NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- What is the Committee's view on the generalisability of the ARISTOTLE trial to a UK setting? In particular, were the following characteristics of people in ARISTOTLE consistent with the UK population for whom apixaban treatment would be expected to be considered:
  - average age of 69 years
  - proportion of population (4%) needing 2.5 mg dose of apixaban
  - mean time in therapeutic range on warfarin of 62%
  - distribution of $CHADS_2$ scores (measure of stroke risk) 0, 1, 2, 3, 4, 5 and 6 of [redacted] and [redacted] respectively?

- The manufacturer performed a network meta-analysis to compare the efficacy of apixaban, warfarin, rivaroxaban and dabigatran using data from the ARISTOTLE, RE-LY and ROCKET-AF trials and noted that:
  - the mean $CHADS_2$ score was 2.1 in ARISTOTLE and RE-LY but was 3.6 in ROCKET-AF (to be eligible for ROCKET-AF, people needed to have 2 or more risk factors)

  - the mean time in therapeutic range (TTR) was 62% in ARISTOTLE, 64% in RE-LY and 55% in ROCKET-AF.

  Given these differences in baseline characteristics of the trial populations, are the estimates of the relative clinical and cost effectiveness robust?

- The manufacturer assumed that the relative risk of ischaemic stroke compared with systemic embolus was dependent on the agent used. Does the Committee consider this justified?
- The degree of severity of ischaemic strokes or haemorrhagic strokes was also considered to be specific to the treatment used. Is this reasonable?
- The manufacturer provided data from the AVERROES study for an additional comparator, aspirin, which was not included in the final scope, for people who are unable or unwilling to take warfarin. Does the Committee consider aspirin to be a valid comparator in this appraisal? Would all people in AVERROES be suitable for anticoagulation?

- Cost effectiveness

- No health-related quality-of-life data were collected in the apixaban clinical trials and utility values for health states were derived from a systematic review of health-state utility value studies. Does the Committee think that the utilities used were plausible?
- In the manufacturer's model, people who have stroke (ischaemic and haemorrhagic), systemic embolism and myocardial infarction remain in these health states until they die (or have a recurrent stroke in the stroke health states). Clinical experts advised the Evidence Review Group (ERG) that patients would be expected to recover well from myocardial infarction without needing costly long-term care. Are the permanent utility decrements for these health states appropriate?
- The model assumed that people switched to aspirin as second-line treatment. This was consistent with the treatment sequences in 'Dabigatran

etexilate for the prevention of stroke and systemic embolism in atrial fibrillation' (NICE technology appraisal 249) and 'Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation' (NICE technology appraisal guidance 256). The ERG considered that some patients who stop therapy with apixaban, dabigatran or rivaroxaban may be eligible for treatment with warfarin or a different oral anticoagulant. Which treatment sequence does the Committee consider appropriate?

- The ERG noted that the cost of systemic embolism in the apixaban submission was higher than the costs in the rivaroxaban and dabigatran submissions. This was considered in its scenario analysis, which informed its revised base case. Are the costs used for the health states appropriate?
- The ERG produced a revised base case which incorporated the following changes:
  - other-cause mortality assumed to be independent of the treatment received
  - utility adjusted for age
  - stroke severity distribution and bleed type assumed to independent of the treatment received
  - people with systemic embolism and myocardial infarction assumed to be at risk of recurrent stroke
  - acute cost of systemic embolism equal to the cost used in the NICE technology appraisal guidance 256
  - time horizon of 26 years.

  The ERG's revised base case increased the incremental cost-effectiveness ratio (ICER) for apixaban, compared with warfarin, from £11,008 to £12,757 per quality-adjusted life year (QALY) gained. Which assumptions are most plausible, the ERG's or the manufacturer's?

