Cost-effectiveness of Apixaban Compared With Edoxaban for Stroke Prevention in Nonvalvular Atrial Fibrillation

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ABSTRACT

Purpose: The purpose of this analysis was to assess the cost-effectiveness of apixaban 5 mg BID versus high- and low-dose edoxaban (60 mg and 30 mg once daily) as intended starting dose strategies for stroke prevention in patients from a UK National Health Service perspective.

Methods: A previously developed and validated Markov model was adapted to evaluate the lifetime clinical and economic impact of apixaban 5 mg BID versus edoxaban (high and low dose) in patients with nonvalvular atrial fibrillation. A pairwise indirect treatment comparison was conducted for clinical end points, and price parity was assumed between apixaban and edoxaban. Costs in 2012 British pounds, life-years, and quality-adjusted life-years (QALYs) gained, discounted at 3.5% per annum, were estimated.

Findings: Apixaban was predicted to increase life expectancy and QALYs versus low- and high-dose edoxaban. These gains were achieved at cost-savings versus low-dose edoxaban, thus being dominant and nominal increases in costs versus high-dose edoxaban. The incremental cost-effectiveness ratio of apixaban versus high-dose edoxaban was £6763 per QALY gained.

Implications: Apixaban was deemed to be dominant (less costly and more effective) versus low-dose edoxaban and a cost-effective alternative to high-dose edoxaban. (*Clin Ther*. 2015;37:2476–2488) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: apixaban, atrial fibrillation, clinical impact, cost-effectiveness, edoxaban.

INTRODUCTION

Nonvalvular atrial fibrillation (NVAF) is the most common sustained cardiac arrhythmia and a major cause of stroke and thromboembolism, associated with increased mortality, increased morbidity, and high medical costs.[1,2] Anticoagulation treatment is therefore recommended to mitigate the risk of stroke.[3]

The 2012 European Society of Cardiology guidelines recommend the consideration of the non–vitamin K oral anticoagulants (NOACs) dabigatran, rivaroxaban, and apixaban, for the prevention of stroke in patients[3] with NVAF because they offer relative efficacy, tolerability, and convenience by addressing certain limitations associated with traditional vitamin K antagonists (VKAs).

The NOACs have been compared with VKAs in large Phase III randomized trials. The Randomized Evaluation of Long-term Anticoagulation Therapy[4] trial revealed superiority for dabigatran 150 mg BID and noninferiority for dabigatran 110 mg BID versus dose-adjusted VKAs in reducing the primary efficacy end point of stroke and systemic embolism. In addition, dabigatran 110 mg was superior to dose-adjusted VKAs in reducing the risk of major hemorrhage, whereas dabigatran 150 mg[4] was noninferior. The Rivaroxaban Once Daily Oral Direct Factor Xa

Accepted for publication September 6, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.09.005
0149-2918/$ - see front matter

Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation[5] trial found rixaroxaban 20 mg once daily to be noninferior to dose-adjusted VKAs in efficacy and tolerability. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[6] trial found that apixaban 5 mg BID was superior to dose-adjusted VKAs in reducing stroke and systemic embolism, major bleeding, and all-cause death. Finally, the Phase III Study of Apixaban in Patients With Atrial Fibrillation (AVERROES)[7] trial, evaluating apixaban 5 mg BID versus aspirin, in VKA-unsuitable patients, found apixaban's superiority to aspirin in reducing the risk of stroke and systemic embolism without significantly increasing the risk of major hemorrhage.[7] Lack of monitoring requirement and strength of efficacy-tolerability data as observed in NOAC trials resulted in the European Society of Cardiology guidelines recommendation of NOACs instead of dose-adjusted VKA treatment.[3]

None of the NOACs has been evaluated against each other in head-to-head trials. Indirect treatment comparisons (ITCs) have indicated no significant differences between the NOACs in efficacy[8,9]; however, they found a reduced risk of major bleeding among patients treated with apixaban or dabigatran 110 mg compared with dabigatran 150 mg and rivaroxaban.[8–10] Apixaban is the only NOAC that received a Class 1, Evidence A classification from the American Heart Association/American Stroke Association because it appears to have the best combination of efficacy and tolerability at the tested doses.[11] However, no clear recommendation for the use of one NOAC over another is provided; rather, cost is highlighted as an important consideration in the choice of agent.[3]

Most evaluations comparing a NOAC against dose-adjusted VKAs for stroke prevention in patients with NVAF concluded that the NOACs offer superior benefits and were cost-effective compared with dose-adjusted VKAs.[12–15] In addition, studies that compared cost-effectiveness among the NOACs suggest that apixaban may be the most cost-effective NOAC (compared with rivaroxaban and dabigatran 150 mg and 110 mg) for stroke prevention among patients with NVAF.[13–15]

A recently introduced NOAC, edoxaban, is another oral factor Xa inhibitor that has been studied in dosages of 30 mg once daily (low dose) and 60 mg once daily (high dose) versus dose-adjusted VKAs in a double-blind randomized clinical trial called Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE-AF)—Thrombolysis in Myocardial Infarction 48 (TIMI-48)[16] and has recently received European marketing authorization.[17] Low-dose edoxaban was numerically worse whereas high-dose edoxaban once daily was numerically better than dose-adjusted VKAs in reducing stroke and systemic embolism. Both doses resulted in significantly less bleeding.[16] Comparatively, low-dose edoxaban had a better bleeding profile but worse stroke prevention than high-dose edoxaban.[16]

A recently published ITC[10] reported that a high-dose edoxaban regimen was broadly comparable in efficacy to apixaban and dabigatran 110 mg, but apixaban was associated with lower risks of major or clinically relevant nonmajor gastrointestinal bleeding. High-dose edoxaban was broadly comparable in efficacy and tolerability to dabigatran 110 mg BID but had lower efficacy compared with dabigatran 150 mg. There were no differences in efficacy end points between high-dose edoxaban and rivaroxaban, but the latter was associated with more bleeding. Low-dose edoxaban was less efficacious compared with apixaban, dabigatran 150 mg, and rivaroxaban but had fewer major bleedings and was generally more tolerable than all the other alternatives.

The addition of edoxaban to the options of available NOACs may change the relative value of these NOACs from a payer perspective. A holistic assessment of clinical benefits versus risks extrapolated over lifetime is required to determine the relative value and overall clinical benefit of various NOACs. The aim of this study was to reexamine the hypothesis that apixaban may be the most cost-effective NOAC, taking the emergence of edoxaban into account. We therefore assessed the cost-effectiveness of apixaban 5 mg BID versus edoxaban (low dose and high dose) as intended starting-dose strategies for stroke prevention in patients with NVAF from the UK National Health Service (NHS) payer perspective.

METHODS

A previously developed and validated[18,19] Markov model[12,13] was adapted to evaluate the lifetime clinical and economic impact of apixaban versus edoxaban (low and high dose) in patients with NVAF.

Long-term costs resulting from a lifetime model, as opposed to one with a specified duration, tend to be high. This Markov model explored how a hypothetical cohort of patients with NVAF move between discrete health states during a lifetime. During each 6-week cycle, the recurring fixed interval that determines disease progression, patients transitioned through or remained in the following mutually exclusive states: NVAF, ischemic stroke (including nonspecified strokes), systemic embolism, intracranial hemorrhage, other major bleeds, clinically relevant nonmajor bleeds, myocardial infarction, treatment discontinuations, and death. Possible transitions among the end points based on the likelihood of occurrence of events are presented in Figure 1, as described in previous publications.[12,13] Similarly to assumptions used in earlier studies,[12,13] patients discontinuing their first-line treatment were assumed to receive aspirin as a second-line treatment (Figure 1).

Model inputs on patient characteristics and rates of clinical events per 100 patient-years for apixaban and warfarin users were based on ARISTOTLE,[6] as obtained from a previously published cost-effectiveness analysis,[12,13] and briefly summarized in Tables I, II, and III. Patients discontinuing their first-line treatment were treated with aspirin, and event rates due to the subsequent treatment were drawn from a cohort of patients in the AVERROES trial with prior VKA exposure.[7,12,13] Further details on the model design, inputs, and ITC estimations of event rates of low- and high-dose edoxaban versus apixaban are available in the Appendix.

Table I. Demographic characteristics of the study participants.[12,13]

Characteristic	Finding
Starting age, y	70
Sex, %	
Male	64.7
Female	35.3
$CHADS_2$ distribution, %	
0–1	34.0
2	35.8
3–6	30.2

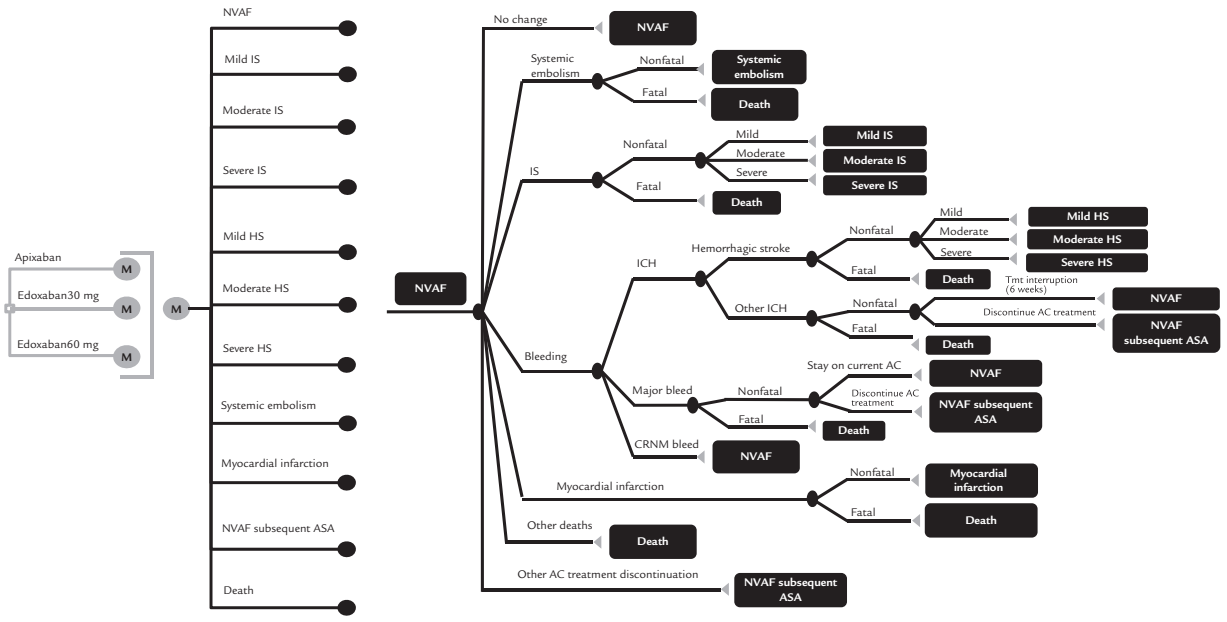

Figure 1. Schematic representation of the Markov model. AC = anticoagulant; ASA = aspirin; CRNM = clinically relevant nonmajor; HS = hemorrhagic stroke; ICH = intracranial hemorrhage; IS = ischemic stroke; MI = myocardial infarction; NVAF = nonvalvular atrial fibrillation; SE = systemic embolism; Tmt = Treatment.

Table II. Clinical event rates per 100 patient-years.[12,13]

Event	Event Rate per 100 Patient-years, Mean (number of events)		HR Versus Apixaban (95% CI)*	
	Apixaban	Aspirin (Subsequent Treatment)	Edoxaban (30 mg)	Edoxaban (60 mg)
Ischemic stroke	0.981 (162)	3.45 (43)	1.480 (1.120–1.960)	1.040 (0.780–1.390)
Intracranial hemorrhage	0.330 (52)	0.32 (4)	0.740 (0.460–1.200)	1.110 (0.710–1.730)
Other major bleed	1.790 (274)	0.89 (11)	0.660 (0.530–0.830)	1.130 (0.910–1.390)
Clinically relevant nonmajor bleed	2.083 (318)	2.94 (36)	0.950 (0.800–1.130)	1.250 (1.060–1.480)
Other treatment discontinuation	13.177 (2047)	NA	1.040 (0.960–1.130)	1.100 (1.010–1.190)
Myocardial infarction	0.530 (90)	1.11 (14)	1.370 (0.950–1.960)	1.070 (0.741–1.550)
Systemic embolism	0.090 (15)	0.40 (13)	1.390 (0.570–3.360)	0.740 (0.290–1.920)
Other cardiovascular hospitalization	10.460	12.09	1.000 (0.900–1.100)	1.000 (0.900–1.100)
Other death rate†	3.082 (528)	NA	1.000 (0.900–1.100)	1.000 (0.900–1.100)

HR = hazard ratio; NA = not applicable.
*Data are based on the Appendix except for other cardiovascular hospitalization and other death rate, which are based on assumption.
†Based on all-cause mortality excluding deaths attributable to stroke, bleeding, myocardial infarction, and systemic embolism.

In summary, relative effects in the form of hazard ratios (HRs) were computed using the Bucher method on the following studies: ARISTOTLE[6] (apixaban 5 mg BID versus warfarin; dose adjusted to maintain an international normalized ratio [INR] of 2.0–3.0) and ENGAGE-AF[16] (low- and high-dose edoxaban versus warfarin; dose adjusted to maintain an INR of 2.0–3.0). That is, the HR between both doses of edoxaban and apixaban were made via the warfarin common arm in ENGAGE-AF[16] and ARISTOTLE.[6] The (indirect) HR between apixaban and the edoxaban is determined as follows:

$$\log(HR_{EVA}) = \log(HR_{EVW}) - \log(HR_{AVW})$$

With the SE determined as follows:

$$SE[\log(HR_{EVA})] = \sqrt{SE[\log(HR_{EVW})]^2 + SE[\log(HR_{EVA})]^2}$$

Mortality modelling was based on sex- and age-specific UK life tables[12,13,20] taking into consideration increased mortality for patients with atrial fibrillation (AF)[21] and that associated with various end points (ie, stroke, systemic embolism, or myocardial infarction).[22–24] Utility estimates were similarly obtained from a UK EuroQol-5D–based catalogue,[25] as detailed in earlier publications (Table IV).[12,13]

The UK NHS perspective was adopted where only direct medical costs, expressed in 2012 British pounds, were considered (Tables V and VI). Detailed cost calculations and assumptions have been previously published.[12] Acute event costs were revised to reflect updated NHS reference costs.[27] In addition, estimates of the health care costs associated with strokes were revised based on an updated population-based study, The Oxford Vascular Study.[28] In the absence of pricing information for edoxaban, price parity to apixaban was assumed. Cost and health outcomes were discounted at a rate of 3.5% per annum[29] during a lifetime.

