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Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation

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Aims Warfarin, a vitamin K antagonist (VKA), has been the standard of care for stroke prevention in patients with atrial fibrillation (AF). Aspirin is recommended for low-risk patients and those unsuitable for warfarin. Apixaban is an oral anticoagulant that has demonstrated better efficacy than warfarin and aspirin in the ARISTOTLE and AVERROES studies, respectively, and causes less bleeding than warfarin. We evaluated the potential cost-effectiveness of apixaban against warfarin and aspirin from the perspective of the UK payer perspective.

Results and methods A lifetime Markov model was developed to evaluate the pharmacoeconomic impact of apixaban compared with warfarin and aspirin in VKA suitable and VKA unsuitable patients, respectively. Clinical events considered in the model include ischaemic stroke, haemorrhagic stroke, intracranial haemorrhage, other major bleed, clinically relevant non-major bleed, myocardial infarction, cardiovascular hospitalization and treatment discontinuations; data from the ARISTOTLE and AVERROES trials and published mortality rates and event-related utility rates were used in the model. Apixaban was projected to increase life expectancy and quality-adjusted life years (QALYs) compared with warfarin and aspirin. These gains were expected to be achieved at a drug acquisition-related cost increase over lifetime. The estimated incremental cost-effectiveness ratio was £11 909 and £7196 per QALY gained with apixaban compared with warfarin and aspirin, respectively. Sensitivity analyses indicated that results were robust to a wide range of inputs.

Conclusions Based on randomized trial data, apixaban is a cost-effective alternative to warfarin and aspirin, in VKA suitable and VKA unsuitable patients with AF, respectively.

Keywords Vitamin K antagonist • Aspirin • Stroke prevention • Apixaban • Cost-effectiveness • Atrial fibrillation

Introduction

Atrial fibrillation (AF) is associated with a four- to five-fold increase in risk of stroke and thrombo-embolic events,[1] resulting in significant morbidity, mortality, and costs.[2] Until recently, vitamin K antagonists (VKA) were the only oral anticoagulants recommended for antithrombotic therapy in patients with moderate-to-high risk of stroke.[3] Although VKAs are effective in preventing thrombo-embolic events,[4] therapeutic management is complicated by variable dose requirements, multiple drug–food and drug–drug interactions and the need for frequent monitoring of international normalized ratios (INR). As a result, bleeding complications are relatively frequent, and a high proportion of patients discontinues or receives suboptimal therapy in clinical practice.[5] In patients who cannot tolerate VKA or in whom VKA treatment is contraindicated , aspirin, a modestly effective treatment option,[4] has often been prescribed instead.[6] Recent guidelines from the European Society of Cardiology recommend the use of novel oral anticoagulants (NOACs) as alternatives to

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conventional VKA therapy or anti-platelet therapy in most patients requiring stroke prevention in AF.[3]

Apixaban, an orally active inhibitor of coagulation factor Xa, has been approved by European Medicines Agency[7] for stroke prevention in AF patients. Apixaban has been studied vs. dose-adjusted warfarin and aspirin, in the VKA suitable and unsuitable populations, respectively, in two large multinational randomized trials, the ARISTOTLE and the AVERROES trials.[8,9] Apixaban was superior to warfarin in the prevention of stroke and systemic embolism, bleeding outcomes and mortality.[8] In VKA unsuitable patients, apixaban reduced the risk of stroke and systemic embolism without significantly increasing the risk of major bleeding compared with aspirin.[9]

In view of the increasing demand from healthcare providers and payers to assess the economic value of new therapies, the clinical benefits of apixaban need to be weighed against increases in drug treatment costs. The objective of this study was to assess cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with non-valvular AF (NVAF) from the United Kingdom (UK) National Health Service payer perspective.

Methods

Model

A Markov cohort model was developed, in accordance with good modelling practices,[10] conceptualizing the course of the disease in terms of mutually exclusive health 'states' and the possible transitions among them, accruing direct healthcare costs, life years, and quality-adjusted life years (QALYs) (*Figure 1*). The health states considered were NVAF (i.e. the starting health state for all patients), ischaemic or unspecified strokes (*referred hereafter as ischaemic stroke*), systemic embolism, myocardial infarction (MI), intracranial haemorrhage, other major bleed, clinically relevant non-major bleed, cardiovascular hospitalization unrelated to the events modelled or death. A detailed description of the model can be found in Supplementary material online, *Appendix SC*.