1 Background: clinical need and practice

1.1 Atrial fibrillation is the most common heart rhythm disturbance and its main characteristic is an erratic and rapid heartbeat. One of the most serious consequences of this condition is that blood may not be fully expelled from the atrial chambers in the heart, which may lead to the formation of a thrombus (blood clot). These thrombi can leave the heart and enter the circulation. If they travel to the brain they will cause an ischaemic stroke, and if they travel elsewhere in the body they cause systemic embolism. Sometimes, small amounts of haemorrhage will be seen in an ischaemic stroke caused by an embolus from the heart, but haemorrhagic stroke is commonly caused by a primary bleed into the brain. Primary haemorrhagic stroke is much less common than ischaemic stroke in people with atrial fibrillation, but it is an adverse effect of anticoagulant treatment, rather than being caused by the atrial fibrillation itself. Bleeding may also occur elsewhere in the body, for example over the surface of the brain or in the gastrointestinal tract.

1.2 Atrial fibrillation is uncommon in people under 50 years, but incidence increases with age. It has an incidence of around 1% in people between 55 and 64 years, and 7–13% in people over 85 years. It is estimated that there are approximately 640,000 people with atrial fibrillation in England and Wales. It is also estimated that approximately 74–93% of people with atrial fibrillation have nonvalvular atrial fibrillation (NVAF) which corresponds to around 470,000 to 600,000 people.

1.3 Annually in England and Wales, 130,000 people experience a stroke episode and there are 60,000 deaths from stroke. More than 20% of these strokes are attributed to atrial fibrillation. In people with atrial fibrillation, a stroke is associated with greater mortality,

morbidity and longer hospital stays than in people without atrial fibrillation. Approximately a third of people who have a stroke are likely to die within the first 10 days, about a third are likely to make a recovery within 1 month, and the remaining third are likely to be left with disabilities needing rehabilitation. Stroke is the leading cause of disability in adults. Depending on the area of the brain that has been damaged, a patient can experience problems with speech and language, orientation, movement and memory.

1.4 The risk of stroke and systemic embolism in people with atrial fibrillation can be reduced with antithrombotic treatment. The choice of antithrombotic treatment is based on a balance between the benefits of treatment (reduction in the risk of stroke and other thromboembolic events) and the increased risk of bleeding associated with anticoagulation or antiplatelet therapy. 'The management of atrial fibrillation' (NICE clinical guideline 36) (currently being reviewed) recommends that people with atrial fibrillation at high risk of stroke or thromboembolism should receive anticoagulation with warfarin, and people at low risk should receive aspirin. For people at moderate risk of stroke or thromboembolism, the guideline recommends that treatment with warfarin or aspirin should be decided on an individual basis, by balancing the risks and benefits of warfarin compared with aspirin. Since publication of the clinical guideline, NICE technology appraisal guidance 249 and 256 recommend dabigatran etexilate, and rivaroxaban as alternative anticoagulant treatment options for people with nonvalvular atrial fibrillation with 1 or more risk factors for stroke or systemic embolism.

2 The technology

2.1 Apixaban (Eliquis, Bristol-Myers Squibb and Pfizer) is a potent, oral, direct and highly selective active site inhibitor of factor Xa. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation by thrombin. On 20 September 2012, the Committee for Medicinal Products for Human Use adopted a positive opinion recommending a variation to the terms of the marketing authorisation for apixaban to include a new indication for the existing 2.5 mg strength and a new 5 mg strength as follows: 'prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, such as prior stroke or transient ischaemic attack; age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)'.

2.2 The summary of product characteristics lists the following adverse reactions for apixaban: epistaxis (nosebleed), contusion (bruising), haematuria (blood in urine), haematoma, eye haemorrhage, and gastrointestinal haemorrhage. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The provisional cost per day for both doses (2.5 mg and 5 mg) of apixaban (excluding VAT) is £2.20, and the provisional annual cost for both doses is £803. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: 'To appraise the clinical and cost effectiveness of apixaban within its licensed indication for the prevention of stroke and systemic

embolism in people with non-valvular atrial fibrillation with one or more risk factors for stroke or systemic embolism'.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with nonvalvular atrial fibrillation who are at risk of stroke or systemic embolism.	
Intervention	Apixaban	
Comparators	• warfarin (in people for whom warfarin is suitable) • dabigatran etexilate • rivaroxaban	As per the final scope plus aspirin for people for whom warfarin is unsuitable