Analyses

The total number of clinical events observed among a cohort of 1000 patients treated with apixaban compared with high- and low-dose edoxaban was

Table III. Distributions and probabilities by treatment.[12,13,16]

Stroke Severity	No. (%) of Patients			
	Apixaban	Aspirin (Subsequent Treatment)	Edoxaban (30 mg)	Edoxaban (60 mg)
Stroke severity distribution*				
Mild (mRS score, 0–2)	57 (53)	35 (36)	135 (50)	102 (47)
Moderate (mRS score, 3–4)	23 (21)	37 (38)	78 (22)	50 (18)
Severe (mRS score, 5)	9 (8)	15 (15)	28 (8)	18 (6)
Fatal (mRS score, 6)	19 (18)	10 (11)	73 (20)	80 (29)
Hamorrhagic stroke among intracranial hemorrhage	40 (77)	9 (55)	41 (69)	61 (75)
Hemorrhagic stroke severity distribution*				
Mild (mRS score, 0–2)	7 (23)	1 (7)	135 (50)	102 (47)
Moderate (mRS score, 3–4)	10 (32)	3 (20)	78 (22)	50 (18)
Severe (mRS score, 5)	3 (10)	4 (27)	28 (8)	18 (6)
Fatal (mRS score, 6)	11 (35)	7 (46)	73 (20)	80 (29)
Gastrointestinal bleeds among other major bleeds†	105 (38)	7 (39)	129 (61)	232 (65)
Patients experiencing dyspepsia	152 (1.67)	44 (1.58)	152 (1.67)	152 (1.67)

mRS = modified Rankin scale.
*The number of nondisabling (mRS 0–2), disabling (mRS 3–6), and fatal (mRS 6) strokes was available for edoxaban; therefore, the distribution of disabling strokes between mRS 3 to 4 and mRS 5 was calibrated assuming the same distribution as that observed in the apixaban arm. The number of mild, moderate, severe and fatal strokes in patients treated with subsequent aspirin was estimated based on pooled data from both the apixaban and aspirin arms in AVERROES due to small number of events.
†Based on all-cause mortality excluding deaths attributable to stroke, bleeding, myocardial infarction, and systemic embolism.

assessed during a lifetime. Key clinical events included were total number of strokes and systemic embolisms, including first and recurrent ischemic and hemorrhagic strokes, and total number of major bleeds. In addition, total costs, life-years gained, and quality-adjusted life-years (QALYs) gained were estimated for each treatment during a lifetime. Relative economic value was assessed through the use of incremental cost-effectiveness ratios (ICERs), using the UK payer's commonly used willingness-to-pay threshold of £20,000 to 30,000 per QALY gained.[29]

To explore the impact of various inputs, univariate sensitivity analyses were performed, where event risks, HRs, utility, and cost inputs were varied by their CIs. The most influential parameters were depicted through tornado diagrams.

Probabilistic sensitivity analysis was performed, whereby key model inputs were varied by randomly selecting values from assigned probability distributions during 2000 simulated model runs (called trials runs) to produce a number of incremental QALYs and costs in the form of a scatterplot.[12,13] A cost-effectiveness acceptability curve was then produced based on the probability of generating the maximum net benefit across comparators. The parameters and ranges, as well as distributions used in the univariate and probabilistic sensitivity analysis, are detailed in the Appendix.

RESULTS

Base Case Analysis

Table VII gives the predicted number of clinical events that correspond to each treatment for a cohort of 1000 VKA-suitable patients with NVAG during a lifetime. Apixaban, in comparison with low-dose edoxaban and high-dose edoxaban, resulted in 18 and 6 fewer strokes or systemic embolisms, respectively. Apixaban caused 53 more major bleeds than low-dose edoxaban but 9 fewer compared with high-dose edoxaban.

Table IV. Utility estimates for each health state.[24,26]

Health state	Utility, Mean (SE)
Health state	
Nonvalvular atrial fibrillation	0.7270 (0.0095)
Ischemic or hemorrhagic stroke	
Mild	0.6151 (0.0299)
Moderate	0.5646 (0.0299)
Severe	0.5142 (0.0299)
Myocardial infarction	0.6098 (0.0299)
Systemic embolism	0.6265 (0.0299)
Transient health state or anticoagulant use*	
Other intracranial hemorrhage (6 weeks)	0.1511 (0.0401)
Other major bleeds (2 weeks)	0.1511 (0.0401)
Clinically relevant nonmajor bleeds (2 days)	0.0582 (0.0173)
Other cardiovascular hospitalization (6 days)	0.1276 (0.0259)
Treatment with warfarin (while receiving treatment)	0.0130 (0.00–0.08)
Treatment with apixaban, edoxaban, or aspirin (while receiving treatment)	0.0020 (0.00-0.04)

*Utility decrements.

Table V. Drug acquisition costs.[30]

Drug	Daily Cost, £
Apixaban (5 mg BID)	2.20
Warfarin (mean, 5 mg daily)	0.04
Aspirin (75 mg BID)	0.02
Edoxaban (30 mg once daily)*	2.20
Edoxaban (60 mg once daily)*	2.20

*Data are based not only on Electronic Drug Tariff 2013, Department of Health by the NHS Business Services Authority, NHS Prescription Services[30] but also on assumption.

The reduction in stroke and systemic embolism events resulted in 0.073 gains in QALYs and in cost-savings of £48 per patient over a lifetime, when comparing apixaban with low- and high-dose edoxaban. The same event reduction resulted in 0.037 gains in QALYs and in additional costs of £248 per patient for apixaban compared with high-dose edoxaban.

Positive gains in QALYs and cost-savings deemed apixaban a dominant treatment alternative to low-dose edoxaban. Apixaban was deemed to be cost-effective versus high-dose edoxaban with an ICER of £6703 per QALY gained, below the commonly accepted threshold of £20,000 per QALY gained.[29]

Sensitivity Analyses

The tornado diagrams (Figure 2A and B) present the deterministic sensitivity analyses results, depicting the parameters with the greatest impact on the ICER. The ICERs of apixaban versus low-dose edoxaban were below the commonly accepted threshold of £20,000 per QALY in all variations studied and varied between apixaban being dominant (ie, apixaban costing less while being at least as effective as the comparator) and £9511 per QALY gained. For the analysis of apixaban versus high-dose edoxaban, the ICERs similarly varied from apixaban being dominant in some scenarios to being dominated in one scenario. Key sensitivity analysis scenarios in which apixaban was not a cost-effective alternative versus high-dose edoxaban were the following: (1) assuming a reduction in ischemic stroke risk for high-dose edoxaban and (2) assuming high-dose edoxaban has a benefit compared with apixaban in reducing the risk of deaths unrelated to stroke and major bleedings.

Probabilistic Sensitivity Analysis

Results of the probabilistic sensitivity analysis are plotted as the difference in the total aggregate costs between apixaban and edoxaban on the y-axis versus difference in QALYs accrued through lifetime use of these drugs on the x-axis (also known as cost-effectiveness plane) (Figure 3). The cost-effectiveness planes illustrate the cost and effect combinations of different strategies, as obtained by accounting for the uncertainty surrounding the base case inputs.

As depicted in Figure 3, in comparison to low-dose and high-dose edoxaban, most simulations were

Table VI. Cost input from UK National Health Service payer perspective.[27,28,30]

Event	Acute Care Cost, £ (95% CI)	Long-term Maintenance Cost per Month, £ (95% CI)
Ischemic stroke		
Mild	3639 (0–27,660)	190 (0–1144)
Moderate	18,986 (304–74,273)	371(0–2370)
Severe	25,931 (3667–69,504)	564 (0–4448)
Fatal	3273 (136–11,228)	
Hemorrhagic stroke		
Mild	10,597 (3351–21,939)	190 (0–1144)
Moderate	27,224 (10,922–50,840)	371 (0–2370)
Severe	46,050 (26,322–71,206)	564 (0–4448)
Fatal	1704 (12–7292)	
Myocardial infarction	2368 (1721–2826)	9 (5–13)
Systemic embolism	4221 (0–27,910)	190 (0–1144)
Other intracranial hemorrhage	3231 (2415–3796)	
Gastrointestinal bleeds	1625 (1274–1854)	
Nonintracranial or nongastrointestinal-related bleed	3847 (2496–4560)	
Clinically relevant nonmajor bleeding	1183 (864–1372)	
Other cardiovascular hospitalization	1770 (1275–1999)	

located in the northeast and southeast quadrants, indicating that apixaban was more effective than either of these treatment options. Compared with low-dose edoxaban, apixaban was cost-saving and more effective in 36% of simulations. Apixaban was more effective, albeit at a slight incremental cost accrued due to lower discontinuation rates, with an ICER below £20,000 per QALY gained (ie, cost-effective) in 87% of simulations (Figure 3A). Compared with high-dose edoxaban, apixaban was dominant (ie, cost-saving and more effective) in 39% of simulations. Apixaban was more costly and more effective, with an ICER below the £20,000 per QALY gained threshold in 72% of simulations (Figure 3B). The cost-effectiveness acceptability curve, including apixaban and low- and high-dose edoxaban 60 mg (Figure 4), highlights that apixaban has the highest probability of being the most cost-effective treatment at a willingness-to-pay threshold of £3000 per QALY gained and above.

DISCUSSION

In this study, we found that apixaban provided cost-savings and greater QALY gains (thus dominant) versus low-dose edoxaban and was a cost-effective alternative to high-dose edoxaban for the prevention of stroke and other thromboembolic events during a lifetime. From the payer perspective, our analysis reveals that apixaban has the potential not only to be cost-effective compared with dabigatran and rivaroxaban but also to yield dominance or robust cost-effectiveness against edoxaban.

The model used in this study followed the established structure of a previously published cost-effectiveness model[12,13] but was expanded to include indirect comparisons against both doses of edoxaban, using the updated cost data from the most recent published estimates for costs of stroke[28] and current NHS reference costs.[27] This analysis is the first to compare the cost-effectiveness of a NOAC versus edoxaban, with only one study previously assessing the cost-effectiveness of edoxaban versus warfarin from an Italian NHS perspective.[31] Our analysis indicates that apixaban-dominated low-dose edoxaban was cost-effective compared with high-dose edoxaban at an ICER of £6703 per QALY gained. We only found 2 clinical scenarios in which apixaban was not cost-effective to high-dose edoxaban, namely, (1) assuming

Table VII. Base case results: total number of events, costs, life-years, and QALYs in cohort of 1000 patients with nonvalvular atrial fibrillation.

Variable	Apixaban	Edoxaban (30 mg)	Edoxaban (60 mg)
No. of events			
Stroke or systemic embolism*	298	316	304
Major bleeding†	204	151	213
Myocardial infarction	84	92	87
Other cardiovascular hospitalization	1,186	1,156	1,184
Other treatment discontinuation	635	633	656
Health outcomes (per patient)			
Life-years (undiscounted)	8.810	8.728	8.761
QALYs (discounted)	6.260	6.187	6.223
Costs (discounted per patient), £			
Clinical event costs	7223	7334	7182
Anticoagulants and management	3547	3484	3333
Monitoring	109	109	116
Total	10,879	10,927	10,631
Incremental results (apixaban vs edoxaban)			
QALYs		0.073	0.037
Costs, £		−48	248
Incremental cost-effectiveness ratio, £		Dominant	6703

QALYs = quality-adjusted life-years.
*Stroke or systemic embolism: first and recurrent ischemic and hemorrhagic stroke and systemic embolism.
†Major bleeding: first and recurrent hemorrhagic stroke, other intracranial hemorrhage, and other major bleeds.

an ischemic stroke risk reduction for high-dose edoxaban compared with apixaban and (2) assuming high-dose edoxaban has a benefit in reducing the risk of deaths unrelated to stroke and major bleedings compared with apixaban. However, ITC data based on ENGAGE-AF and ARISTOTLE does not support either of these scenarios. This finding is consistent with findings from other published ITCs that found no significant differences between high-dose edoxaban and apixaban in reducing stroke or systemic embolism or all-cause mortality.[10] Such evidence weakens the plausibility of high-dose edoxaban having a relative effect of 0.80 and 0.90 compared with apixaban in the reduction in the risk of ischemic stroke and death, respectively (the ranges tested in scenario analysis). Finally, clinical experts advise that there is no reason to believe that the NOACs would differ in mortality unrelated to stroke and bleeding events, further weakening the plausibility that edoxaban has a positive impact on other-cause mortality.

Assuming price parity between apixaban and edoxaban, apixaban provided cost-savings versus low-dose edoxaban mainly because of a reduction in stroke events and subsequently health care costs associated with stroke during a lifetime. In our estimation, payers may prefer a NOAC that yields cost-savings while also producing greater benefits in terms of QALYs gained. Compared with high-dose edoxaban, reduction in health care costs with apixaban due to the slight reduction in number of strokes was offset by additional drug costs in apixaban-treated patients due to longer life expectancy and fewer major bleeds and subsequent discontinuations, both of which lead to longer treatment times. Although data are limited at this time, these aspects may prove to be important from the patient perspective as ideal aspects of anticoagulant care.

Similarly to the earlier published analyses,[12,13] several caveats apply to our analysis. The use of clinical trial data to inform event rates may not reflect actual clinical practice rates in the UK population,

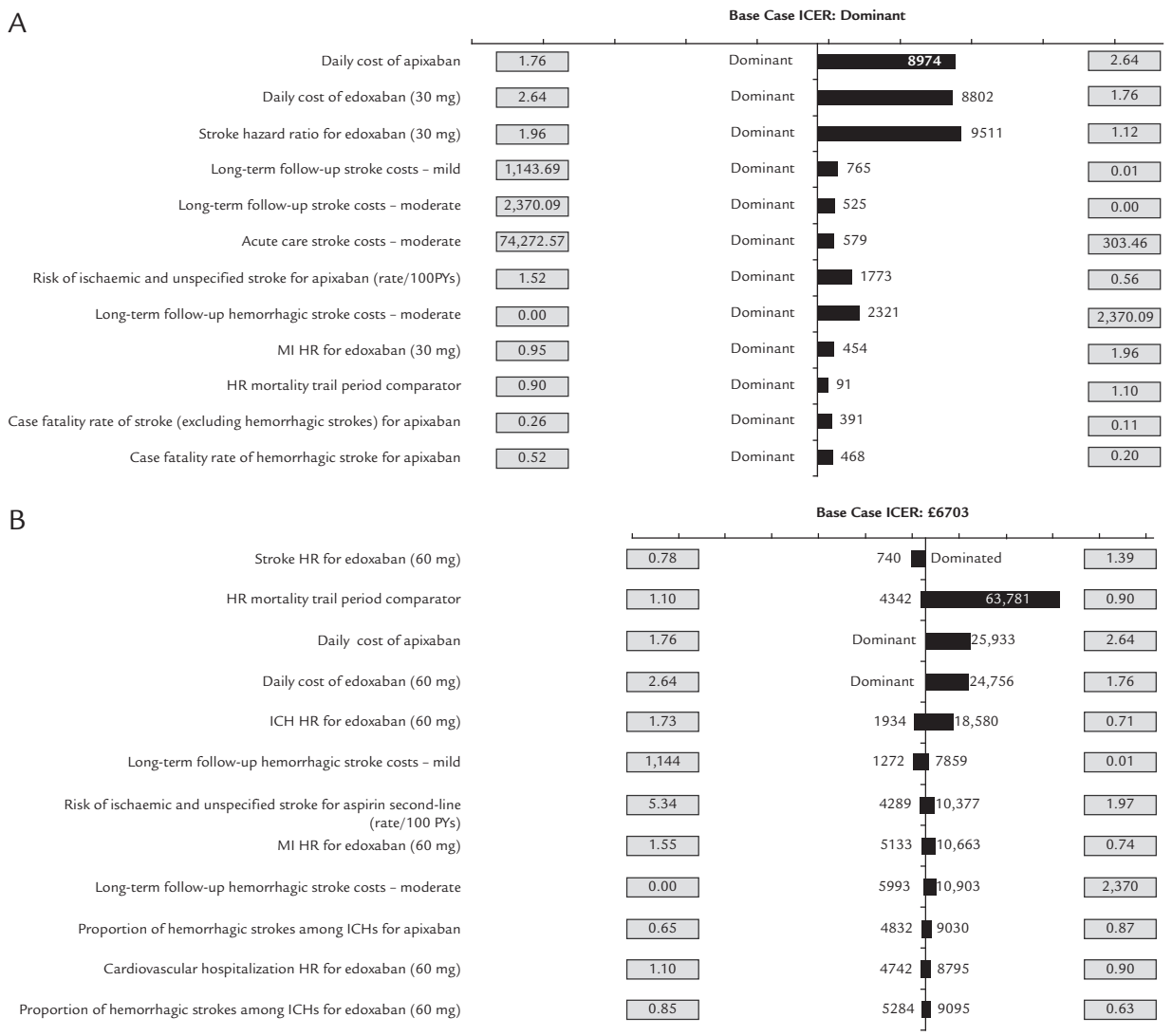

Figure 2. One-way sensitivity analysis of apixaban versus edoxaban 30 mg (A) and apixaban versus edoxaban 60 mg (B). HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ICH = intracranial hemorrhage; MI = myocardial infarction; PY = patient-years.

although there is broad comparability between clinical trials and real-world data for the NOACs.[32] Baseline characteristics used were similarly as observed in ARISTOTLE for consistency with the event rates used. However, an analysis of the UK General Practice Research Database suggests the AF population in the United Kingdom has a slightly higher mean age compared with the mean observed in ARISTOTLE (74 vs 70 years) and a higher proportion of patients with low risk of score (ie, $CHADS_2$ scores, 0–1).[33] We therefore examined results when baseline characteristics were set to be equivalent to those observed in a UK population in terms of age and $CHADS_2$ profile. Compared with high-dose edoxaban, this scenario resulted in a slight increase of the ICER to £7044 per QALY gained, whereas compared with low-dose edoxaban, apixaban remained dominant. This finding suggests that our base case conclusions remain unaltered, regardless of the source used to inform baseline characteristics.

