore, an analysis based on the data from the Hokusai-VTE clinical trial might have underestimated the cost-effectiveness of edoxaban relative to warfarin in real-world clinical practice.

Second, in clinical practice, patients may switch from one anticoagulant to another when they develop side effects from a particular agent. However, data on the frequency and reasons for oral anticoagulant switching are limited in published literature. In the absence of data on switching from the Hokusai-VTE clinical trial, we took a conservative approach and assumed that 50% of the patients who discontinued study medication in the clinical trial would switch to an alternative oral anticoagulant included in the model. Although the robustness of this assumption was supported by one-way sensitivity analysis, our model did not consider switching related to other factors such as change of insurance coverage or non-adherence. Switching in the model was also limited to warfarin and edoxaban and did not include other available NOACs (e.g., dabigatran, rivaroxaban and apixaban). Additional data on oral anticoagulation switching are needed to further understand the impact of switching on the cost-effectiveness of oral anticoagulant therapy.

Third, our model considered only direct medical costs from the U.S. perspective. Indirect costs such as lost productivity and transportation cost related to INR monitoring were not considered in the analysis. The exclusion of these indirect costs may have underestimated the cost-effectiveness of edoxaban. Finally, we modeled the cost and consequences of OAC treatment for VTE up to 1 year to be consistent with the study duration of Hokusai-VTE study. Because VTE patients have a long-term risk of recurrence, treatment beyond 1-year and in some cases lifelong is warranted.[30] Our study is limited to model duration of 1 year due to data availability. Hence, we did not consider the costs and consequences of longer-term complications such as severe post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension that are associated with recurrent VTE events.[31,32]

Notwithstanding these limitations, our findings are similar to other recent studies that found NOACs to be cost-effective treatment alternatives to warfarin. Rivaroxaban was cost-effective compared to warfarin in three different Markov models using different model time frame from the perspective of U.S. health-care system.[16–18] Dabigatran was found to be cost-saving or cost-effective compared to vitamin K antagonists for the treatment of DVT in an analysis based on INR monitoring cost data from a Dutch hospital.[33] Lifetime treatment of apixaban was shown to be cost-effective compared to rivaroxaban, dabigatran and low molecular weight heparin/Vitamin-K antagonist in a Markov model performed from UK cost perspective.[34] These data, together with the results of the current study that showed edoxaban to be cost-effective or cost-saving relative to warfarin, suggest that all NOACs are generally cost-effective when compared to warfarin. By alleviating the burden of regular coagulation monitoring, reducing the risk of bleeding and food–drug interactions compared to warfarin, the NOACs

are providing incremental economic value to the health-care system.

Nevertheless, it is important to note that the clinical efficacy and safety data from the Phase 3 clinical trials of the NOACs cannot be compared directly given the significant differences in individual study design and patient characteristics.[35] For example, rivaroxaban's Phase 3 clinical trials were open-label,[36,37] but the trials for dabigatran, apixaban and edoxaban were double-blind.[38–40] There is also wide variation in treatment duration, the proportion of unprovoked/provoked VTE cases, the number of PE patients and the disease extensiveness that were studied in the Phase 3 clinical trials. Furthermore, differences in the pharmacological and pharmacokinetic profiles [41] also led to differences in dosing frequency and food–drug interactions across the NOACs. Hence, depending on their clinical characteristics, patients may be better suited to one agent over another in clinical practice. The availability of various treatment options on hospital formulary will be essential to allow individualized care be provided to optimize patient outcomes.

Conclusion

Cost-effectiveness analysis plays an important role in health-care decision-making. This study demonstrates that edoxaban is a cost-effective alternative to warfarin for the treatment of VTE based on clinical event and inpatient resource utilization data derived from the Hokusai-VTE trial.

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