Population

Two populations were included: patients with NVAF who are suitable and unsuitable for VKA (*Table 1*). Inputs on patient characteristics were drawn from patient characteristics in the ARISTOTLE and the AVERROES trials, respectively.[8,9]

Risk of clinical events

Clinical event rates were obtained from the AVERROES and the ARISTOTLE trials (Supplementary material online, *Appendices SA* and *SB*) (*Table 1*). Rates of ischaemic stroke, bleedings, and MI were adjusted over time to account for the increased risk associated with ageing by a factor (95% confidence interval) of 1.46 (0.80–2.16), 1.97 (1.79–2.16), and 1.30 (0.74–2.01) per decade of life, respectively.[11–13] Risk of recurrence after any stroke was assumed to be independent of treatment and estimated to be 2.72 (95% confidence interval 1.68–4.01) per 100 patient-years (PYs) based on subgroup analysis on patients with prior stroke or transient ischaemic attack from ARISTOTLE.[14]

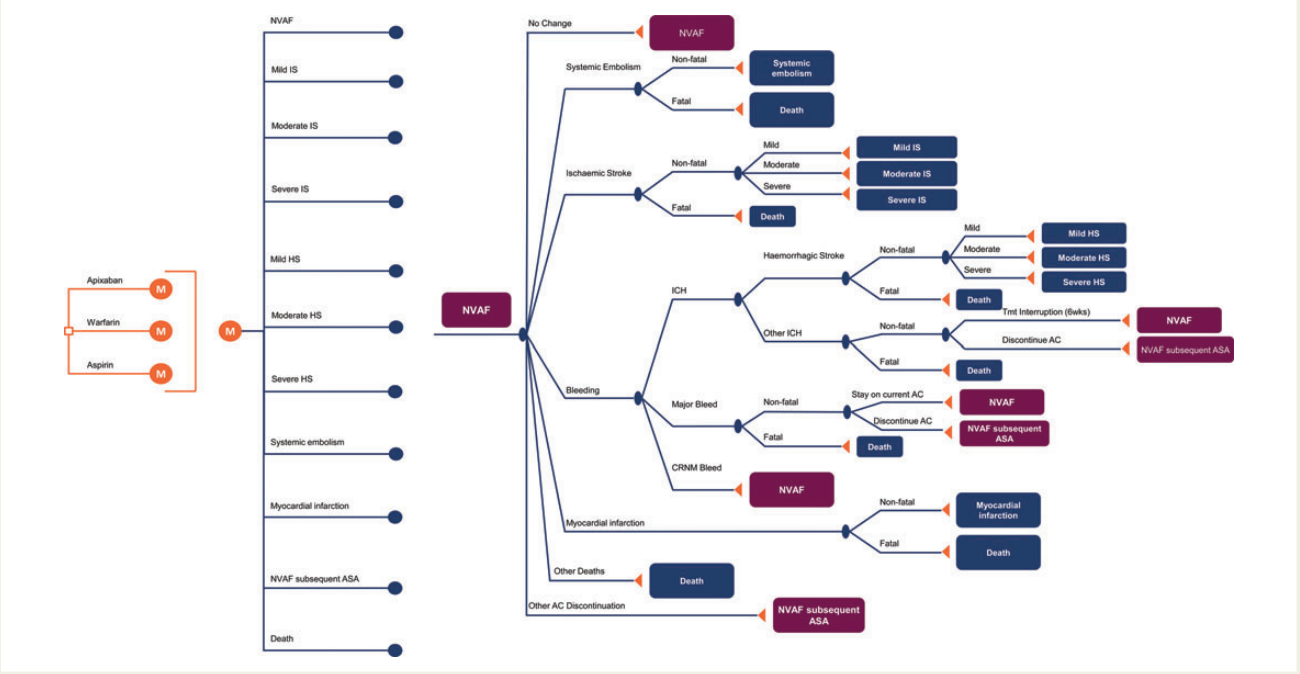

Figure 1 Schematic representation model. ASA, aspirin CRNM, clinically relevant non-major; ICH, intracranial haemorrhages; NVAF, non-valvular atrial fibrillation; AC, anticoagulant; IS, ischaemic stroke; HS, haemorrhagic stroke. 'M' represents a Markov process with 11 health states that are identical for each of the treatment options. All patients remain in the 'NVAF' state until one of stroke, bleed, SE, MI, treatment discontinuation, or death occurs. The transition probabilities of these events depend on the treatment. For patients on second-line aspirin 'NVAF subsequent ASA' the events are identical however patients cannot experience any further discontinuation. Triangles indicate which health state the patient enters after an event. Health states coloured in blue are permanent health states, with the remainder being transient health states occurring for a maximum period of 6 weeks before returning to the prior or subsequent health state.