Furthermore, there is currently no available retail price listed for edoxaban; therefore, our base case

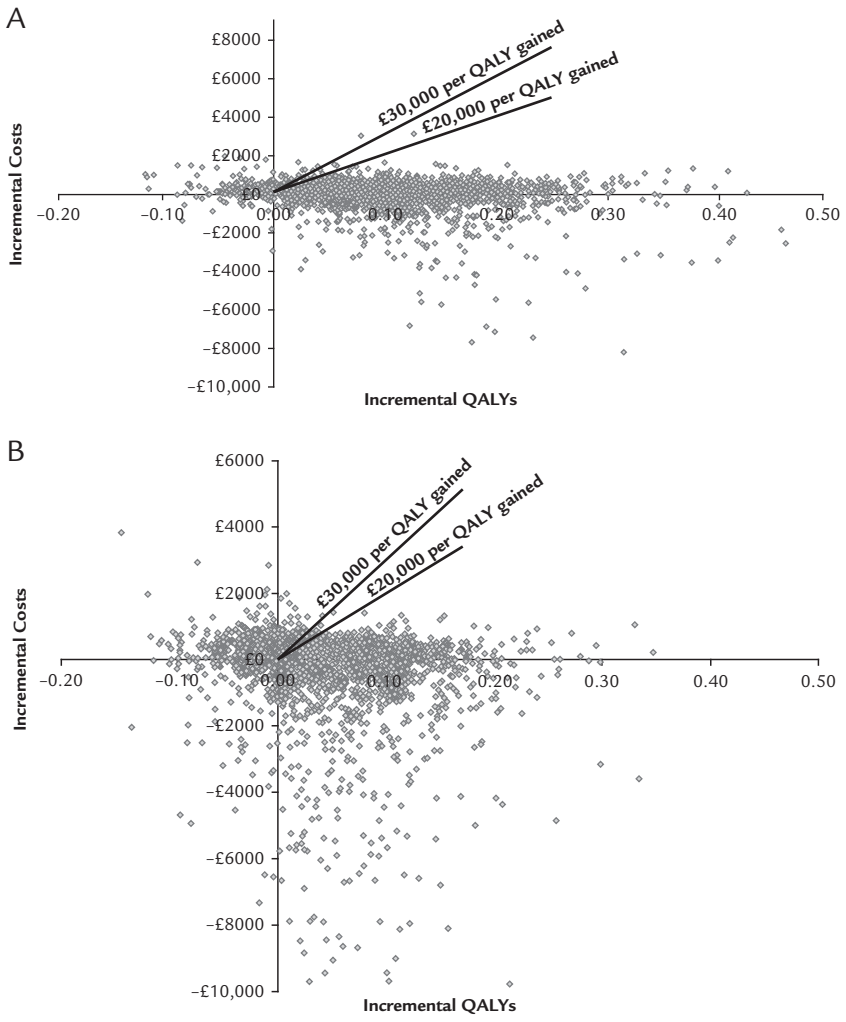

Figure 3. Probabilistic sensitivity analyses for apixaban versus edoxaban 30 mg (A) and apixaban versus edoxaban 60 mg (B). The scatterplots are a graphical illustration of cost-effectiveness.[29] Simulations appearing in the northeast quadrant denote the intervention of interest is more costly but generates more QALYs. Simulations appearing in the southeast quadrant denote the intervention is cost-saving and more effective. From a payer's perspective, new treatments should provide more value in terms of QALYs for a patient, while not exceeding the payer's willingness-to-pay threshold. QALY = quality-adjusted life-year.

analysis assumes price parity to apixaban and dabigatran. To address this limitation, the daily price of both low- and high-dose edoxaban was varied by 20% as part of the univariate sensitivity analysis, which resulted in apixaban being cost-effective versus both doses of edoxaban at willingness-to-pay thresholds below £30,000 per QALY gained.

In the absence of head-to-head trials, an ITC was used to obtain the treatment effects between apixaban and both edoxaban doses. The ITC did not control for differences in baseline patient characteristics, such as stroke risk measured by $CHADS_2$ or quality of INR control. Although the median center–based time in therapeutic range was similar between the 2 trials (66% in ARISTOTLE[6] and 68% in ENGAGE-AF[16]), the mean $CHADS_2$ score was higher in ENGAGE-AF (2.1[6] vs. 2.8[16], respectively). The higher $CHADS_2$ score is of particular importance because of its contribution to stroke and major bleeding rates, which could explain the differences observed in the VKA arm between

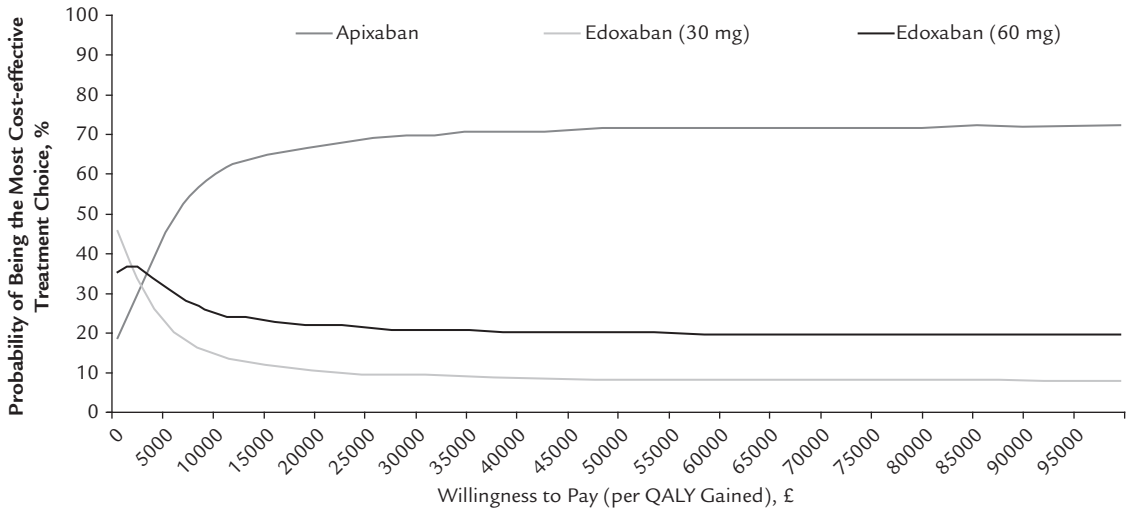

Figure 4. Cost-effectiveness acceptability curves indicating preferred treatment option at various willingness-to-pay thresholds. The cost-effectiveness acceptability curve provides the probability of an intervention being the most cost-effective alternative, given the uncertainty surrounding inputs. QALY = quality-adjusted life-year.

ARISTOTLE[6] and ENGAGE-AF.[16] For example, the event rate per 100 patient-years observed among VKA-treated patients for stroke was 1.51 in ARISTOTLE and 1.69 in ENGAGE-AF. The major bleeding rate per 100 patient-years was 3.09 and 3.43 in ARISTOTLE[16] and ENGAGE-AF.[6] A numerically improved HR for stroke was observed among patients with higher $CHADS_2$ scores for both edoxaban and apixaban compared with VKA.[6,16] It is therefore possible that the higher $CHADS_2$ score may have yielded a larger effect size for edoxaban in ENGAGE-AF in stroke outcomes. The converse may be possible for major bleeding outcomes because the effect size for both apixaban and edoxaban was numerically worsened among patients with higher $CHADS_2$ scores. However, the differences in treatment effects observed for stroke and major bleeding between the $CHADS_2$ subgroups were not significant in either of the trials. We subsequently found the treatment effects used in our analysis to reflect the best available evidence in absence of head-to-head trials.

Results from the univariate sensitivity and probabilistic analysis revealed that apixaban still remained a cost-effective alternative to both doses of edoxaban. Therefore, the use of ITC data reflects a conservative scenario and the best available evidence to inform this analysis.

From the payer perspective, it is of interest that apixaban has the potential to be not only cost-effective compared with dabigatran and rivaroxaban but also dominant or cost-effectiveness against edoxaban. This finding can be attributed to the superiority of apixaban versus warfarin in efficacy and tolerability outcomes,[6] whereas both doses of edoxaban have superiority to warfarin in tolerability outcomes and noninferiority in efficacy outcomes.[16] In this indirect analysis, apixaban subsequently revealed a unique efficacy and tolerability balance versus edoxaban when compared based on dosing regimens studied in NVAF trials.

CONCLUSION

Apixaban 5 mg BID provided cost-savings and greater QALY gains (thus dominant) versus low-dose edoxaban and was a cost-effective alternative to high-dose edoxaban for the prevention of stroke and other thromboembolic events during a lifetime from the UK NHS perspective. Our study adds to the evidence base with regard to the cost-effectiveness of apixaban versus edoxaban, which would potentially be the fourth NOAC drug to become available for the treatment of patients with NVAF.

ACKNOWLEDGMENTS

The authors would like to thank Karen Trewick for her assistance in editing the manuscript and creating figures.

All authors contributed equally to study design, data interpretation, revisions of the manuscript for important intellectual content and approval of the submission draft. Model programming and data collection was initially conducted by Tereza Lanitis and Thitima Kongnakorn, and reviewed by all co-authors. The initial outline and draft of the manuscript was developed by Corina Chalkiadaki and reviewed and edited by all co-authors.

FUNDING SOURCES

This work was funded by the BMS-Pfizer collaboration, employees of which were involved in the study design and writing and reviewing of the manuscript.

CONFLICTS OF INTEREST

G.Y.H. Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers' bureau or Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. T. Lanitis, T. Kongnakorn, and C. Chalkiadaki are employees of Evidera and were paid consultants to BMS/ Pfizer in connection with the development of this manuscript and of the model. H. Phatak and J. Lawrence are employees of BMS with ownership in stocks. J. Lawrence is an employee of Pfizer Inc with ownership in stocks. A. Kuznik was an employee of Pfizer with ownership in stocks at the time the study was conducted. P. Dorian has received consulting fees and research support from BMS, Pfizer, Bayer and Boehringer Ingelheim and served on the steering committee of the ARISTOTLE trial. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIALS

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.clinthera.2015.09.005.

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SUPPLEMENTARY APPENDIX TO "COST–EFFECTIVENESS OF APIXABAN COMPARED WITH EDOXABAN FOR STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION"

Technical Model Documentation

OBJECTIVE

The objective of this appendix is to provide additional technical documentation to the manuscript entitled "Cost–effectiveness of Apixaban Compared with Edoxaban for Stroke Prevention in Non-valvular Atrial Fibrillation" to enable full technical transparency. In the sections below we provide further granularity and details on the model more specifically on structure, inputs and detailed results to accompany the manuscript. This appendix largely follows that published in Doran et al (2014).[1]

MODEL STRUCTURE

NVAF STATE

All patients start with the non-valvular atrial fibrillation (NVAF) state, defined as patients with AF on anticoagulation who have not yet experienced any event within the model. Patients with NVAF may remain in the same health state staying on anticoagulation assigned at baseline if no events occur. The model simulates the following clinical outcomes depending on treatment:

- Ischaemic/unspecified stroke (non-hemorrhagic)
  - Non-fatal
    - Mild
    - Moderate
    - Severe
  - Fatal
- Non-fatal mild/moderate/severe and fatal recurrent ischemic/unspecified stroke
- Intracranial hemorrhages (ICH)
  - Non-fatal
    - Hemorrhagic stroke
      - Mild
      - Moderate
      - Severe
    - Other ICH
  - Fatal ICH
    - Hemorrhagic stroke
    - Other ICH
  - Recurrent hemorrhagic strokes are considered separately.
- Other Major bleeds
  - Non-fatal
    - Gastrointestinal (GI)
    - Other non-ICH and non-GI
  - Fatal
    - Gastrointestinal (GI) bleeds
    - Other non-ICH and non-GI
- Clinically relevant non-major (CRNM) bleeds
- Myocardial infarction (MI)
  - Non-fatal
  - Fatal
- Systemic embolism (SE)
  - Non-fatal
  - Fatal
- Other treatment discontinuations (discontinuations unrelated to stroke (all types), SE, MI and bleeding)
- Other cardiovascular hospitalizations (CV hospitalizations unrelated to stroke (all types) and MI)
- Other deaths (deaths unrelated to stroke (all types) and bleeding)

Detailed descriptions and assumptions around each clinical outcome (i.e., each event branch in Figure A1) are described below.

Stroke

Stroke events are segregated by ischemic and hemorrhagic due to their different natures. Hemorrhagic strokes are considered as part of bleeding types. The risk of ischemic stroke is dependent on current anticoagulant and is adjusted each cycle to reflect increased risks over time. Baseline ischemic stroke risks for the cohort are determined by $CHADS_2$ distribution among the cohort (i.e., weighted average risk of distribution of $CHADS_2$ and ischemic stroke risk for each $CHADS_2$ level). The model permits analysis of the impact of $CHADS_2$ on outcome through changes in baseline characteristics of the population (e.g., distribution of $CHADS_2$ scores). However, the model does not model change in $CHADS_2$ and its associated ischemic stroke risk during the model time horizon (e.g., when patients become older than 75 years old or experience a stroke). The model, however, increases the risk of ischemic stroke on per decade basis as described in the manuscript.