The manufacturer justified their inclusion of aspirin as a comparator on the basis that it is recommended in NICE clinical guideline 36 for people with atrial fibrillation who cannot take warfarin or for people at low risk of stroke, and because aspirin is still widely used in clinical practice in England and Wales. The manufacturer highlighted that, despite its recognised limitations, aspirin is still being used in inappropriate patient groups in the UK. The ERG did not consider that the trial described and analysed in the manufacturer's submission that compared apixaban to aspirin in a warfarin-unsuitable population (AVERROES) met the inclusion criteria for this technology appraisal. Therefore, the ERG did not critically appraise data presented from this trial. Additionally, as there were no data for rivaroxaban or dabigatran in a warfarin-unsuitable population, the ERG considered the network meta-analysis presented by the manufacturer for the warfarin-unsuitable population to be potentially flawed.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • stroke • non-central nervous system systemic embolism • myocardial infarction • mortality • transient ischaemic attacks • adverse effects of treatment including haemorrhage • health-related quality of life.	As per the final scope with the exception of transient ischaemic attacks.

The manufacturer explained that transient ischaemic attacks were not recorded in the ARISTOTLE trial. In addition, the ERG commented that treatment-specific health-related quality-of-life data were not collected in ARISTOTLE or AVERROES. Consequently, health-related quality-of-life data presented within the manufacturer's submission were limited to generic atrial fibrillation health-related quality-of-life data identified from a systematic review of the literature. The ERG commented that there are no publically available health-related quality-of-life data for either dabigatran or rivaroxaban in patients with nonvalvular atrial fibrillation; therefore, the ERG was unable to comment on the potential impact of treatment on health-related quality-of-life.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	

4 Clinical-effectiveness evidence

4.1 The manufacturer performed 2 systematic reviews for randomised controlled trial (RCT) evidence and for non-RCT evidence on the

efficacy and safety of apixaban and relevant comparators for stroke prevention in patients with atrial fibrillation at moderate to high risk of stroke. The systematic review identified 2 international, multicentre double-blind, double-dummy RCTs, using placebo tablets to match the active treatments, which had investigated apixaban. ARISTOTLE (n=18,201) compared apixaban (5 mg twice daily; 2.5 mg twice daily in selected patients) with warfarin (with an International Normalised Ratio [INR] target range of 2.0–3.0). AVERROES (n=5598) compared apixaban (5 mg twice daily; 2.5 mg twice daily in selected patients) with aspirin (81–324 mg once daily) in people 50 years or over with atrial fibrillation and at least 1 additional risk factor for stroke, in whom treatment with warfarin had failed, or for whom warfarin was unsuitable or those who were unwilling to take warfarin. No head-to-head data were available for apixaban compared with dabigatran or rivaroxaban, so an indirect comparison was performed using network meta-analysis (see section 4.6).

4.2 The primary objective of ARISTOTLE was to determine if apixaban was non-inferior to warfarin for the combined endpoint of stroke and systemic embolism. Stroke included both ischaemic and haemorrhagic stroke (caused by embolism from the heart, and primary haemorrhage related to anticoagulant treatment). The primary endpoint therefore included both efficacy and haemorrhagic stroke adverse event outcomes. Individual components of the composite endpoints were not pre-specified secondary endpoints in the trial. ARISTOTLE included adults with atrial fibrillation or atrial flutter not resulting from a reversible cause and at least 1 additional risk factor for stroke (assessed by $CHADS_2$ criteria). ARISTOTLE enrolled patients from 39 countries; 40% of participants were from Europe and included people from 41

sites in the UK. The average age was 69 years and 65% of the population were male. The mean TTR for patients in the warfarin arm was 62.2% and the median TTR was 60%. Approximately 4% of the study population received 2.5 mg apixaban (they had 2 or more of the following criteria: 80 years or older; a body weight of 60 kg or less; or a serum creatinine level of 1.5 mg/dL or more). The mean $CHADS_2$ score at baseline was 2.1 and 65% of patients had a $CHADS_2$ score 2 or more. The proportions of people with a $CHADS_2$ score of 0, 1, 2, 3, 4, 5 and 6 were [redacted] respectively. The primary objective of AVERROES was to determine if apixaban was superior to aspirin for preventing the composite outcome of stroke or systemic embolism in adults with at least 1 risk factor for stroke who were unable to take warfarin.