Table 1 **Demographic characteristics and clinical event rates (per 100 patient-years)**

	VKA suitable			VKA unsuitable			Source
	Patient characteristics (*n*/min–max)						
Starting age	70 (63–76)			70 (48–100)			[8,9]
Gender							
% males	64.7% (11 785)			58.5% (3277)			[8,9]
% females	35.3% (6416)			41.5% (2321)			[8,9]
$CHADS_2$ distribution							
$CHADS_2$: 0–1	34.0% (6183)			38.2% (2142)			[8,9]
$CHADS_2$: 2	35.8% (6516)			35.2% (1973)			[8,9]
$CHADS_2$: 3–6	30.2% (5502)			26.6% (1483)			[8,9]
Average $CHADS_2$ score	2.1			2.0			
Clinical event rates[a](*n*)	Apixaban	Warfarin	Hazard ratio (95% CI)	Apixaban	Aspirin	Hazard ratio (95% CI)	Aspirin (Subsequent treatment)
Intention to treat population (N)	9120	9081		2807	2791		1107
On treatment population (N)	9088	9052		2798	2780		1104
Ischaemic stroke rate							
$CHADS_2$: 0–1	0.52 (31)	0.46 (27)	0.88 (0.52–1.47)	0.83 (10)	1.41(17)	1.70 (0.78–3.71)	
$CHADS_2$: 2	0.95 (57)	0.93 (56)	0.98 (0.68–1.42)	1.53 (18)	3.36 (36)	2.21 (1.25–3.88)	
$CHADS_2$: 3–6	1.53 (74)	1.94 (92)	1.27 (0.93–1.72)	1.96 (15)	5.20 (44)	2.66 (1.48–4.78)	
Average stroke rate	0.98 (162)	1.08 (175)	1.09 (0.89–1.35)	1.37 (43)	3.10 (97)	2.27 (1.59–3.23)	3.45 (43)
Stroke severity distribution:							
Mild (mRS 0–2)	53% (57)	45% (49)		40% (17)	36% (35)		36% (35)
Moderate (mRS 3–4)	21% (23)	30% (32)		28% (12)	38% (37)		38% (37)
Severe (mRS 5)	8% (9)	10% (11)		12% (5)	15% (15)		15% (15)
Fatal (mRS 6)	18% (19)	15% (16)		20% (9)	11% (10)		11% (10)
Intracranial haemorrhage rate	0.33 (52)	0.80 (122)	2.38 (1.72–3.33)	0.34 (11)	0.35 (13)	1.01 (0.44–1.26)	0.32 (4)
% of haemorrhagic strokes among intracranial haemorrhage	77% (40)	64% (78)		55% (6)	55% (9)		55%
Haemorrhagic stroke severity distribution							
Mild (mRS 0–2)	23% (7)	20% (13)		7% (1)	7% (0)		7% (0)
Moderate (mRS 3–4)	32% (10)	15% (10)		20% (1)	20% (2)		20% (2)
Severe (mRS 5)	10% (3)	12% (8)		27% (0)	27% (4)		27% (4)
Fatal (mRS 6)	35% (11)	53% (34)		46% (4)	46% (3)		46% (3)

Continued

Table I *Continued*

	VKA suitable			VKA unsuitable			Source
	Patient characteristics (*n*/min–max)						
Other major bleed rate	1.79 (274)	2.27 (340)	1.27 (1.08–1.47)	1.07 (34)	0.57 (18)	0.54 (0.30–0.95)	0.89 (11)
% of gastrointestinal bleeds among other major bleeds	38% (105)	35% (119)		35% (12)	39% (7)		39% (7)
Clinically relevant non-major bleed rate	2.08 (318)	2.99 (444)	1.43 (1.24–1.66)	3.11 (96)	2.37 (84)	0.76 (0.56–1.03)	2.94 (36)
Myocardial infarction rate	0.53 (90)	0.61 (102)	1.14 (0.86–1.52)	0.76 (24)	0.89 (28)	1.16 (0.68–2.00)	1.11 (14)
Systemic embolism rate	0.09 (15)	0.10 (17)	1.11 (0.57–2.27)	0.06 (2)	0.41 (13)	6.83 (1.47–33.33)	0.41 (13)
Other cardiovascular hospitalization rate	10.46	10.46	1.00 (0.90–1.10)	10.46	12.09	1.16 (0.99–1.35)	12.09
Other treatment discontinuation rate	13.18 (2047)	14.41 (2182)	1.08 (1.02–1.15)	17.31 (495)	19.01 (537)	1.11 (0.99–1.24)	
% of patients experiencing dyspepsia	1.67% (152)	1.81% (164)		1.67% (26)	1.58% (44)		1.58% (44)
Other death rate*	3.08 (528)	3.34 (568)	1.08 (0.96–1.22)	2.97 (94)	3.59 (114)	1.21 (0.92–1.59).	N/A
Case-fatality rates after event (*n*)							Source
Other intracranial haemorrhage**	13.0% (8)						[a]
Other major bleed**	2.0% (15)						[a]
Systemic embolism**	9.4% (3)						[a]
Myocardial infarction	Males: 10.8%; females: 15.6%						[25]