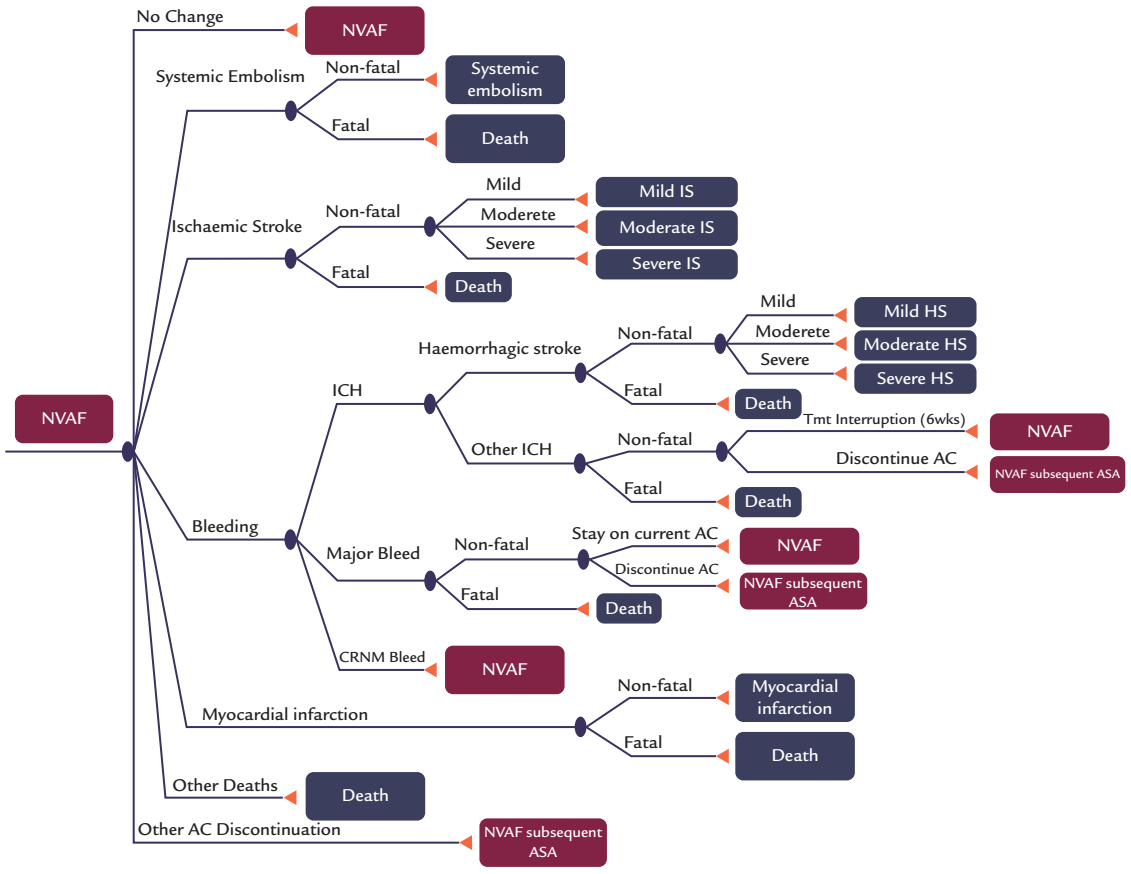

Figure A1. Decision sub-tree for NVAF.

On the occurrence of an ischemic stroke, a distribution of the modified Rankin scale (mRS) is applied to determined fatal strokes (i.e., mRS 6) and three severity levels of non-fatal strokes: mild (mRS 0-2), moderate (mRS 3-4) and severe (mRS 5). All fatal strokes are transferred to death state in the next cycle. Patients who survived an ischemic stroke transition to the three ischemic stroke health states: (i.e., mild, moderate, severe) according to the severity distribution. Patients in each of the three ischemic stroke health states are at risk of recurrent ischemic stroke independently of prior treatment. Those determined to have a recurrent ischemic stroke transition to recurrent stroke states (i.e., mild, moderate, severe) according to the severity distribution while the remaining patients stay on the same ischemic stroke health states. The severity distribution of recurrent ischemic stroke is conditioned on the severity of the prior stroke. Recurrent ischaemic stroke states are treated as tunnel states where an acute care cost is applied per episode then the patients will transition to the most severe of the first or recurrent stroke health states. Only one recurrent ischemic stroke is allowed for each patient. All non-fatal ischemic stroke health states are modelled as semi-absorbing states (Figure A2). This means that once patients experience a non-fatal ischemic stroke (including the recurrences); they can only transition to death state, indicating that subsequent events are not modeled.

Costs and health outcomes as well as hazard ratios (HRs) of death vary by ischemic stroke severity. A utility is assigned to patients with ischemic stroke based on their severity. Post- ischemic stroke resource use and costs are separated into acute and long-term maintenance phases. Acute phase comprises the time spent in hospitalization and rehabilitation facility.

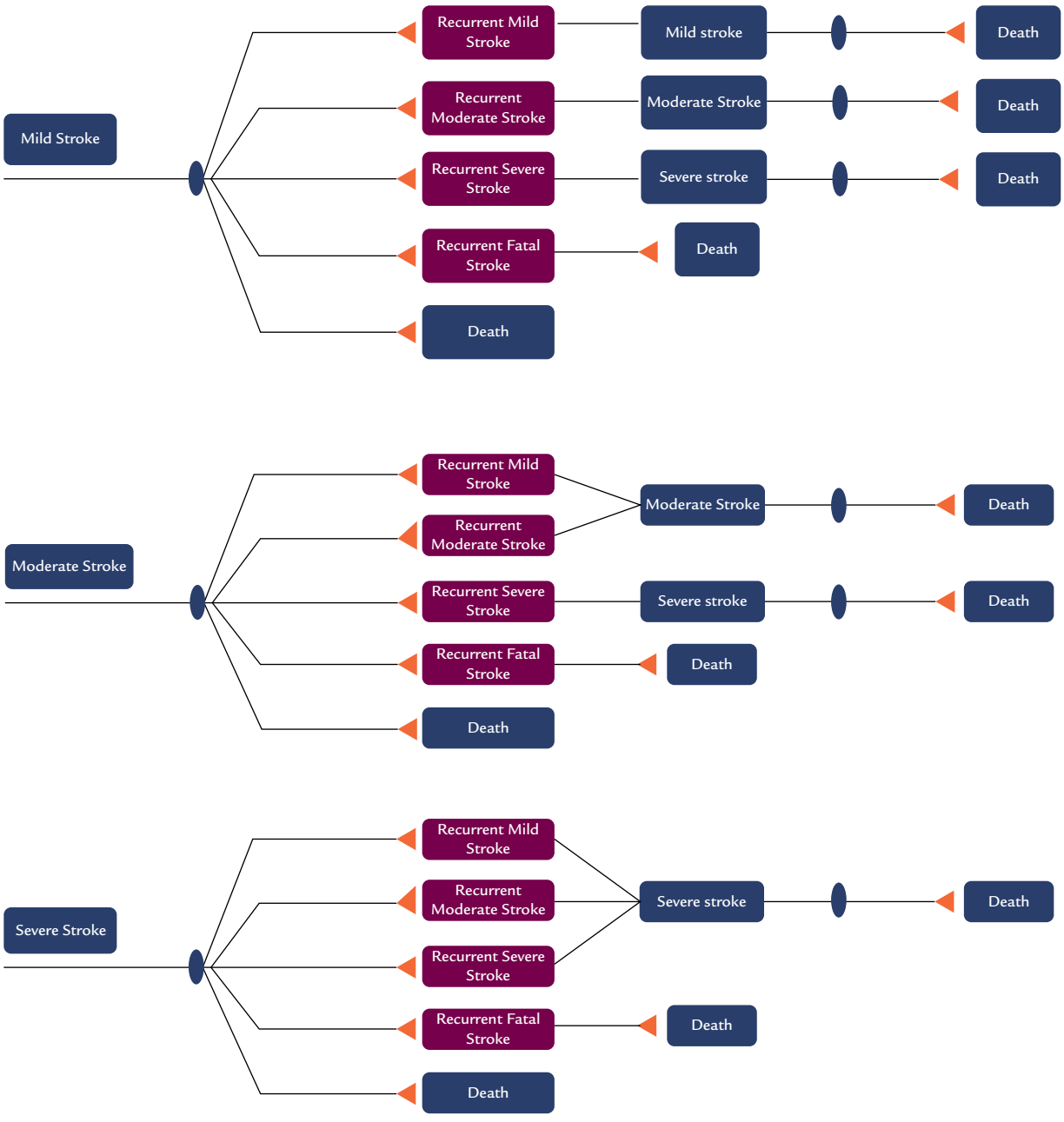

Figure A2. Decision sub-trees for stroke (ischemic and hemorrhagic).

Upon the occurrence of an ischemic stroke event patients may stay on the initially assigned anticoagulant or switch to warfarin. Warfarin was selected as a switch treatment as it is current standard of care (SoC) across the world and physicians are more likely to prescribe warfarin if a decision is made to switch patients after occurrence of stroke. while, this has no impact in terms of effectiveness, it reduces anticoagulation costs upon switch to warfarin.

Intracranial Hemorrhage (ICH)

Event rates for ICHs are differed across treatments and are adjusted each cycle to reflect an

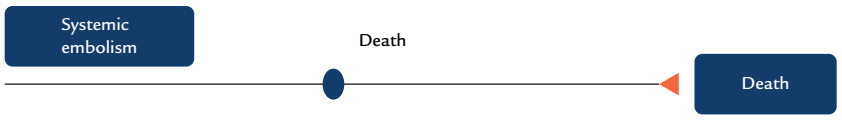

Figure A3. Decision sub-tree for systemic embolism.

increase in risk over time (e.g., due to aging). As described earlier, the model allows an option of having bleeding risks (i.e., risks of ICH, other major bleeds, and CRNM bleeds) adjusted based on quality of INR control represented as distribution of cTTR. ICHs are further categorized into haemorrhagic strokes and other ICHs (i.e., subdural hemorrhage). Similarly to the risk of recurrent ischemic strokes in patients who have already experienced such an event, patients experiencing hemorrhagic stroke are at risk of the recurrent hemorrhagic strokes. Recurrent hemorrhagic stroke health states are modeled as tunnel states where the acute care costs are accrued and the patients' then transition to the most severe of first or recurrent hemorrhagic stroke health states. Hemorrhagic stroke states are modelled as semi-absorbing health states (Figure A2); therefore no subsequent events are modeled after the occurrence of a hemorrhagic stroke apart from recurrent hemorrhagic stroke events. Similar to ischemic strokes, the risk of hemorrhagic stroke increases over decade as described in the manuscript. Similarly to ischemic strokes, severity levels according to mRS are assigned to non-fatal cases with costs, health outcomes and HRs of death varying according to severity. Upon the occurrence of a hemorrhagic stroke it is assumed that all patients discontinue anticoagulant treatment completely. Utilities are assigned based on severity level and acute care costs and long-term maintenance costs are accumulated similarly to patients with stroke.

Upon the occurrence of the other ICH, the non-fatal cases may discontinue anticoagulant treatment temporarily for a period of a cycle (six weeks) as advised by experts or discontinue anticoagulant treatment completely according to observations of patients restarting anticoagulation after warfarin-associated ICH. Patients having their initially assigned anticoagulant treatment interrupted are modelled as transient state.* Patients who completely discontinue their current anticoagulant are transferred to the NVAF with subsequent ASA state and start on a second line treatment which is assumed to be aspirin in the base case. Apart from the acute mortality associated with other ICHs, the model assumes no additional impact on mortality. Utility decrement is applied upon the occurrence of the other ICH for the duration of six weeks.

Other Major Bleeds

Similar to the ICHs, event rates for other major bleeds are differed across treatments and are adjusted each cycle to reflect an increase in risk over time and can be adjusted by the distribution of cTTR. Other major bleeds are classified into GI bleeds and non-GI/non-ICH related bleeds. Patients who survive GI or non-GI/non-ICH related bleeds may stay on their initially assigned anticoagulant or discontinue the current anticoagulant treatment. Those staying on the initial anticoagulant are modeled as transient state.* Those discontinuing the treatment are transitioned to the NVAF with subsequent ASA health state and get second line treatment started (i.e., aspirin as base case). Upon the occurrence of other major bleed, utility decrement is applied for two weeks as used in Freeman et al. (2011)[2] and no impact on long term mortality is assumed. No differentiation in utilities is made between the two types of major bleeds. Resource use associated with other major bleeds includes acute care costs which are applied on a per episode basis. Other major bleeds are segregated by GI bleeds and other non-ICH non-GI major bleeds and costed accordingly.

*When an event is modeled as a *transient state,* the model processes the event in such a way that: 1) Event cost is applied based on a per-episode basis, i.e., a one-time fixed cost; 2) Utility decrement is applied for a defined duration; 3) Patients cycle back to their previous health state after the event is processed, i.e., the model assumes no impact on subsequent event risks and the AC treatment that follows.

CRNM Bleeds

Similar as the other types of bleeding, CRNM bleeds event rates are adjusted each cycle to reflect an increase in risk over time and can be adjusted by quality of INR control (i.e., by distribution of cTTR). All patients experiencing CRNM bleeds are assumed staying on their initially assigned anticoagulant and are modeled as a transient state[†]. By definition of the CRNM bleeds, no acute mortality and impact on long term mortality are assumed. Utility decrement is applied for a user-defined duration (i.e., two days as base case) and acute care costs are accrued upon the occurrence of the event.

Myocardial Infarction (MI)

Event rates for MI are differed across treatments and are adjusted each cycle to reflect an increase in risk over time (e.g., due to aging). Patients who experience an MI are assumed to discontinue treatment as advised by experts. MI is a semi-absorbing state therefore patients are not at risk for additional events. Patients are expected to get standard anticoagulant hence such costs are not considered incremental in nature. A utility associated with MI is applied to patients in the health state. Post-MI resource use consists of acute care. Maintenance costs are accrued over a patient's lifetime. Patients can experience a fatal or non-fatal MI based on gender specific case fatality rates. The long term impact of MI on mortality is taken into account through applying increased HRs of death.

Systemic Embolism (SE)

Patients who experience an SE may stay on the initially assigned anticoagulant or switch to warfarin. Warfarin was selected as a switch treatment as it is the current SoC across the world and physicians are more likely to prescribe warfarin if a decision is made to switch patients after occurrence of SE. This has no impact in terms of effectiveness but impacts anticoagulation costs. SE is a semi-absorbing state therefore patients are not at risk for additional events. A utility associated with SE is applied to patients in the health state. Post-SE resource use consists of acute care and maintenance costs are accrued over a patient's lifetime. Patients can experience a fatal or non-fatal SE and the long term impact of SE on mortality is taken into account through applying increased HRs of death.

[†]When an event is modeled as a *transient state,* the model processes the event in such a way that: 1) Event cost is applied based on a per-episode basis, i.e., a one-time fixed cost; 2) Utility decrement is applied for a defined duration; 3) Patients cycle back to their previous health state after the event is processed, i.e., the model assumes no impact on subsequent event risks and the AC treatment that follows.

Other Deaths

Other deaths represent deaths from causes unrelated to strokes (all types), MI, SE and bleedings. Patients identified experiencing deaths are transferred to death state.