4.3 In the intention-to-treat (ITT) population, apixaban met non-inferiority criteria using a non-inferiority margin of 1.38, over a median follow up of 1.8 years. Apixaban was associated with a significantly lower rate of stroke and systemic embolism than warfarin (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.66 to 0.95, p=0.01). The rate of fatal or disabling stroke was significantly lower in the apixaban group than the warfarin group (HR 0.71, 95% CI 0.54 to 0.94). When the outcomes included in the composite primary outcome (ischaemic or uncertain type, haemorrhagic stroke and systemic embolism) were analysed separately, apixaban was associated with a significant reduction in haemorrhagic stroke compared with warfarin (HR 0.51, 95% CI 0.35 to 0.75, p<0.001). However, the numeric decrease of apixaban compared with warfarin in ischaemic or uncertain type stroke or systemic embolism was not statistically significant. The rates of myocardial infarction and pulmonary embolism or deep

vein thrombosis were numerically lower with apixaban than warfarin, but were not statistically significant (HR 0.88, 95% CI 0.66 to 1.17, p=0.37, and HR 0.78, 95% CI 0.29 to 2.10, p=0.63 respectively). Apixaban was associated with significantly fewer all-cause deaths than warfarin 3.52% and 3.94% respectively (HR 0.89, 95% CI 0.80 to 0.99, p=0.047).

4.4 The manufacturer presented results for the primary efficacy outcomes for 21 pre-specified subgroups in ARISTOTLE including subgroups broken down by baseline risk of stroke or systemic embolism (grouped by $CHADS_2$ scores ≤1, 2, ≥3). Many of the results in the pre-specified subgroups were not statistically significant and ARISTOTLE was not statistically powered to demonstrate superiority in subgroup analyses. The hazard ratios for apixaban relative to warfarin for stroke and systemic embolism in the 3 stroke risk subgroups were consistent ([redacted] as were the hazard ratios for stroke and systemic embolism between the higher and lower dose of apixaban ([redacted]). The manufacturer also presented data for subgroups based on INR (International Normalised Ratio) control using quartiles of centre TTR (cTTR) (less than 58.0%, 58.0–65.7%, 65.7–72.2% and more than 72.2%). A centre's TTR was calculated as the median of individual TTRs among the centre's patients on warfarin. The manufacturer reported that the benefits of apixaban over warfarin in preventing stroke or systemic embolism were consistent (HR <1) regardless of INR control (< 580% HR 0.77, 95% CI 0.56 to 1.06; 58.0- 65.7% HR 0.80, 0.56 to 1.15; 65.7-72.2% HR 0.79, 95% CI 0.54 to 1.13; >72.2% HR 0.81, 95% CI 0.52 to 1.26).

4.5 The adverse events and safety analyses were reported for the on-treatment population in ARISTOTLE (all people who received at least 1 dose of study medication). Apixaban was superior to warfarin for the primary safety outcome of time from first dose of study drug to first occurrence of confirmed International Society on Thrombosis and Haemostasis (ISTH) major bleeding (HR 0.69, 95% CI 0.60 to 0.80; p<0.01). Apixaban resulted in significantly fewer bleeding events than warfarin for all of the major bleeding and clinically relevant non-major (CRNM) bleeding events reported by the manufacturer apart from major gastrointestinal bleeding for which the numeric difference between apixaban and warfarin was not statistically significant (HR 0.89, 95% CI 0.70 to 1.15, p=0.37) (see table 1). There were similar proportions of people who experienced adverse events with apixaban (81.5%) and warfarin (83.1%) and a lower proportion of people who experienced bleeding adverse events with apixaban (25.2%) compared with warfarin (32.7%). Serious adverse events occurred in 35.0% of people treated with apixaban and 36.5% of people treated with warfarin. Fewer people stopped the study drug in the apixaban group than the warfarin group (25.3% compared with 27.5% respectively, p=0.001); 7.6% of people in the apixaban arm and 8.4% of people in the warfarin arm stopped treatment because of an adverse event. The safety of apixaban was maintained across patients at different levels of stroke risk, regardless of warfarin control (TTR) and in patients who needed dose reduction.