Rates are displayed per 100 patient-years; the number of patients experiencing each event is detailed in parenthesis.
mRS, modified Rankin scale; VKA, vitamin K antagonists; CI, confidence interval.
*Based on all-cause mortality excluding deaths attributable to stroke, bleeding, myocardial infarction, and systemic embolism.
**Pooled sample percentages.
[a]Supplementary material online, *Appendices SA* and *SB*.

Table 2 Utility and mortality estimates

Health states	Utility (standard error)	Source	Hazard ratios vs. general population (95% CI)	Source
Non-valvular atrial fibrillation	0.7270 (0.0095)	26	1.34 (1.20–1.53)	27
Stroke or haemorrhagic stroke				
Mild	0.6151 (0.0299)	26	3.18 (1.82–4.92)	24,28,29
Moderate	0.5646 (0.0299)	26	5.84 (4.08–7.60)	24,28,29
Severe	0.5142 (0.0299)	26	15.75 (13.99–17.51)	24,28,29
Myocardial infarction				
Females	0.6151 (0.0299)	26	4.16 (2.27–2.88)	30,31
Males	0.5646 (0.0299)	26	2.56 (3.44–5.03)	30,31
Systemic embolism	0.6265 (0.0299)	26	1.34 (1.20–1.53)	Assumption
Transient health states/anticoagulation use	Utility decrement (standard error/95% CI)	Source	Utility decrement duration	Source
Other intracranial haemorrhage	0.1511 (0.0401)	26	6 weeks	Assumption
Other major bleeds	0.1511 (0.0401)	26	2 weeks	Assumption
Clinically relevant non-major bleed	0.0582 (0.0173)	26	2 days	Assumption
Other cardiovascular hospitalization	0.1276 (0.0259)	26	6 days	Assumption
Apixaban or aspirin	0.0020 (0.00–0.04)	32	While on apixaban or aspirin	
Warfarin	0.0120 (0.00–0.08)	32	While on warfarin	

CI, confidence interval.

Subsequent anticoagulation treatment

Clinical event rates for 'subsequent aspirin' (i.e. aspirin used in case of post-treatment discontinuation) were based on a subgroup of patients in AVERROES that were previously prescribed but failed to continue on VKA and hence were treated with aspirin (*Table 1*, Supplementary material online, *Appendix SB*).

After experiencing other intracranial haemorrhages, 56% ($n = 29$) of the patients switched treatment to aspirin.[15] The remaining 44% ($n = 23$) had a 6-week treatment interruption and resumed the assigned anticoagulant. For other major bleeds, we assumed 25% of the patients switched treatment to aspirin, similarly to other models.[16]

When ischaemic stroke or systemic embolism occurred, patients initially assigned aspirin were assumed to switch to warfarin, while patients on apixaban or warfarin were assumed to continue on their initial treatment. Patients experiencing haemorrhagic stroke or MI were assumed to discontinue the treatment permanently.

Mortality

On the occurrence of each event, an acute case-fatality rate was applied and a hazard ratio (HR) to account for an increased risk of mortality associated with stroke, systemic embolism, or MI was applied to the non-fatal cases (*Tables 1* and *2*).

Treatment-specific rates of death for patients in the NVAF health state (due to reasons other than clinical events modelled) were derived from the published trials and applied for 1.8 and 1.1 years for the VKA suitable and unsuitable populations, respectively (i.e. mean follow-up for the two trials, respectively). Beyond that, mortality was modelled based on age- and gender-specific general UK life tables,[17] and an HR adjusted for the impact of AF, including the increased risk of mortality vs. the general population after accounting for events modelled.

Utilities

Utility decrements associated with permanent events were applied for the remainder of patients' lifetime, vs. those for temporary events were applied only for the respective duration (*Table 2*). As patients treated with apixaban had a similar safety profile to aspirin,[9] the same utility losses associated with the use of the treatment were assumed.

Costs

Costs and sources are detailed in *Table 3* (2011 prices). For strokes, MI, and systemic embolism, costs were segregated by acute care costs, consisting of time spent in hospital and rehabilitation facilities (assumed to be 2 weeks) and maintenance costs applied over a lifetime.