Other Treatment Discontinuation

Treatment discontinuations that are unrelated to stroke (all types), MI, SE, and bleeding are explicitly modelled. If patients discontinue treatment, they are transferred to the NVAF with subsequent ASA state. The patients are assumed to switch to second line aspirin in the base case.

CV Hospitalization

CV hospitalisation is modeled in the background and not as a health state. CV hospitalizations are associated with an acute cost and a decrement in utility. Since stroke (all types) and MI hospitalisations are explicitly modeled, CV hospitalization rates exclude hospitalizations due to strokes (all types) and MIs to avoid double counting.

Stroke Health State (Figure 2)

As described earlier, non-fatal ischemic strokes and non-fatal hemorrhagic health states are modeled as semi-absorbing states, i.e. no risk associated with subsequent events other than death. This means that once patients experience a non-fatal stroke or hemorrhagic stroke patients can only transition to death either through the tunnel state of one recurrent stroke or through the semi-absorbing stroke health state when their life expectancy have been reached. Thus after the first stroke event no subsequent events are modelled apart from recurrence. Only one recurrence is modeled.

SE and MI Health State (Figure A3 and Figure A4)

As described earlier, non-fatal SEs and MIs are modeled as semi-absorbing states. This means that once patients experience a non-fatal SE or MI,

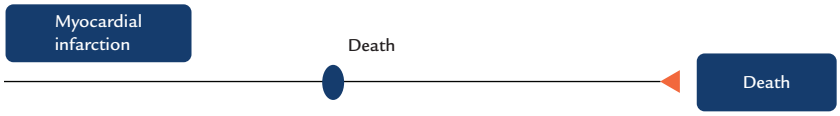

Figure A4. Decision sub-tree for myocardial infarction.

patients can only transition to death when their life expectancy have been reached, indicating that subsequent events after SE or MI are not modelled.

NVAF with Subsequent ASA Health State (Figure A5)

Patients can discontinue treatment due to reasons unrelated to stroke (all types), SE, MI or bleeds or

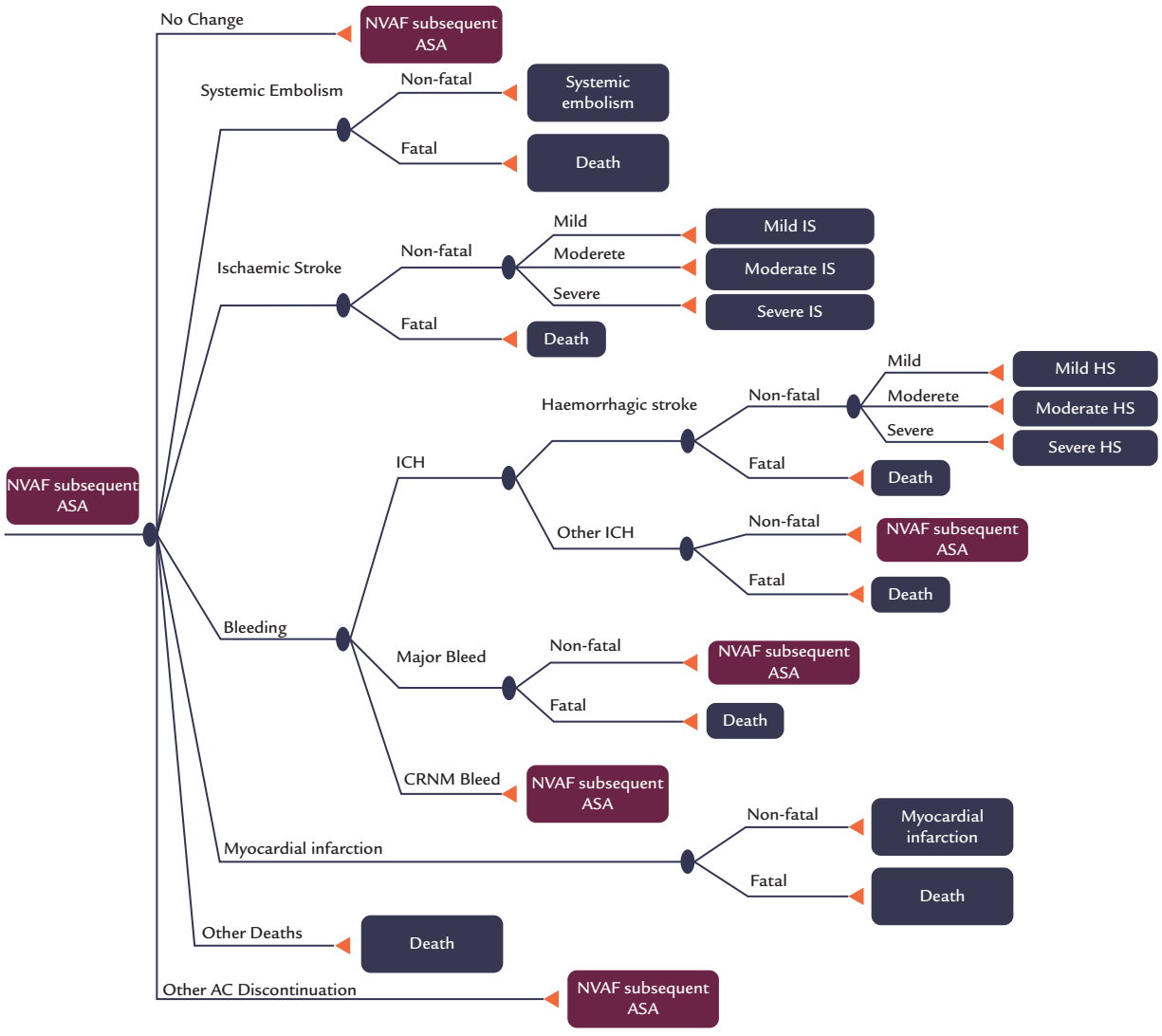

Figure A5. Decision sub-tree for NVAF subsequent ASA.

discontinue due to ICH or other major bleed. Patients, who discontinue transition to NVAF with subsequent ASA health state, are assumed to start a second line aspirin treatment in the base case. However, the model also allows for warfarin and no treatment (i.e., completely discontinue) as second line treatment options. Note that warfarin is allowed as a second line treatment only for the VKA suitable patients if the comparator analysed is not warfarin. For patients who receive aspirin as their initial AC treatment, the model assumes no treatment discontinuation if the second-line treatment choice is aspirin. Upon a switch to second-line use of aspirin, this model assumes no subsequent treatment discontinuations and a constant risk of bleeding, stroke, SE, and MI independent of duration of second line treatment use, and prior anticoagulant treatment or patient characteristics.

Anticoagulant Treatment Choice Post an Event

Upon the occurrence of stroke or SE, all patients' initially assigned aspirin were assumed to discontinue their current treatment and switch to warfarin. All patients on apixaban or warfarin were assumed to continue on the original treatments, according to the expert opinions.

After an ICH, 56% of the patients switched treatment (i.e., to aspirin in the base case). The remaining 44% had treatment interruption for six weeks.[3] While for an occurrence of other major bleeds, the same assumption as in the Sorensen et al. (2009)[4] was employed in which 25% of the patients had treatment switch (i.e., to aspirin in the base case).

Clinical Event Rates

The clinical event rates in the model were obtained from the apixaban clinical trials (i.e., AVERROES[5] and ARISTOTLE[6]) as detailed in the manuscript and previous publications.[1,7] The rates per 100 patient years were converted into risks per cycle (i.e., 6 weeks – 42 days) using the following formula:

- Rate per day = Rate per 100 patient years/365.25/100
- Risk per cycle = $1-e^{-(0.0038\%*42)}$

For example, the rate per 100 patient years of MI for patients on apixaban in the VKA suitable population and in the NVAF state is 0.53. The transition probability from NVAF to MI per cycle is calculated as follows:

- Rate per day (MI) = 0.53/365.25/100 = 0.0145%
- Risk per cycle (MI) = $1-e^{-(\text{Rate per day } *42)}$ = 0.061%

Clinical event rates for edoxaban were derived using the Indirect Treatment Comparison (ITC) approach consistently with a previously published study.[7] In particular, indirect comparisons between apixaban and edoxaban via warfarin as the common comparator were made using the Bucher method[8] and the reported hazard ratios (HRs). The (indirect) HR between apixaban and the edoxaban is given by:

$$\log(HR_{AVB}) = \log(HR_{AVC}) - \log(HR_{BVC})$$

With standard error given by:

$$SE[\log((HR_{AVB})] = \sqrt{SE[\log((HR_{AVC})]^2 + SE[\log((HR_{BVC})]^2}$$

The obtained HRs for edoxaban are detailed in the manuscript. For application in the model the event rate for edoxaban was calculated using the following formula:

- Rate per day (edoxaban) = Rate per day (apixaban)* HR (edoxaban)

The transition risks from the NVAF health state estimated in the first cycle for a male population are displayed in Table A1. Transition risks are only displayed for the first cycle, thus subsequent transitions from each health state are not displayed, but can be calculated in the same manner.

Utilities

Patients were assigned utilities according to their health states. Utility inputs were obtained from UK-based utility catalogue.[9] A baseline utility was applied to all patients, based on a utility score specific for patients with AF. Utilities were updated upon the occurrence of stroke or haemorrhagic strokes with different utility scores for different severity level (i.e., mild, moderate, severe).Utility for stroke health states was calculated by subtracting the disutility associated with acute cerebrovascular disorders as well as the disutility associated with chronic co-morbidities from the baseline AF utility. The utility did not vary by severity, therefore to proxy for mild, moderate and severe strokes weights of 0.5, 1, and 1.5 were applied to the disutility respectively. Similarly utilities for MI

Table A1. Transition Matrix from NVAF state for apixaban.

	Apixaban	Edoxaban 30mg	Edoxaban 60mg
NVAF	(100%-0.354%)*(100%-0.113%-0.038%-0.206%-0.239%-0.010%-0.061%-1.504%) = 97.48%	(100%-0.354%)*(100%-0.167%-0.028%-0.136%-0.227%-0.014%-0.084%-1.564%)= 97.78%	(100%-0.354%)*(100%-0.117%-0.042%-0.232%-0.299%-0.008%-0.065%-1.653%)= 97.24%
Ischemic stroke (IS)[†]	**0.113%**	**0.167%**	**0.117%**
Mild IS	= 0.113%*53% = 0.060%	= *0.167%*50% = *0.084%*	= *0.117%*47% = *0.055%*
Moderate IS	= 0.113%*21% = 0.024%	= *0.167%*22% = *0.037%*	= *0.117%*18% = *0.021%*
Severe IS	= 0.113%*8% = 0.009%	= *0.167%*8% = *0.013%*	= *0.117%*6% = *0.007%*
Fatal IS	= 0.113%*18% = 0.020%	= *0.167%*20% = *0.033%*	= *0.117%*29% = *0.034%*
Intracranial hemorrhage (ICH)[†]	**0.038%**	**0.028%**	**0.042%**
Hemorrhagic stroke	= *0.038%*77% = 0.029%*	= 0.028%*69% = *0.019%*	= *0.042%*75% = 0.032%*
Mild HS	= 0.029%*23% = 0.007%	= *0.019%*50% = *0.010%*	= *0.032%%*47% = *0.000%*
Moderate HS	= 0.029%*32% = 0.009%	= *0.019%*22% = *0.004%*	= *0.032%*18% = *0.006%*
Severe HS	= 0.029%*10% = 0.003%	= *0.019%*8% = *0.002%*	= *0.032%*6% = *0.002%*
Fatal HS	= 0.029%*35% = 0.010%	= *0.019%*20% = *0.004%*	= *0.032%*29% = *0.009%*
Other intracranial hemorrhage	= *0.038%*23% = 0.009%*	= 0.028%*31% = *0.009%*	= *0.042%*25% = 0.011%*
Non-fatal other ICH	= 0.009%*87% = 0.008%	= 0.009%*87% = 0.008%	= 0.009%*87% = 0.008%
Fatal other ICH	= 0.009%*13% = 0.001%	= 0.009%*13% = 0.001%	= 0.009%*13% = 0.001%
Other major bleeds[†]	**0.206%**	**0.136%**	**0.232%**
Non-fatal other major bleeds	= *0.206%*98% = 0.202%*	= *0.136%*98%*=0.013%	= 0.232%*98% =0.023%
Gastrointestinal bleeds	= 0.206%*38% = 0.078%	= *0.136%*61%*=0.083%	= 0.232%*65% =0.015%
Other non-gastrointestinal and non-ICH major bleeds	= 0.206%*62% = 0.127%	= *0.136%*39%*=0.053%	= 0.232%*35% = 0.081%
Fatal other major bleeds	= *0.206%*2% = 0.004%*	= *0.136%*2%*=0.003%	= 0.232%*2% =0.005%
Clinically relevant non-major bleeds[†]	**0.239%**	**0.227%**	**0.299%**
Systemic embolism	**0.010%**	**0.014%**	**0.008%**
Fatal systemic embolism	= *0.010%*9% = 0.001%*	= *0.014%*9%*=0.001%	= *0.008%*9%*=0.001%
Non-fatal systemic embolism	= *0.010%*91% = 0.009%*	= *0.014%*91%*=0.013%	= *0.008%*91%*=0.007%

(continued)

Table A1. (continued).

	Apixaban	Edoxaban 30mg	Edoxaban 60mg
Myocardial infarction[†]	0.061%	0.084%	0.065%
Fatal Myocardial infarction	*= 0.061%*11% = 0.007%*	*= 0.084%*11%- =* 0.009%	*= 0.065%*11%* = 0.007%
Non-fatal Myocardial infarction	*= 0.061%*89%* = 0.054%	*= 0.084%*89%* = 0.075%	*= 0.065%*89%* = 0.058%
NVAF subsequent ASA	1.504%	1.564%	1.653%
Death[‡]	0.354%	0.354%	0.354%

Note: Risks of IS, ICH, other major bleeds, CRNM bleeds, systemic embolism, myocardial infarction are applied to the cohort remaining alive thus the risk of transition to each event is adjusted, however the unadjusted transition risks have been presented to demonstrate how the clinical data has been translated.
[†]Risks of these events are adjusted each cycle by a factor.
[‡]Applied for the duration of ARISTOTLE i.e. 1.9 years. UK mortality rates with adjustment factors used thereafter.

and SE were calculated by subtracting the disutility associated with acute myocardial infarction and arterial embolism from the utility of patients with AF. Utility decrements were applied to patients upon the occurrence of other ICHs, other major bleeds, CRNM bleeds, and CV hospitalizations (unrelated to stroke and MI) for certain duration specific for each event. Utility decrements associated with use of warfarin and aspirin were obtained from a study by Gage et al. (1996).[10] Utility decrements were applied additively. Calculations performed to obtain the utility estimates for health states are displayed in Table A2.