Table 1 Bleeding outcomes from ARISTOTLE. Hazard ratios are for apixaban compared with warfarin

	Hazard ratio (95% CI)	P value
Primary safety outcome: ISTH major bleeding	0.69 (0.60–0.80)	<0.001
• intracranial	0.42 (0.30–0.58)	<0.001
• other location	0.79 (0.68–0.93)	0.004
• gastrointestinal	0.89 (0.70–1.15)	0.37
Major or CRNM bleeding	0.68 (0.61–0.75)	<0.001
• GUSTO severe bleeding	0.46 (0.35–0.60)	<0.001
• GUSTO moderate or severe bleeding	0.60 (0.50–0.71)	<0.001
• TIMI major bleeding	0.57 (0.46–0.70)	<0.001
• TIMI major or minor bleeding	0.63 (0.54–0.75)	<0.001
• any bleeding	0.71 (0.68–0.75)	<0.001
Net clinical outcomes		
• stroke, systemic embolism or major bleeding	0.77 (0.69–0.86)	<0.001
• stroke, systemic embolism, major bleeding or death from any cause	0.85 (0.78–0.92)	<0.001

CI, confidence interval; CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; GUSTO, Global use of strategies to open occluded arteries; TIMI, Thrombolysis in Myocardial Infarction.

4.6 In the intention to treat population in AVERROES, apixaban reduced the rate of stroke and systemic embolism compared to aspirin over a mean follow up of 1.1 years (HR 0.45, 95% CI 0.32 to 0.62, p< 0.001). The rates of disabling or fatal stroke were also lower in people who received apixaban compared with people who received aspirin (HR 0.43, 95% CI 0.28 to 0.65, p<0.001). When considered as a separate outcome aspirin reduced the rates of ischaemic stroke compared with aspirin (HR 0.37, 95% CI 0.25 to 0.55 p<0.001) but did not statistically significantly reduce the rates of haemorrhagic stroke (HR 0.67, 95% CI 0.24 to 1.88, p=0.45). Apixaban was associated with a higher rate of all bleeding than

aspirin (HR 1.30, 95% CI 1.10 to 1.53, p=0.002). Although apixaban was associated with higher numeric rates of major bleeding or major or clinically relevant non-major bleeding than aspirin, the differences in rates were not statistically significant (HR 1.54, 95% CI 0.96 to 2.45, p=0.07 for major bleeding and HR 1.38, 95% CI 1.07 to 1.78, p=0.01 for major or clinically relevant non-major bleeding).

4.7 The manufacturer conducted 2 network meta-analyses. The first meta-analysis (NMA1) included people suitable for treatment with warfarin and it compared apixaban, warfarin, dabigatran and rivaroxaban. The second meta-analysis (NMA2) was intended to assess a population of patients for whom warfarin was unsuitable, comparing apixaban, dabigatran rivaroxaban and aspirin. The manufacturer noted there were no data for rivaroxaban and dabigatran in a population for whom warfarin was unsuitable so data from ROCKET-AF, which assessed rivaroxaban compared with warfarin, and RE-LY, which assessed dabigatran compared with warfarin, were included, alongside ARISTOTLE and AVERROES. This meant that the second meta-analysis represented a mix of warfarin suitable and unsuitable populations. The first meta-analysis included ARISTOTLE, RE-LY and ROCKET-AF. There were differences between the trials of apixaban, dabigatran and rivaroxaban: ARISTOTLE and ROCKET-AF were double-blind, double-dummy trials, whereas RE-LY was an open-label trial; the population in ROCKET-AF had a higher stroke or systemic embolism risk at baseline (baseline $CHADS_2$ 3.6 [ROCKET-AF], 2.1 [ARISTOTLE], 2.1 [RE-LY]) and the mean percentage TTR was lower in ROCKET-AF (55%) than ARISTOTLE (62%) and RE-LY (64%). Where possible, the manufacturer used ITT data from each trial. However, the

manufacturer highlighted that there was an absence of published ITT outcomes data for some secondary outcomes from ROCKET-AF including fatal stroke, disabling stroke and non-disabling stroke, and therefore, data from the on-treatment population was also used (see table 2).