Health and cost outcomes were discounted at 3.5% per annum.[18]

Analyses

The relative clinical benefit of apixaban vs. standard of care was assessed using the incremental cost-effectiveness ratio (ICER), which assessed if the benefit was accrued within UK payers' willingness to pay £20 000 (a commonly used *threshold value*) per added QALY.[18]

The effects of change in various model inputs were examined in univariate sensitivity analyses. Subgroup analyses were also performed to examine the potential cost-effectiveness of apixaban among specific groups of patients based on $CHADS_2$ score distribution or patients being managed in centres with different levels of INR control. Event rates calculated by the $CHADS_2$ score and HRs by cTTR quartile are detailed in Supplementary material online, Appendices *SA* and *SB*.

Probabilistic sensitivity analysis was conducted where values of key input parameters were assigned a probability distribution and varied concurrently. The analysis was run for 2000 simulations by randomly

Table 3 Resource use and costs

	Cost (minimum–maximum)	Daily dose	Source
Apixaban (daily)	£2.20	10 mg	33
Warfarin (daily)	£0.04	5 mg average	33
Aspirin (daily)	£0.02	150 mg	33
Monitoring (monthly)	£20.69 (£17–£25)		34
Dyspepsia (yearly)	£83.19 (£48–£129)		33,34
Stroke (ischaemic and haemorrhagic)	Acute cost per episode (95% CI)	Maintenance cost per month (95% CI)	
Mild	£6815.00 (£5993–£7410)	£145.24 (£86–£200)	35
Moderate	£6436.88 (£5793–£6870)	£158.31 (£98–£216)	35
Severe	£14 107.41 (£12 589–£15 166)	£445.82 (£375–£200)	35
Fatal	£9063.23 (£7158–£12 978)	–	35
Other intracranial haemorrhage	£3010.00 (£2190–£3456)	–	34
Other major bleeds			
Gastrointestinal bleeds	£1493.68 (£1237–£1825)	–	34
Non-gastrointestinal related	£3947.92 (£2508–£4554)	–	34
Clinically relevant non-major bleed	£1133.93 (£751–£1284)	–	34
Myocardial infarction	£2018.84 (£1596–£2554)	£6.45 (£4–£10)	34,36
Systemic embolism	£6815.00 (£5993–£7410)	£145.24 (£86–£200)	35
Other cardiovascular hospitalization	£1570.89 (£1140–£1798)	–	34

CI, confidence interval.

drawing sets of inputs from their respective distributions and producing numerous pairs of incremental QALYs and costs.

Further details on the model structure, inputs, uncertainty analysis and results are included in Supplementary material online, *Appendix SC*.

Results

Base–case analysis

Among a cohort of 1000 VKA suitable patients over a lifetime, compared with warfarin, use of apixaban is predicted to result in 20 fewer strokes (including first and recurrent ischaemic and haemorrhagic strokes) or systemic embolism, 44 fewer major bleeds (including first and recurrent haemorrhagic strokes other intracranial haemorrhages and other major bleeds), and 21 fewer cardiovascular-related deaths (*Table 4*). The model estimates that 56 patients need to be treated with apixaban over a lifetime to avoid one stroke compared with warfarin, and that apixaban is a dominant treatment in terms of a reduction in bleeding events.

In the VKA unsuitable population, 1000 patients treated with apixaban compared with aspirin over a lifetime are predicted to experience 66 fewer strokes (including first and recurrent ischaemic and haemorrhagic strokes) or systemic embolism and 57 fewer cardiovascular-related deaths. There are an additional 38 major bleeds (including first and recurrent haemorrhagic strokes other intracranial haemorrhages and other major bleeds) and 38 cardiovascular hospitalizations. Over a lifetime, 18 patients needed to be treated with apixaban to avoid one stroke and 26 additional patients need to be treated to cause one major bleed event.

The reduction in events resulted in 0.181 QALYs gained at an incremental cost of £2157 when compared with warfarin leading to an ICER of £11 909 per QALY gained. Similarly, comparing with aspirin, apixaban led to 0.268 QALYs gained at an incremental cost of £1930, resulting in an ICER of £7196 per QALY gained (*Table 4*).