Resource Use and Unit Costs

Costs are reflected in 2011-2012 prices. Where publications were used all costs were inflated. The model accrues costs for the following resource use categories:

- Treatment costs (i.e., costs of ACs)
- Monitoring costs (for patients treated with warfarin)
- Management costs (i.e., costs related to dyspepsia, renal monitoring required)
- Acute care costs associated with clinical events (stroke, hemorrhagic stroke, other ICH, GI bleed, non ICH and non ICH related major bleed, CRNM bleed, and MI)
- Costs of fatal ischemic and hemorrhagic strokes
- Long-term care costs for stroke, hemorrhagic stroke, and MI
- Costs associated with other CV hospitalization

Treatment costs were obtained from the NHS drug tariffs and the Monthly Index of Medical Specialties (MIMS),[11,12] and in the case of Edoxaban, price parity with Apixaban was assumed. Table A3-A6

In the model, AC use is detailed by the size of the tablets, the cost per tablet, and the daily dose. Using these inputs, the number of tablets required per day and thus the average cost per day were calculated (Table III). Daily dose requirements were inputted according to guidelines. Note that the model assumes a change in average daily dose has no impact on treatment efficacy.

In addition to AC costs, a management cost per month was applied for all ACs. Costs were obtained from NHS reference costs.[14]

Routine care, monitoring costs, and costs associated with the clinical events were obtained from published literature and expert opinion.

Stroke costs were classified according to haemorrhagic or non-hemorrhagic (i.e., stroke), degree of severity (mild, moderate, severe) and type of cost (acute or long term maintenance). Acute care consisted of time spent in hospital and rehabilitation facility. Following the acute care period, patients

Table A2. Calculation of utility estimates used in model from EQ-5D catalogue.

	ICD-9 / CCC Disease Classification		Utility		
Health state	Code	Description	Disutility for Condition	Mean	SE
Atrial fibrillation	ICD-9 427	Cardiac Dysrhythmias	-0.0384	0.7270	0.0095
Stroke (ischemic and hemorrhagic stroke)	CCC109	Acute Cerebrovascular Disease	-0.1009	0.5646*	0.0299
Mild Stroke	CCC109	Acute Cerebrovascular Disease	-0.05045	0.6151*	0.0299
Moderate Stroke	CCC109	Acute Cerebrovascular Disease	-0.1009	0.5646*	0.0299
Severe Stroke	CCC109	Acute Cerebrovascular Disease	-0.1535	0.5142*	0.0299
Myocardial infarction	CCC100	Acute Myocardial Infarction	-0.0557	0.6098*	0.0193
Systemic embolism	ICD-9 444	Arterial embolism	-0.039	0.6265*	0.0191
Other ICH	ICD-9-442	Other aneurysm	-0.0983	-0.1511†	0.0401
Other Major Bleeds	ICD-9-442	Other aneurysm	-0.0983	-0.1511†	0.0401
CRNM Bleeds	ICD-9-599	Other urinary tract disorder	-0.0053797	-0.0582†	0.0173
Other CV Hospitalization	ICD-9-411; 413; 414; 428; 435; 443; 444; 453	Angina pectoris, Other chronic ischaemic heart disorder; heart failure; transient cerebral ischemia; arterial embolism; other venous thrombosis;	-0.0747498‡	-0.1276†	0.0259

Source: Sullivan et al. (2011)[9]

*The utility for semi-absorbing health states was calculated by subtracting the disutility for the condition and the disutility of total number of chronic conditions, ncc=2 corresponding to -0.0615 from the baseline atrial fibrillation utility.

†The utility decrement for transient health states was calculated by subtracting the disutility of total number of chronic conditions, ncc=2 for ICD-9 codes corresponding to -0.0528.

‡Average disutility weighted by sample size.

accumulated maintenance costs until death. The acute phase was assumed to be two weeks in the base case as advised by experts. Costs for acute phase and long-term maintenance for mild, moderate, severe and fatal strokes were obtained from a published estimates of a cost of illness model based on a large, randomised, prospective study detailing UK costs of stroke to the NHS.[16] Costs were available for acute phase and for ongoing care consisting of resource use items including resource use in hospital, primary care, healthcare contacts, and utilization of social services. The paper did not distinguish costs between patients with hemorrhagic stroke or ischemic stroke. It was therefore assumed that costs for hemorrhagic strokes were the same as costs for ischemic strokes. Acute care costs for SE, were assumed to be the same as those for mild stroke.[16]

Costs of other major bleeds and ICH were obtained from NHS reference costs.[14] The national average cost for hemorrhagic cerebrovascular disorders was used to detail the cost per event of ICH. Costs of major bleeds were broken down by the nature of the bleed (GI bleeds, non ICH and non GI related bleeds). To estimate the average cost of a GI related bleed to the NHS, national average costs for GI bleeds with and without major complications and the costs of major procedures for GI bleeds were weighed according to the observed activity levels (i.e. major procedures were

Table A3. Anticoagulant use.

	Tablet Size	Cost Per Tablet	Average Daily Dose	Number of Tablets Per Day	Average Cost Per Day
Apixaban*	5mg	£1.10	10mg	2	£2.20
Warfarin†	5mg	£0.04	5mg	1	£0.04
Edoxaban (30mg)‡	5mg	£1.10	10mg	2	£2.20
Edoxaban (60mg)‡	5mg	£1.10	10mg	2	£2.20

Source:
*British National Formulary (BNF).[13]
†Monthly index of medical specialties (MIMS).[12]
‡Assuming price parity with Apixaban.

not as common as minor GI bleeds, therefore a smaller weight according to activity was applied to that cost to obtain the average). The cost of GI bleeds can be seen in the table below.

Similarly, the average cost of non-ICH and non-GI related bleeds was obtained from a weighted average of spinal cord conditions, non-surgical ophthalmology, general abdominal procedures, non-inflammatory bone or joint disorders, and cardiac conditions according to observed activity levels (Table A7).[14]

For CRNM bleeds (Table A8), the same calculation was used however with costs and activities related to unspecified haematuria and intermediate nose procedures without major complications as well as mild GI bleeds requiring a length of stay of 1 day or less.[2]

Costs for the acute phase of MI were also obtained from NHS reference costs,[14] using the national average of acute or suspected MI. Additional costs of £480 (cardiac rehabilitation and coronary revascularization assessment for all patients) were applied for 12 months following MI, as described in Table A9. Long term maintenance costs consisted of medication costs including ACE inhibitors, beta blockers, and statins. (Table A10).

Table A4. Management costs.‡

Anticoagulant	% of Patients Experiencing Dyspepsia Whilst on Treatment	% of Patients Requiring Annual Renal Monitoring Once on Treatment	Total Monthly Management Cost
Apixaban*	1.67%*	0.00%†	£ 0.04
Warfarin*	1.81%*	0.00%†	£ 0.04
Edoxaban (30mg)	1.67%†	0.00%†	£ 0.04
Edoxaban (60mg)	1.67%†	0.00%†	£ 0.04
Unit cost of renal monitoring		£ 3.00§	

Source:
*ARISTOTLE case study report.[6]
†Assumption.
‡NHS reference costs, PSSRU.[14,15]
§NHS reference costs.[14]

Table A5. Resource use for routine care and monitoring.

	Of Visits per Month
Frequency of routine care*	
Apixaban	1.0
Aspirin	1.0
Warfarin	1.0
Edoxaban (30mg)	1.0
Edoxaban (60mg)	1.0
Frequency of INR monitoring†	
cTTR < 58%	1.50
58% ≤ cTTR < 65.7%	1.50
65.7% ≤ cTTR < 72.2%	1.50
cTTR ≥ 72.2%	1.50

Source:
*Expert opinion.
†NHS reference costs.[14]

Costs per episode of CV hospitalisation were similarly calculated using average national costs and activity levels from NHS reference costs (Table A11).[14] The average cost was calculated using national costs of transient ischemic attack, chest pain, deep vein thrombosis, heart failure or shock, non-surgical peripheral vascular disease and non interventional acquired cardiac conditions. Currency codes and the cost of CV hospitalization can be seen in the following table.

MORTALITY

Rates of death based on all-cause mortality in the AVERROES and the ARISTOTLE excluding deaths attributable to stroke, bleeding, MI and SE (i.e., the events modelled) to avoid double counting are used for patients in the NVAF health state for duration of the trial period (i.e., 1.8 years for the VKA suitable population).

Beyond the duration of the trial period, mortality is modeled based on background general mortality Gompertz curves which were derived by fitting a Gompertz survival function to the 2009 UK life tables (i.e., latest data available was 2009).[17] Gompertz curves were fitted instead of using the raw data from the life table to allow a more refined estimation of the risk of mortality for every 6- week cycle (i.e., life tables data are yearly), and to allow for the hazard from the fitted Gompertz to be adjusted by the use of HRs for other events. Gompertz parameters to estimate background life expectancy according to age and gender are detailed in Table A12.

In addition to background mortality, the model allows risk adjustment factors implemented as HRs to take into account the potential increase in mortality rates associated with AF, strokes, haemorrhagic strokes by severity level, MI and SE as detailed in the manuscript. Note that since mortality due to strokes, MI, SE, and bleedings were explicitly modelled at the occurrence of the event, increased mortality for patients with AF due to these reasons were excluded from the calculation of the HR to avoid double counting. HR of death for patients with AF in comparison the general population was calculated

Table A6. Cost of GI bleeds.

HRG Code	HRG Description	Activity	National Average Unit Cost
FZ38D	Gastrointestinal bleed with length of stay 2 days or more with Major CC	16,116	£2,042
FZ38E	Gastrointestinal bleed with length of stay 2 days or more without Major CC	19,304	£1,431
FZ38F	Gastrointestinal bleed with length of stay 1 day or less	2,806	£561
Weighted average			£1,625

Table A7. Cost of non-ICH and non-GI related major bleeds.

HRG Code	HRG Description	Activity	National Average Unit Cost
HC28B	Spinal Cord Conditions with CC	1,436	£6,047
HC28C	Spinal Cord Conditions without CC	1,416	£3,315
HD24A	Non-Inflammatory Bone or Joint Disorders with Major CC	3,906	£3,392
BZ24A	Non-Surgical Ophthalmology with length of stay 2 days or more	6,809	£2,132
PA23A	Cardiac Conditions with CC	2,680	£4,523
FZ12D	General Abdominal - Very Major or Major Procedures 19 years and over with Major CC	4,173	£5,905
FZ12E	General Abdominal - Very Major or Major Procedures 19 years and over with Intermediate CC	1,888	£4,114
FZ12F	General Abdominal - Very Major or Major Procedures 19 years and over without CC	2,999	£3,893
Weighted average			£3,847

based on mortality data obtained from a prospective Swedish study.[18]

ANALYSIS

Univariate Sensitivity Analysis

Univariate deterministic sensitivity analysis was performed where each parameter was varied according to the 95% confidence intervals and standard deviations where applicable while holding all other parameters constant. Where confidence intervals and standard deviations were unavailable, the standard error was assumed to be 25% of the mean. Table A13 presents the range and source of variation for the univariate sensitivity analysis for apixaban versus edoxaban 30mg and 60mg in the VKA suitable population. The probability distributions employed included the beta, lognormal, uniform, gamma, and dirichlet distributions. The distributions chosen for the commonly employed parameters in the model (i.e., probabilities, distributions [e.g., stroke severity], costs, risks and HRs, and utilities) are detailed in Section 8.2 (Probabilistic Sensitivity Analysis).

Probabilistic Sensitivity Analysis

In order to account for variability in outcomes due to statistical uncertainty in inputs, a PSA was performed. The model was set to the probabilistic setting and ran for 2,000 simulations to generate ICER's by varying event rates, costs, risks and utilities simultaneously. Time horizon, population characteristics and model settings were kept constant. Key inputs were varied from replication to replication by sampling from probability distributions. A number of probability distributions were employed including the beta, lognormal, uniform, gamma, and dirichlet distributions. This section describes how the distributions

Table A8. Cost of CRNM bleeds.

Currency Code	Currency Description	National Average Unit Cost
FZ38F	Gastrointestinal Bleed with length of stay 1 day or less	£562
CZ13Y	Intermediate Nose Procedures 19 years and over without CC	£946
LB38B	Unspecified Haematuria without Major CC	£1,451
Weighted average		£1,183

Table A9. MI acute costs.

HRG Code	HRG Description	Activity	National Average Unit Cost	
EB10Z	Actual or Suspected MI	56,823	£1967	
Component	**Unit Cost**	**Source**	**% Patients**	**Expected Cost**
Cardiac rehabilitation	£480	Total cost per patient referred	56%	£269
Coronary revasculation assessment	£170	320 Cardiology from NHS Trusts and PCTs combined Consultant Led: First Attendance Non-Admitted Face to Face	78%	£133

were chosen for the commonly employed parameters in the model (i.e., probabilities, distributions [e.g., stroke severity], costs, risks and HRs, and utilities). The distributions used are detailed in Table A14.

Probabilities

The probabilities used in the model were based on the proportion of the observed outcomes of interest (for example, proportion of hemorrhagic strokes among ICH, with the patients with aemorrhagic strokes considered as success and patients without hemorrhagic stroke considered as failure). It was therefore possible to assume a binomial distribution form with the number of successes denoting the probability used in the model. Rather than using a frequentist approach to generating confidence intervals through a normal distribution which could lead to observations below 0 or above 1,[19] a beta distribution was chosen for probabilities as it is a conjugate of the binomial and is bounded by 0 and 1. The

Table A10. Long-term costs of pharmaco-management of MI.

Therapy	Strength	Pack Size	Pack Price	Price per Pill	Daily Dose	Pills per Day	Monthly Cost	Share of Prescriptions	Weighted Monthly Cost
Beta-blocker (Atenolol)	25mg tablet	28	£0.87	£0.03	100mg	4	£3.78	31.97%	£2.40
	50mg tablet	28	£0.89	£0.03		2	£1.94	53.95%	
	100mg tablet	28	£0.94	£0.03		1	£1.02	14.08%	
ACE inhibitor (Ramipril)	1.25mg capsule	28	£1.15	£0.04	10mg	8	£10.00	24.68%	£4.67
	2.5mg capsule	28	£1.23	£0.04		4	£5.35	1.43%	
	5mg capsule	28	£1.32	£0.05		2	£2.87	73.89%	
Statin (simvastatin)	10mg tablet	28	£0.90	£0.03	40mg	4	£3.91	0.37%	£1.50
	20mg tablet	28	£0.97	£0.03		2	£2.11	18.09%	
	40mg tablet	28	£1.24	£0.04		1	£1.35	81.54%	
Total									£8.56

Table A11. Cost of other CV hospitalization.

Currency Code	Currency Description	Activity	National Average Unit Cost
AA29A	Transient Ischemic Attack with CC	10,722	£1,343
AA29B	Transient Ischemic Attack without CC	362	£1,059
PA22Z	Chest Pain	399	£1,175
QZ20Z	Deep Vein Thrombosis	8,715	£1,718
EB03H	Heart Failure or Shock with CC	50,431	£2,716
EB03I	Heart Failure or Shock without CC	23,804	£1,884
QZ17A	Non-Surgical Peripheral Vascular Disease with Major CC	1,545	£3,953
QZ17B	Non-Surgical Peripheral Vascular Disease with Intermediate CC	10,946	£2,528
QZ17C	Non-Surgical Peripheral Vascular Disease without CC	2,473	£1,848
EB01Z	Non interventional acquired cardiac conditions	102,395	£1,217
Weighted average			**£1,770**

parameterisation of the beta used consists of denoting the shape parameter (i.e., alpha) as the number of successes (hemorrhagic stroke observations in this example) and the scale parameter (i.e., beta) as the number of failures (non-haemorrhagic stroke observations). The source of variation where probabilities were involved was therefore patient numbers obtained from the trials or published estimates.