Table 2 Summary of differences between trials included in the first network meta-analysis (NMA1)

	ARISTOTLE	RE-LY	ROCKET-AF
Population	People with atrial fibrillation and at least 1 additional risk factor for stroke	People with atrial fibrillation and at least 1 additional risk factor for stroke	People with atrial fibrillation and at least 2 additional risk factors for stroke
Intervention	Apixaban (5 mg twice daily; 2.5 mg twice daily in selected patients)	Dabigatran 110 mg twice daily Dabigatran 150 mg twice daily	Rivaroxaban 20 mg once daily
Comparator	Warfarin (dosed to achieve a target INR 2.0–3.0)	Warfarin (dosed to achieve a target INR 2.0–3.0)	Warfarin (dosed to achieve a target INR 2.0–3.0)
Blinding	Double-blind, double-dummy	Open-label	Double-blind, double-dummy
Baseline $CHADS_2$	2.1	2.1	3.6
Mean TTR (warfarin arm)	62%	64%	55%
Analysed population in publication	ITT: efficacy OT: safety	ITT: all outcomes ITT data from an updated publication was available for some efficacy outcomes	ITT: primary outcome only OT was used to treat for superiority if non-inferiority was achieved for outcome in PP population OT: safety Supplemented with ITT for efficacy outcomes from other sources[1] excluding fatal or disabling stroke outcomes

[1] FDA slide set for rivaroxaban, rivaroxaban summary of product characteristics

INR, International Normalised Ratio; ITT, intention-to-treat; OT, on-treatment (all subjects who received at least 1 dose of double-blind study drug); PP, per protocol

4.8 The manufacturer used a Bayesian Markov Chain Monte Carlo stimulation in WinBUGS to conduct the network meta-analyses. Model fit was determined using the deviance information criterion and residual deviance for each outcome was assessed. There was little difference in model fit between the fixed- and random-effects

models, and the manufacturer used the fixed-effects model for all outcomes. The manufacturer did not present any statistical analysis of heterogeneity but commented that potential sources of clinical heterogeneity between the trials were the differences in baseline stroke risk scores, study blinding, and whether the ITT or on-treatment populations had been used to assess efficacy and safety outcomes. Additionally, the manufacturer highlighted a statistically significant difference in myocardial infarction at baseline between treatment groups in ROCKET-AF.

4.9 The base-case results of the first meta-analysis indicated that there were no statistically significant differences between apixaban and rivaroxaban or dabigatran in the incidence of stroke, systemic embolism and all-cause mortality. The results did however suggest that apixaban was associated with a significantly lower incidence of myocardial infarction compared with dabigatran (150 mg or 110 mg) (HR [redacted] respectively). Apixaban was associated with a significantly lower incidence of all bleeding outcomes compared with rivaroxaban (intracranial haemorrhage, HR [redacted]; major bleeding, HR [redacted]; gastrointestinal bleeding, HR [redacted]; other major bleeding, HR [redacted]; CRNM bleeding HR [redacted]; any bleeding, HR [redacted]). Apixaban had a significantly lower incidence of all bleeding events except intracranial haemorrhage and CRNM bleeding (which was not measured in RE-LY) than dabigatran 150 mg (major bleeding, HR [redacted]; gastrointestinal bleeding HR [redacted]; other major bleeding, HR [redacted]; any bleeding, HR

[redacted]). Apixaban had a significantly lower incidence of any bleeding than dabigatran 110 mg (HR [redacted]). In addition, apixaban was associated with significantly fewer discontinuations compared with dabigatran 150 mg, dabigatran 110 mg and rivaroxaban (HR [redacted]; HR [redacted]; HR [redacted] respectively). The manufacturer reported that the results for apixaban compared with warfarin generated by the first meta-analysis were consistent with the pair-wise comparisons between warfarin and apixaban in ARISTOTLE. See table 3 for full results from the first meta-analysis.