Sensitivity analyses

Figure 2 presents the results from the deterministic sensitivity analyses, on the top 15 parameters that had the most impact on the ICERs. The results comparing apixaban to warfarin showed that the ICERs from all scenarios varied between £4901 and £24 033 per QALY (*Figure 2A*). Only one of the scenarios tested, increasing the stroke risk to 1.52 per 100 PYs for apixaban (55% higher than that observed in ARISTOTLE), resulted in an ICER above the commonly accepted threshold of £20 000 per QALY.[18] Compared with aspirin, the ICERs from all scenarios varied between £3368 and £14 290 (*Figure 2B*).

Subgroup analysis for varying baseline $CHADS_2$ scores demonstrated that in patients with low risk of stroke ($CHADS_2 \leq 1$) the ICERs were £13 152 (£7467– £27 676) and £16 744 (£3923– £86 518) per QALY, when compared with warfarin and aspirin, respectively, and in those with $CHADS_2 = 2$ they were £13 262 (£7094–£31 240) and £6,848 (£754–£24 341). The ICERs were most favourable in high-risk patients ($CHADS_2 \geq 3$), £9769 (£4979–£20 769), and £3331 (dominant–£15 241).

The ICER from the subgroup analysis on quality of INR control for each of the different cTTR ranges varied from £7 194 (£3777–£15 002) to £17 826 (£5 462–£115 681). This indicated that even when compared with patients who managed in a well-controlled

Table 4 **Deterministic cost and health outcomes predicted over lifetime per patient results (2.5 and 97.5th percentiles observed in probabilistic analysis)**

	VKA suitable population			VKA unsuitable population		
	Apixaban	**Warfarin**	**Difference**	**Apixaban**	**Aspirin**	**Difference**
Health outcomes (per patient)						
Life years (undiscounted)	11.14 (10.53–11.87)	10.88 (10.28–11.64)	0.26 (0.10–0.44)	11.09 (10.45–11.86)	10.65 (9.91–11.49)	0.44 (0.19–0.83)
QALYs (discounted)	6.26 (5.83–6.57)	6.08 (5.65–6.39)	0.18 (0.09–0.28)	6.22 (5.78–6.55)	5.95 (5.48–6.32)	0.27 (0.13–0.48)
Costs (£ discounted per patient)						
Anticoagulant and management	£3555 (£2729–£4547)	£100 (£92–£111)	£3455 (£2636–£4439)	£3071 (£2334–£4101)	£78 (£72–£85)	£2993(£2257–£4021)
Monitoring	£106 (£58–£174)	£1065 (£807–£1426)	−£959 (−£1324–£703)	£123 (£69–£198)	£256 (£171–£383)	−£133 (−£238–£76)
Clinical events	£5417 (£4208–£6993)	£5755 (£4542–£7375)	−£338 (−£873–£209)	£5731 (£4434–£7497)	£6662 (£5070–£8967)	−£931 (−£1974–£387)
Total	£9078 (£7639–£10812)	£6920 (£5669–£8594)	£2158 (£1453–£3033)	£8925 (£7458–£10 883)	£6995 (£5342–£9397)	£1930 (£892–£2891)
Incremental cost-effectiveness ratio (apixaban vs. comparator)						
£ per quality-adjusted life year gained		£11 909 (£7151–£24 596)			£7196 (£2437–£17 395)	