Distributions

Some probabilities used in the model however cannot be described by positive and negative occurrences, but were however used to describe the distribution of patients amongst a number of different occurrences (e.g., in the case of assigning stroke severity where patients are segregated by mild, moderate, severe and fatal). The distribution of severity was important to include in the PSA as it varied by comparators. In addition, as noted in the methods section, alternative costs, HRs of deaths, and utilities were assigned according to the severity level so it was imperative to capture the uncertainty around them. The Dirichlet distribution, a multivariate generalisation of the beta distribution was used for these parameters as it allowed for a number of categories to be fit in a probabilistic manner. We followed a normalised sum of independent gamma or normal variable as described in Briggs et al. (2003).[20] This involved generating the number of patients in each of the mild, moderate, severe and fatal health states in each simulation and calculating the proportion in each health state from their total sum. A gamma distribution was used to generate the patient numbers using the number of patients observed in each category as the shape parameter (i.e., alpha) and one as the scale parameter (i.e., beta). Alternatively a normal distribution was used using the number of patients observed in each category as the mean and the square root of the number of patients as the standard deviation. The gamma was chosen when patient numbers was small to avoid the normal generating negative patient numbers.

Table A12. Background mortality — Gompertz survival functions.

	Lambda	Gamma
Males <75 years old	−9.2268	0.0745
Males ≥ 75 years old	−9.3652	0.0835
Females <75 years old	−9.6037	0.0717
Females ≥ 75 years old	−10.9334	0.0986

Costs

With resource use and unit costs it was imperative that the distribution chosen had a lower bound of 0 to avoid the generation of any "negative" costs. The gamma distribution is therefore often used due to its

Table A13. Range of variation for univariate sensitivity analysis apixaban versus edoxaban 30mg/ 60mg VKA suitable population.

Description	Base Case Value	Lower Value	Upper Value
Gender (% Male)	0.65	0.63	0.66
Mean age for males	70.00	63.00	77.00
Mean age for females	70.00	63.00	77.00
Risk of ischemic and unspecified stroke for apixaban (Rate/100 PYs)	0.98	0.56	1.52
Risk of ischemic and unspecified stroke for warfarin (Rate/100 PYs)	1.08	0.87	1.33
Risk adjustment factor for stroke per decade	1.46	0.80	2.16
Case fatality rate of stroke (excluding hemorrhagic strokes) for apixaban	0.18	0.11	0.26
Case fatality rate of stroke (excluding hemorrhagic strokes) for Edoxaban (30mg)/(60mg)	0.20/0.29	0.15/0.22	0.25/0.36
Risk of intracranial hemorrhage (ICH) for apixaban (Rate/100 PYs)	0.33	0.19	0.51
Risk of intracranial hemorrhage (ICH) for warfarin (Rate/100 PYs)	0.80	0.35	1.87
Risk adjustment factor for ICH per decade	1.97	1.79	2.16
Proportion of hemorrhagic strokes among ICHs for apixaban	0.77	0.65	0.87
Proportion of hemorrhagic strokes among ICHs for Edoxaban (30mg)/(60mg)	0.69/0.75	0.56/0.63	0.80/0.85
Case fatality rate of hemorrhagic stroke for apixaban	0.35	0.20	0.52
Case fatality rate of hemorrhagic stroke for Edoxaban (30mg)/(60mg)	0.20/0.29	0.15/0.22	0.25/0.36
Risk of other major bleeds for apixaban (Rate/100PYs)	1.79	1.02	2.77
Risk of other major bleeds for warfarin (Rate/100PYs)	2.27	1.30	3.51
Risk adjustment factor for other major bleeds per decade	1.97	1.79	2.16
Proportion of gastrointestinal (GI) bleeds among other major bleeds for apixaban	0.38	0.32	0.44
Proportion of GI bleeds among other major bleeds for Edoxaban (30mg)/(60mg)	0.61/0.65	0.56/0.60	0.66/0.70
Risk of clinically relevant non major bleeds (CRNMB) for apixaban (Rate/100PYs)	2.08	1.19	3.22
Risk of CRNMB for warfarin (Rate/100PYs)	3.00	2.59	3.45
Risk adjustment factor for CRNMB per decade	1.97	1.79	2.16
Case fatality rate of ICH for apixaban	0.13	0.06	0.22
Case fatality rate of ICH for Edoxaban (30mg)/(60mg)	0.13/0.13	0.06/0.06	0.22/ 0.0.22
Case fatality rate of other major bleeds for apixaban	0.02	0.01	0.03
Case fatality rate of other major bleeds for Edoxaban (30mg)/(60mg)	0.02/0.02	0.01/0.01	0.03/0.03
% switch treatment post ICH for apixaban	0.56	0.43	0.69
% switch treatment post ICH for Edoxaban (30mg)/(60mg)	0.56/0.56	0.43/0.43	0.69/0.69
% switch treatment post GI for apixaban	0.25	0.01	0.69
% switch treatment post GI for Edoxaban (30mg)/(60mg)	0.25/0.25	0.01/0.01	0.69/0.69
Risk of MI for apixaban (Rate/100PYs)	0.53	0.30	0.82
Risk of MI for warfarin (Rate/100PYs)	0.61	0.45	0.80
Risk of cardiovascular (CV) hospitalization for apixaban (Rate/100 PYs)	10.46	5.98	16.17
Risk of cardiovascular (CV) hospitalization for warfarin (Rate/100 PYs)	10.46	5.98	16.17
Risk of other treatment discontinuations for apixaban (Rate/100 PYs)	13.18	7.53	20.38

(continued)

Table A13. (continued).

Description	Base Case Value	Lower Value	Upper Value
Risk of other treatment discontinuations for warfarin (Rate/100 PYs)	14.41	8.23	22.27
Risk of ischaemic and unspecified strokes for aspirin 2nd line (Rate/100 PYs)	3.45	1.97	5.34
Risk of ICH for aspirin 2nd line (Rate/100 PYs)	0.32	0.18	0.50
Risk of other major bleeds for aspirin 2nd line (Rate/100 PYs)	0.89	0.51	1.37
Risk of CRNMB for aspirin 2nd line (Rate/100 PYs)	2.94	1.68	4.54
Risk of MI for aspirin 2nd line (Rate/100 PYs)	1.11	0.63	1.72
Risk of CV hospitalization for aspirin 2nd line (Rate/100 PYs)	13.57	7.76	20.98
Case fatality rate of stroke (excluding hemorrhagic strokes) for aspirin 2nd line	0.11	–	–
Utility AF	0.73	0.71	0.75
Utility stroke mild	0.62	0.56	0.67
Utility stroke moderate	0.56	0.51	0.62
Utility stroke severe	0.51	0.46	0.57
Utility hemorrhagic stroke mild	0.62	0.56	0.67
Utility hemorrhagic stroke moderate	0.56	0.51	0.62
Utility hemorrhagic stroke severe	0.51	0.46	0.57
Utility decrement: ICH	0.15	0.08	0.24
Utility decrement: other major bleed	0.15	0.08	0.24
Utility decrement: CRNMB	0.06	0.03	0.10
Utility decrement: MI	0.61	0.57	0.65
Utility decrement: Other CV hospitalisation	0.13	0.08	0.18
Utility decrement: aspirin 2nd line	0.00	–	0.04
Utility decrement: Warfarin	0.01	–	0.08
Hazard Ratio for long-term mortality post ischemic & unspecified stroke mild	3.18	1.42	4.94
Hazard Ratio for long-term mortality post ischemic & unspecified stroke moderate	5.84	4.08	7.60
Hazard Ratio for long-term mortality post ischemic & unspecified stroke severe	15.75	13.99	17.51
Hazard Ratio for long-term mortality post hemorrhagic stroke mild	3.18	1.82	4.92
Hazard Ratio for long-term mortality post hemorrhagic stroke moderate	5.84	3.34	9.03
Hazard Ratio for long-term mortality post haemorrhagic stroke severe	15.75	9.00	24.35
Daily cost of apixaban	1.10	0.88	1.32
Daily cost of edoxaban (30mg)/(60mg)	1.10/ 1.10	0.88/0.88	1.32/ 1.32
Monitoring visit cost	14.27	11.94	17.05
Routine care cost	–	–	113.00
Acute care stroke costs mild	3,639.20	0.00	27,659.60
Long-term follow-up stroke costs mild	190.38	0.01	1,143.69
Acute care stroke costs Moderate	18,985.67	303.46	74,272.57
Long-term follow-up stroke costs Moderate	371.39	0.00	2,370.09
Acute care stroke costs Severe	25,931.29	3,667.32	69,504.41
Long-term follow-up stroke costs Severe	563.91	0.00	4,448.40

(continued)

Table A13. (continued).

Description	Base Case Value	Lower Value	Upper Value
Acute care hemorrhagic stroke costs mild	10,596.58	3,350.63	21,939.02
Long-term follow-up hemorrhagic stroke costs mild	190.38	0.01	1,143.69
Acute care hemorrhagic stroke costs Moderate	27,223.89	10,922.42	50,840.05
Long-term follow-up hemorrhagic stroke costs Moderate	371.39	0.00	2,370.09
Acute care hemorrhagic stroke costs Severe	46,050.13	26,321.63	71,205.64
Long-term follow-up hemorrhagic stroke costs Severe	563.91	0.00	4,448.40
Other ICH cost	3,231.13	2,415.24	3,796.05
Cost of GI	1,624.88	1,273.70	1,853.55
Non ICH and non GI Major bleed cost	3,846.67	2,495.78	4,560.37
CRNM bleeds cost	1,183.13	864.36	1,371.45
MI Acute care cost	2,367.92	1,721.00	2,826.00
MI long-term follow-up cost	8.56	4.89	13.24
CV hospitalization cost	1,770.42	1,275.29	1,998.88
Stroke Hazard ratio for Edoxaban (30mg)/(60mg)	1.48/ 1.04	1.12/0.78	1.96/1.39
ICH Hazard ratio for Edoxaban (30mg)/(60mg)	0.74/ 1.11	0.46/0.71	1.20/1.73
MI Hazard ratio for Edoxaban (30mg)/(60mg)	1.37/ 1.07	0.95/0.74	1.96/1.55
Cardiovascular hospitalization Hazard ratio for Edoxaban (30mg)/(60mg)	1.00/ 1.00	0.90/0.90	1.10/1.10
Major Bleed Hazard ratio for Edoxaban (30mg)/(60mg)	0.66/ 1.13	0.53/0.91	0.83/1.39
CRNM Hazard ratio for Edoxaban (30mg)/(60mg)	0.95/ 1.15	0.80/1.06	1.13/1.48
Treatment discontinuation Hazard ratio for Edoxaban (30mg)/(60mg)	1.04/ 1.10	0.96/1.01	1.13/1.19
Risk of recurrent IS	2.72	3.41	4.91
Risk of recurrent HS	2.72	2.02	4.46
Risk of SE for apixaban (Rate/100PYs)	0.09	0.05	0.14
Risk of SE for warfarin (Rate/100PYs)	0.10	0.06	0.15
Utility: SE	0.63	0.59	0.66
Case fatality rate of SE for apixaban	0.09	0.02	0.21
Case fatality rate of SE for Edoxaban (30mg)/(60mg)	0.09/0.09	0.02/0.02	0.21/0.21
Hazard Ratio for long-term mortality post systemic embolism	1.34	1.20	3.18
Hazard Ratio for long-term mortality post MI females	4.16	3.44	5.03
Hazard Ratio for long-term mortality post MI males	2.56	2.27	2.88
Case fatality rate of MI females	0.16	0.09	0.24
Case fatality rate of MI females	0.11	0.06	0.17
Acute care SE costs	4,221.30	0.01	27,909.69
Long-term follow-up SE cost	190.38	0.01	1,143.69
Management cost of apixaban	0.04	0.02	0.06
Management of Edoxaban (30mg)/(60mg)	0.04/0.04	0.02/0.02	0.06/0.06
SE Hazard ratio for Edoxaban (30mg)/(60mg)	1.39/0.74	0.57/0.29	3.36/ 1.92
Rate of death apixaban trial period	3.08	2.50	3.72
Rate of death comparator trial period	3.34	2.71	4.04
HR mortality trial period comparator	1.00	0.90	1.10
HR mortality AF	1.34	1.20	1.53
Disutility associated with age	–	–	0.00029

Table A14. Distributions used for probabilistic sensitivity analysis.

Description	Detail	Mean	Distribution	SE	Shape	Scale	Source of Variation
Stroke risk for apixaban VKA suitable population	CHADS = 0-1	0.52	Gamma	0.09	31.38	0.02	Standard errors from source
	CHADS = 2	0.95	Gamma	0.13	56.85	0.02	
	CHADS ≥3	1.53	Gamma	0.18	74.27	0.02	
Stroke risk for warfarin VKA suitable population	CHADS = 0-1	0.46	Gamma	0.09	26.48	0.02	Standard errors from source
	CHADS = 2/	0.93	Gamma	0.12	56.73	0.02	
	CHADS ≥3	1.94	Gamma	0.20	91.71	0.02	
Stroke HR VKA suitable	Edoxaban (30mg)	1.48	Lognormal	0.29			Iterated SE to match 95% Confidence intervals provided by ITC
	Edoxaban (60mg)	1.04	Lognormal	0.29			
Risk adjustment per decade for stroke	VKA Suitable	1.46	Gamma	0.37	16.00	0.09	Assumed 25% SE of the mean
Risk of stroke recurrence	VKA Suitable	0.041	Gamma	0.004	118.15	0.00035	SEs from source
Risk of haemorrhagic stroke recurrence	VKA Suitable	2.720	Gamma	0.594	20.94	0.13	SEs from source
% Mild strokes - VKA suitable population	Apixaban	0.53	Dirichlet	57			Patient numbers from trials
	Edoxaban (30mg)	0.50	Dirichlet	89.00			
	Edoxaban (60mg)	0.47	Dirichlet	90.00			
% moderate strokes - VKA suitable population	Apixaban	0.21	Dirichlet	23.00			Patient numbers from trials
	Edoxaban (30mg)	0.22	Dirichlet	33.00			
	Edoxaban (60mg)	0.18	Dirichlet	34.00			
% severe strokes - VKA suitable population	Apixaban	0.08	Dirichlet	9.00			Patient numbers from trials
	Edoxaban (30mg)	0.08	Dirichlet	12.00			
	Edoxaban (60mg)	0.06	Dirichlet	13.00			
% fatal strokes - VKA suitable population	Apixaban	0.18	Dirichlet	19.00			Patient numbers from trials
	Edoxaban (30mg)	0.20	Dirichlet	48.00			
	Edoxaban (60mg)	0.29	Dirichlet	49.00			
ICH risk apixaban - VKA suitable population	Apixaban	0.33	Gamma	0.08	16.00	0.02	Assumed 25% SE of the mean
ICH risk warfarin- VKA suitable population	Warfarin	0.80	Gamma	0.14	34.60	0.02	

(continued)

Table A14. (continued).