Table 3 Manufacturer's base-case results from the first meta-analysis (pair-wise comparison of apixaban compared with warfarin have been added); HR <1 favours apixaban, HR >1 favours comparator

Outcome	Hazard ratio (95% CrI)				
	Apixaban versus dabigatran 150 mg	**Apixaban versus dabigatran 110 mg**	**Apixaban versus rivaroxaban**	**Apixaban versus warfarin**	**Apixaban versus warfarin** (ARISTOTLE data)
Stroke and systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	**0.79 [0.66 to 0.95]**
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]	**0.79 [0.65 to 0.95]**
Systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	0.87 [0.44 to 1.75]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]	**0.51[0.35 to 0.75]**
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	0.92 [0.74 to 1.13]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	0.88 [0.66 to 1.17]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	**0.89 [0.80 to 0.998]**
Fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	**0.71 [0.54 to 0.94] fatal or disabling stroke**
Disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]	See above
Non to disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]	See above
ICH	[redacted]	[redacted]	[redacted]	[redacted]	**0.42 [0.30 to 0.58]**
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	**0.69 [0.60 to 0.80]**
Gastrointestinal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	0.89 [0.70 to 1.15]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]	**0.79 [0.68 to 0.93]**
CRNM bleeding	NR[1]	NR[1]	[redacted]	[redacted]	**0.68 [0.61 to 0.75] Major or CRNM**

Outcome	Hazard ratio (95% CrI)				
	Apixaban versus dabigatran 150 mg	**Apixaban versus dabigatran 110 mg**	**Apixaban versus rivaroxaban**	**Apixaban versus warfarin**	**Apixaban versus warfarin** (ARISTOTLE data)
					bleeding
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]	**0.71 [0.68 to 0.75]**
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	**Fewer patients discontinued study drug in apixaban group than warfarin group, 25.3% versus 27.5% respectively**

CrI, credibility interval; CRNM, clinically relevant non-major; ICH, intracranial haemorrhage

Results shown in bold are significantly different

[1] Data for this outcome not reported for the RE-LY trial

4.10 The manufacturer carried out a network meta-analysis by stroke risk severity ($CHADS_2$ score) and by centre-level TTR, to explore consistency of the primary efficacy (stroke and systemic embolism) and safety (ISTH major bleed) outcomes in the network meta-analysis. They noted that the $CHADS_2 \leq 1$ subgroup excluded ROCKET-AF as this trial enrolled people who had a $CHADS_2$ score of ≥2. They also noted that because the mean TTR differed across the trials included in the meta-analysis, the centre TTR quartiles defined for each trial were also different. The manufacturer stated that, consistent with the base case, there were no statistically significant differences across $CHADS_2$ and cTTR subgroups, between apixaban, rivaroxaban and dabigatran for the primary efficacy outcomes. Across cTTR and $CHADS_2$ groups, the risk of

major bleeding was numerically consistently lower with apixaban than with rivaroxaban or dabigatran. The subgroup analysis was underpowered to detect statistically significant differences in treatment effects. However, despite this, apixaban demonstrated a significantly significant lower risk of major bleeding compared with rivaroxaban across all $CHADS_2$ subgroups and compared with dabigatran 150 mg for the $CHADS_2 \geq 3$ subgroup. Apixaban had a statistically significantly lower risk of major bleeding compared with rivaroxaban for the second lowest and highest cTTR quartiles and a statistically significantly lower risk of major bleeding compared with dabigatran 150 mg for the highest cTTR quartile.

4.11 The manufacturer performed 2 sensitivity analyses of their base-case network meta-analysis (NMA1). The first used data from a later publication of RE-LY (Connolly et al. 2010) rather than the RE-LY (2009) data. The results for the first sensitivity analysis of NMA1 were generally consistent with the base case, however the reduction in myocardial infarction with apixaban compared with both doses of dabigatran was no longer statistically significantly different (150 mg HR [redacted]; 110 mg HR [redacted]) The second sensitivity analysis used the safety on treatment dataset from ROCKET-AF rather than the ITT data from this trial, which was also generally consistent with the base case [redacted].