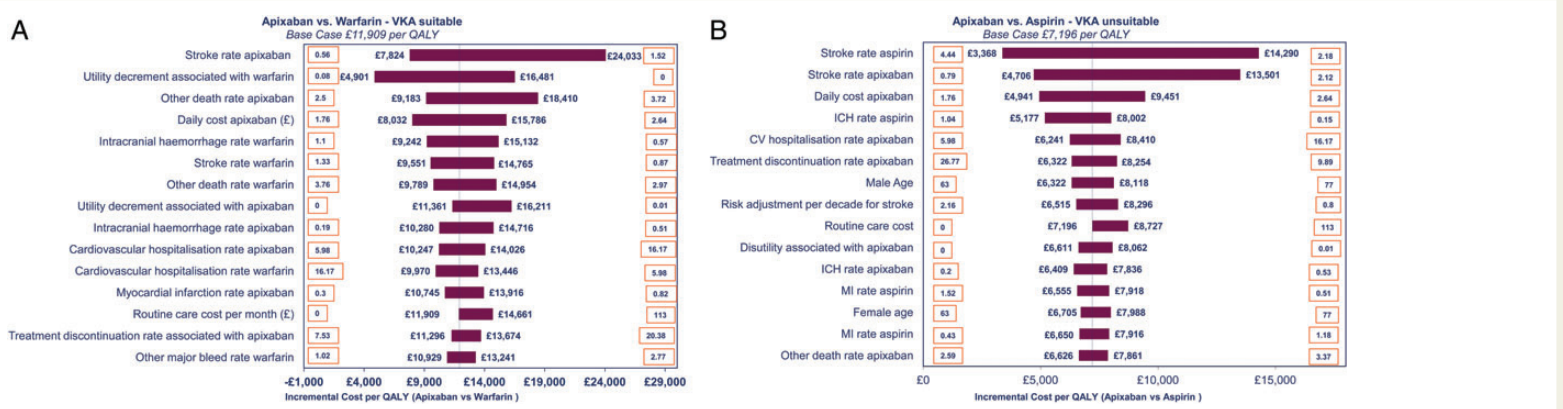

Figure 2 (*A*) One-way sensitivity analysis of apixaban vs. warfarin. (*B*) One-way sensitivity analysis of apixaban vs. aspirin. Rates are displayed per 100 patient-years. The solid vertical line represents the base–case incremental incremental cost-effectiveness ratio for apixaban compared with warfarin or aspirin. Horizontal bars indicate the range of incremental incremental cost-effectiveness ratios obtained by setting each variable to the values shown in the white boxes while holding all other values constant.

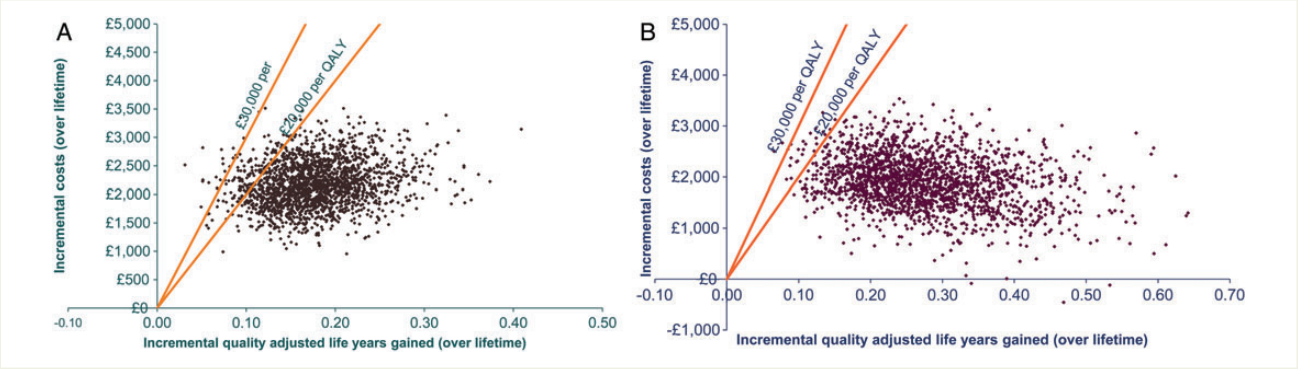

Figure 3 (*A*) Probabilistic sensitivity analyses for apixaban vs. warfarin. (*B*) Probabilistic sensitivity analyses for apixaban vs. aspirin. Each line represents a cost-effectiveness threshold representing the maximum amount society is willing to pay for a QALY gain. Apixaban is a cost-effective alternative in cases that fall to the right of this line; apixaban is not a cost-effective alternative in cases that fall to the left of this line.

setting (cTTR >76.5%), apixaban was considered cost-effective with an ICER relative to warfarin of £11 321 (£5959–£29 542) per QALY gained.

Probabilistic sensitivity analysis

The cost-effectiveness plane suggests that apixaban was more effective and more costly than warfarin or aspirin (*Figure 3*). At a willingness to pay of £20 000 per QALY, apixaban was considered to be a cost-effective treatment representing maximum net benefit over warfarin in 93% of the trials and in 99% of the trials when compared with aspirin. At a willingness to pay threshold of £30 000 per QALY 99% of trials comparing apixaban with warfarin and 100% of trials comparing apixaban with aspirin showed apixaban being a cost-effective alternative[18]

Discussion

This study estimated an ICER of £11 909 and £7 196 per QALY gained with apixaban as a first-line treatment in the prevention of stroke and systemic embolism for patients with AF, compared with warfarin and aspirin, respectively, within the range considered to be cost-effective.[18] Fewer thrombo-embolic events with apixaban translated into life expectancy and QALYs gained. Moreover, a reduced number of clinical events led to lower medical care costs. Increased drug treatment costs were observed in patients treated with apixaban due to the higher drug acquisition costs and additional time spent on treatment, due to a longer expected life span and lower treatment discontinuation rates as observed in the trials (including discontinuation due to bleeding, stroke, as well as other reasons).[8,9]