Description	Detail	Mean	Distribution	SE	Shape	Scale	Source of Variation
ICH HR VKA suitable	Edoxaban (30mg)	0.74	Lognormal	0.49			Iterated SE to match 95% Confidence intervals provided by ITC
	Edoxaban (60mg)	1.11	Lognormal	0.45			
% of hemorrhagic strokes among ICH - VKA suitable	Apixaban	0.77	Beta	52.00	40.04	11.96	Patient numbers from trials
	Warfarin	0.64	Beta	122.00	78.08	43.92	
	Edoxaban (30mg)	0.69	Beta	56.00			
	Edoxaban (60mg)	0.75	Beta	57.00			
% Mild hemorrhagic strokes - VKA suitable population	Apixaban	0.23	Dirichlet	7.00			Patient numbers from trials
	Warfarin	0.20	Dirichlet	13.00			
	Edoxaban (30mg)	0.50	Dirichlet	89.00			
	Edoxaban (60mg)	0.47	Dirichlet	90.00			
% moderate hemorrhagic strokes - VKA suitable population	Apixaban	0.32	Dirichlet	10.00			Patient numbers from trials
	Warfarin	0.15	Dirichlet	10.00			
	Edoxaban (30mg)	0.22	Dirichlet	33.00			
	Edoxaban (60mg)	0.18	Dirichlet	34.00			
% severe hemorrhagic strokes - VKA suitable population	Apixaban	0.10	Dirichlet	3.00			Patient numbers from trials
	Warfarin	0.12	Dirichlet	8.00			
	Edoxaban (30mg)	0.08	Dirichlet	12.00			
	Edoxaban (60mg)	0.06	Dirichlet	13.00			
% fatal hemorrhagic strokes - VKA suitable population	Apixaban	0.35	Dirichlet	11.00			Patient numbers from trials
	Warfarin	0.53	Dirichlet	34.00			
	Edoxaban (30mg)	0.20	Dirichlet	48.00			
	Edoxaban (60mg)	0.29	Dirichlet	49.00			
Major bleed risk apixaban VKA suitable	Apixaban	1.79	Gamma	0.45	16.00	0.11	Assumed 25% SE of the mean
Major bleed risk warfarin VKA suitable	Warfarin	2.27	Gamma	0.57	16.00	0.14	
HR Major bleed VKA suitable	Warfarin	1.27	Lognormal				Iterated SE to match 95% Confidence intervals provided by ITC
	Edoxaban (30mg)	0.66	Lognormal	0.23			
	Edoxaban (60mg)	1.13	Lognormal	0.22			
% Patients with GI bleeds VKA suitable	Apixaban	0.38	Beta	274.00	104.12	169.88	Patient numbers from trials
	Warfarin	0.35	Beta	340.00	119.00	221.00	

(continued)

Table A14. (continued).

Description	Detail	Mean	Distribution	SE	Shape	Scale	Source of Variation
	Edoxaban (30mg)	0.61	Beta	396.00	241.56	154.44	
	Edoxaban (60mg)	0.65	Beta	397.00	258.05	138.95	
CRNM risk apixaban VKA suitable	Apixaban	2.08	Gamma	0.52	16.00	0.13	Assumed 25% SE of the mean
CRNM risk warfarin VKA suitable	Warfarin	3.00	Gamma	0.75	16.00	0.19	
HR CRNM VKA suitable	Warfarin	1.43	Lognormal	0.07			Iterated SE to match 95%
	Edoxaban (30mg)	0.95	Lognormal	1.09			Confidence intervals
	Edoxaban (60mg)	1.25	Lognormal	2.09			provided by ITC
ICH risk per decade adjustment	VKA Suitable	1.97	Gamma	0.49	16.00	0.12	Assumed 25% SE of the mean
Major bleed risk per decade adjustment	VKA Suitable	1.97	Gamma	0.49	16.00	0.12	Assumed 25% SE of the mean
CRNM risk per decade adjustment	VKA Suitable	1.97	Gamma	0.49	16.00	0.12	Assumed 25% SE of the mean
% Case fatality rate for ICH	Apixaban	0.13	Beta	62.00	8.06	53.94	Patient numbers from trials
in the VKA suitable	Warfarin	0.13	Beta	62.00	8.06	53.94	
population	Edoxaban (30mg)	0.13	Beta	63.00	8.19	54.81	
	Edoxaban (60mg)	0.13	Beta	64.00	8.32	55.68	
% Case fatality rate for major	Apixaban	0.02	Beta	750.00	15.00	735.00	Patient numbers from trials
bleeds in the VKA suitable	Warfarin	0.02	Beta	750.00	15.00	735.00	
population	Edoxaban (30mg)	0.02	Beta	751.00	15.02	735.98	
	Edoxaban (60mg)	0.02	Beta	752.00	15.04	736.96	
% Patients that Stop AC for 6	Apixaban	0.44	Beta	52.27	23.00	29.27	Patient numbers
Weeks Post Other ICH	Warfarin	0.44	Beta	52.27	23.00	29.27	
VKA suitable	Edoxaban (30mg)	0.44	Beta	52.27	23.00	29.27	
	Edoxaban (60mg)	0.44	Beta	52.27	23.00	29.27	
% Patients that don't switch	Apixaban	0.75	Beta	0.19	3.25	1.08	Assumed 25% SE of the mean
AC Post GI VKA suitable	Warfarin	0.75	Beta	0.19	3.25	1.08	
	Edoxaban (30mg)	0.75	Beta	0.19	3.25	1.08	
	Edoxaban (60mg)	0.75	Beta	0.19	3.25	1.08	

(continued)

Table A14. (continued).

Description	Detail	Mean	Distribution	SE	Shape	Scale	Source of Variation
% Patients that don't switch AC Post non-GI VKA suitable	Apixaban	0.75	Beta	0.19	3.25	1.08	Assumed 25% SE of the mean
	Warfarin	0.75	Beta	0.19	3.25	1.08	
	Edoxaban (30mg)	0.75	Beta	0.19	3.25	1.08	
	Edoxaban (60mg)	0.75	Beta	0.19	3.25	1.08	
MI risk apixaban VKA suitable	Apixaban	0.53	Gamma	0.13	16.00	0.03	Assumed 25% SE of the mean
MI risk warfarin VKA suitable	Warfarin	0.61	Gamma	0.15	16.00	0.04	
HR MI VKA suitable	Warfarin	1.14	Lognormal	0.13			Iterated SE to match 95% Confidence intervals provided by ITC
MI CFR Males VKA suitable		0.108	Beta	0.03	14.16	116.98	Assumed 25% SE of the mean
MI CFR Females VKA suitable		0.156	Beta	0.04	13.35	72.22	Assumed 25% SE of the mean
MI risk per decade adjustment	VKA Suitable	1.3	Gamma	0.3	16.0	0.1	Assumed 25% SE of the mean
SE risk apixaban VKA suitable	Apixaban	0.090	Gamma	0.023	16.00	0.00563	
SE risk warfarin VKA suitable	Warfarin	0.100	Gamma	0.023	16.00	0.00625	
SE CFR VKA suitable	All comparators	0.094	Beta		3.00	29.00	Based on patient numbers
CV hospitalization risk apixaban VKA suitable	Apixaban	10.46	Gamma	2.62	16.00	0.65	
CV hospitalization risk warfarin VKA suitable	Warfarin	10.46	Gamma	2.62	16.00	0.65	
Other treatment discontinuation risk apixaban VKA suitable	Apixaban	13.17	Gamma	3.3	16.0	0.8	Assumed 25% SE of the mean
Other treatment discontinuation risk warfarin VKA suitable	Warfarin	14.41	Gamma	3.6	16.0	0.9	

(continued)

Table A14. (continued).

Description	Detail	Mean	Distribution	SE	Shape	Scale	Source of Variation
HR Other treatment discontinuation VKA suitable	Edoxaban (30mg)	1.04	Lognormal	0.08			Iterated SE to match 95% Confidence intervals provided by ITC
	Edoxaban (60mg)	1.10	Lognormal	0.08			
Relative rate of death for AF		1.34	Uniform		1.20	1.53	Assumed upper and lower bound based on GPRD studies[18,21]
Other death rate apixaban	VKA suitable	3.08	Gamma	0.31	99	0.03	Calculated based on number of events
HR of death for stroke	Mild (mRS 0-2)	3.18	Gamma	0.80	16	0.20	Assumed 25% SE of the mean
	Moderate (mRS 3-4)	5.84	Gamma	1.46	16	0.37	
	Severe (mRS 5)	15.75	Gamma	3.94	16	0.98	
HR of death for hemorrhagic stroke	Mild (mRS 0-2)	3.18	Gamma	0.80	16	0.20	Assumed 25% SE of the mean
	Moderate (mRS 3-4)	5.84	Gamma	1.46	16	0.37	
	Severe (mRS 5)	15.75	Gamma	3.94	16	0.98	
MI HR Males		2.56	Gamma	0.64	16	0.16	Assumed 25% SE of the mean
MI HR Females		4.16	Gamma	1.04	16	0.26	Assumed 25% SE of the mean
SE HR		1.34	Gamma	0.34	16	0.08	Assumed 25% SE of the mean
Event costs	Monitoring Visit	£ 14.27	Lognormal	0.09	2.66		Iterated SE to obtain similar confidence intervals as reported in source
	Routine Care Visit	£ 0.00		0.00			
	Mild Ischemic Stroke Acute Care (per episode)	£ 3,639.20	Gamma	8195.42	0.20	18455.95	Assumed 25% SE of the mean
	Mild Ischemic Stroke Maintenance Care (per month)	£ 190.38	Lognormal	327.70	0.34	564.07	Iterated SE to obtain similar confidence intervals as reported in source
	Moderate Ischemic Stroke Acute Care (per episode)	£ 18,985.67	Gamma	20315.73	0.87	21738.97	Assumed 25% SE of the mean
	Moderate Ischemic Stroke Maintenance Care (per month)	£ 371.39	Lognormal	683.75	0.30	1258.82	Iterated SE to obtain similar confidence intervals as reported in source

(continued)

Table A14. (continued).

Description	Detail	Mean	Distribution	SE	Shape	Scale	Source of Variation
	Severe Ischemic Stroke Acute Care (per episode)	£ 25,931.29	Gamma	17411.00	2.22	11690.24	Assumed 25% SE of the mean
	Severe Ischemic Stroke Maintenance Care (per month)	£ 563.91	Lognormal	1328.45	0.18	3129.54	Iterated SE to obtain similar confidence intervals as reported in source
	Fatal stroke cost per episode	£ 3,273.24	Gamma	3004.67	1.19	2758.14	Assumed 25% SE of the mean
	Mild Hemorrhagic Stroke Acute Care (per episode)	£ 10,596.58	Gamma	4825.87	4.82	2197.79	Assumed 25% SE of the mean
	Mild Hemorrhagic Stroke Maintenance Care (per month)	£ 190.38	Lognormal	327.70	0.34	564.07	Iterated SE to obtain similar confidence intervals as reported in source
	Moderate Hemorrhagic Stroke Acute Care (per episode)	£ 27,223.89	Gamma	10309.00	6.97	3903.76	Assumed 25% SE of the mean
	Moderate Hemorrhagic Stroke Maintenance Care (per month)	£ 371.39	Lognormal	683.75	0.30	1258.82	Iterated SE to obtain similar confidence intervals as reported in source
	Severe Hemorrhagic Stroke Acute Care (per episode)	£ 46,050.13	Gamma	11512.53	16.00	2878.13	Assumed 25% SE of the mean
	Severe Hemorrhagic Stroke Maintenance Care (per month)	£ 563.91	Lognormal	1328.45	0.18	3129.54	Iterated SE to obtain similar confidence intervals as reported in source
	Fatal stroke cost per episode	£ 1,703.50	Gamma	2018.09	0.71	2390.78	Assumed 25% SE of the mean
	SE Acute Care (per episode)	£ 4,221.30	Lognormal	8087.34	0.27	15494.06	Assumed 25% SE of the mean
	SE Maintenance Care (per month)	£ 190.38	Lognormal	327.70	0.34	564.07	Assumed 25% SE of the mean
	Other ICH (excluding hemorrhagic stroke)	£ 3,231.13	Lognormal	704.50	21.04	153.60	

(continued)

Table A14. (continued).

Description	Detail	Mean	Distribution	SE	Shape	Scale	Source of Variation
	Other Major Bleed GI (excluding ICH)	£ 1,624.88	Lognormal	295.84	30.17	53.86	
	Other Major Bleed Non-GI (excluding ICH)	£ 3,846.67	Lognormal	1053.36	13.34	288.45	
	CRNM Bleed	£ 1,183.13	Lognormal	258.72	20.91	56.58	
	MI Acute Care (per episode)	£ 2,367.92	Lognormal	563.78	17.64	134.23	
	MI Maintenance Care (per month)	£ 8.56	Gamma	2.14	16.00	0.54	
	Other CV Hospitalization	£ 1,770.42	Lognormal	369.18	23.00	76.98	
Utilities	AF Baseline	0.73	Beta	0.01	1598.04	600.09	SE provided in source
	Mild Ischemic Stroke	0.62	Beta	0.03	162.27	101.55	
	Moderate Ischemic Stroke	0.56	Beta	0.03	154.69	119.28	
	Severe Ischemic Stroke	0.51	Beta	0.03	143.15	135.26	
	Mild Hemorrhagic Stroke	0.62	Beta	0.03	162.27	101.55	
	Moderate Hemorrhagic Stroke	0.56	Beta	0.03	154.69	119.28	
	Severe Hemorrhagic Stroke	0.51	Beta	0.03	143.15	135.26	
Utility decrements	Other ICH	0.15	Beta	0.04	11.88	66.75	SE provided in source
	Other Major Bleed	0.15	Beta	0.04	11.88	66.75	
	CRNM Bleed	0.06	Beta	0.02	10.56	170.95	
	MI	0.12	Beta	0.02	32.53	245.02	
	Other CV Hospitalization	0.13	Beta	0.03	21.01	143.68	
	Warfarin	0.01	Beta	0.00	15.80	1,300.54	Assumed 25% SE of the mean
Utility decrement associated with age		0.0000	Uniform		0.0000	0.00029	Assumed upper bound from Sullivan et al. (2011)[9]

constrained intervals.[19] Standard deviations were used along with the mean to obtain the shape and scale parameters of the gamma distribution. Alternatively the lognormal distribution can be used. Both distributions can be highly skewed to reflect the natural skew in costs. Where standard deviations were not available, the standard deviations were derived from the 95% confidence intervals. Alternatively a 25% standard deviation of the mean was assumed.

Hazard Ratios

For HRs, due to the nature of calculation of the confidence intervals of these parameters in the clinical trials in which the central limit theorem was employed, the natural logarithm of the parameters can often be normally distributed.[19] A log-normal distribution was therefore used where it could replicate the confidence intervals generated from the trials. As confidence intervals were available for some of these parameters the standard deviations were derived to obtain the same confidence intervals from the distributions as those reported. Similarly where confidence intervals were unavailable a 25% standard deviation of the mean was assumed.

For HRs of death, the gamma distribution was used assuming a 25% standard deviation of the mean.

Utilities

For utilities, a beta distribution was used due to the bounds of the distribution (i.e., 0 to 1).[19] Standard deviations were taken from the published literature and in some cases the published papers provided the shape and scale parameters of the distribution.

Other model parameters such as time horizon, population characteristics, anticoagulant costs, duration of utility decrements, and resource use were not varied. The tables below present the inputs, variables and assumptions for the PSA. The PSA for base case were run for 2,000 replications where repeated samples were drawn from probability distributions to determine an empirical distribution for costs, QALYs to construct a range of cost-effectiveness ratios. Cost-effectiveness acceptability curves (CEACs) were then generated.

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