Our model expanded on the structural similarities with other earlier cost-effectiveness studies by modelling strokes and bleeding events in detail and accounting for the impact of treatment discontinuation and stroke severity in a comprehensive manner.[16,19–21] Three earlier studies have assessed the cost-effectiveness of apixaban relative to warfarin, two in the context of primary prevention,[21,22] and one in secondary prevention.[20] These studies concluded apixaban to be a cost-effective alternative to warfarin from a United States payer perspective; our study assessed the cost-effectiveness of apixaban from a UK perspective. Our study enables the assessment of convergent validity of results across different countries and healthcare systems. Unlike these studies, we also compared apixaban with aspirin in patients who are unsuitable for VKA, and also, report on results according to different levels of INR control, an area of uncertainty in earlier models evaluating NOACs.[21–23] Our study demonstrated that apixaban remains a cost-effective alternative to warfarin across all cTTR levels. These results imply that even for regions or centres where patients are well-managed, either due to better systems of anticoagulant care or comprehensive stroke risk management, apixaban will yield higher stroke and bleeding risk reduction, thus, retaining its cost-effectiveness against warfarin. Our study is further strengthened through reporting of results stratified by baseline risk of stroke using $CHADS_2$ scores, highlighting that apixaban remains a cost-effective alternative to current standard of care regardless of baseline stroke risk, attributed to the higher stroke and bleeding risk in patients with higher $CHADS_2$ and relatively constant effect size of apixaban vs. warfarin and aspirin.

Our study used data from large blinded clinical trials and trial-specific detail surrounding treatment discontinuation patterns. We allowed for treatment patterns to vary based on type and severity of bleeding event and treatment discontinuation unrelated to stroke and bleeding events, thus mimicking how antithrombotics are used in real-life. Estimates around the risks of subsequent events for patients on aspirin after treatment discontinuation were based on secondary analysis of patients who had previously failed warfarin enrolled in AVERROES, thus yielding more accurate modelling of stroke and bleeding risk in these patients compared with earlier studies.[16,19–22] We assumed that all patients received aspirin as a second-line treatment, although it is likely that some patients could have permanent discontinuation. However, scenario analysis assuming permanent discontinuation after major bleeds or reasons unrelated to the modelled events, highlighted that the model conclusions remained unaltered regardless of changes in subsequent treatment, resulting in an ICER of £11 773 and £7276 per QALY when compared with warfarin and aspirin, respectively.

In other studies, rates of recurrent stroke were assumed to be treatment specific.[19,21] Our study assumed no additional protective

power of anticoagulants for secondary stroke prevention, This assumption is considered conservative and likely to favour aspirin and warfarin with a poorer efficacy in stroke prevention, particularly in light of evidence that apixaban is a cost-effective alternative to warfarin for secondary prevention.[20]

As with all models; however, there are limitations. First, given ARISTOTLE and AVERROES were multinational trials, clinical and safety estimates were derived from multiple countries rather than a UK or European population. Furthermore in a controlled clinical trial setting patients may receive improved care and enhanced adherence to the drug. Thus the efficacy, and safety and tolerability observed may not reflect outcomes outside a trial setting. This is of particular importance around the projection of treatment discontinuation unrelated to stroke and bleeding events. Although contributing factors to such discontinuation such as severe renal dysfunction are included in the calculated treatment discontinuation rates, an explicit projection of the proportion of patients with discontinuation has not been included, and these rates may vary outside the trial setting. Univariate sensitivity analysis, however, highlighted that apixaban remained a cost-effective alternative to warfarin and aspirin over a wide range of treatment discontinuation rates. Secondly, the number of changes in antithrombotic therapies allowed was limited to two due to the unavailability of the data to support efficacy of these treatments when being used as third-line treatment or beyond. Third, no transitions from one disability level to another were modelled for stroke and/or intracranial haemorrhage health states as there are little data to support these transitions. Fourthly, these cost–benefit assumptions do not take into account the intangible aspects of new oral anticoagulants including convenience and fewer drug–drug interactions. Fifthly, our analysis utilized the $CHADS_2$ rather than the CHA_2DS_2-VASC currently recommended,[3] as $CHADS_2$ was the recommended risk classification scheme at the time, the trials were conducted. Finally, the analyses were based on costs and resource use data specific for the UK, thus results are not necessarily generalizable to other European countries due to differences in practice settings.

In conclusion, the choice of an optimal anticoagulant in AF patients should involve careful consideration of stroke prevention efficacy, bleeding risk, tolerability profile, and resource burden associated with therapeutic management. Our analysis demonstrates that apixaban, when compared with the current standard of care provides a cost-effective alternative for prevention of thrombo-embolic events.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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