4.12 The ERG considered that, of the 2 trials of apixaban, only ARISTOTLE met the inclusion criteria for this technology appraisal, although it did acknowledge that aspirin is used by some people in clinical practice in the UK. The ERG considered that the inclusion and exclusion criteria, the follow-up and statistical analysis of

ARISTOTLE were acceptable and that the baseline characteristics of the randomised populations were well balanced between trial arms. The ERG commented that, based on advice given by clinicians on the TTR expected in a UK population, the mean TTR in ARISTOTLE (62.2%) was acceptable. It also considered the INR monitoring in ARISTOTLE to be consistent with that which would occur routinely in the UK.

4.13 The ERG highlighted that no data on transient ischaemic attack or health-related quality of life were collected in ARISTOTLE or AVERROES, and that the effectiveness of apixaban in reducing transient ischaemic attacks and improving health-related quality of life was therefore unclear.

4.14 The ERG commented that [redacted] and it considered that the distribution of $CHADS_2$ scores in ARISTOTLE was comparable for the UK population for whom apixaban treatment would be considered. However, the ERG highlighted concerns about the subgroup analysis of ARISTOTLE by aggregated $CHADS_2$ scores. [redacted] However, the lack of detailed individual $CHADS_2$ score data, particularly for the higher $CHADS_2$ scores (that is, 3, 4, 5 and 6) limited the ERG from commenting on potential variation in apixaban treatment effect for these subgroups.

4.15 The ERG suggested that in ARISTOTLE the subgroups for geographical region suggest a trend towards people in Europe experiencing less benefit with apixaban compared with people in North America, Latin America or Asia Pacific) with the hazard ratios for stroke, systemic embolism and major bleeding approaching 1. However, it noted that geographical subgroups were not stratified at randomisation and that ARISTOTLE was not statistically powered to detect differences in efficacy and safety in the different geographical subgroups and so, drawing conclusions from the subgroup results would be inappropriate. The ERG stated that, because of the unavailability of weighted region-level percentage TTR, it was unable to comment on any potential relationship between TTR and geographical subgroup outcomes. The ERG commented that the number of events (stroke or systemic embolism) decreased as the cTTR improved in the warfarin arm, which was expected, but also highlighted that there was a similar trend in the apixaban arm, which suggested that there may be other factors other than INR control in people grouped by cTTR that affect the efficacy of apixaban and warfarin.

4.16 With respect to the network meta-analyses, the ERG did not consider the second analysis to be appropriate to determine the relative effectiveness of aspirin, apixaban, rivaroxaban and dabigatran in a warfarin-unsuitable population because the majority of trials in the second network meta-analysis included patients for whom warfarin was suitable. For the first analysis, the ERG felt that the differences between the trials and the potential clinical heterogeneity identified by the manufacturer meant that further head-to-head trials would be useful. However, the ERG acknowledged that no further data were available. Regarding the subgroup analysis for the first network meta-analysis,

[redacted]

5 Comments from other consultees

5.1 Professional groups commented that the advantages of apixaban compared with warfarin are its fixed dose (which benefits patients who are unable to stabilise their INR in the therapeutic range), its predictable pharmacokinetics with few drug and food interactions, and the lack of therapeutic monitoring needed. People with atrial fibrillation who would benefit most from apixaban are those with poor INR control on warfarin; those who have problems with frequent monitoring; those at greater risk of intracranial haemorrhage as the incidence of this complication is lower with dabigatran, rivaroxaban and apixaban than with warfarin; and those who are unable to take drugs that interact with warfarin, who drink alcohol or who have an inconsistent diet. The professional groups were concerned, however, that unlike warfarin, there are no antidotes to rapidly reverse bleeds for apixaban (or rivaroxaban or dabigatran). Because apixaban, rivaroxaban and dabigatran have shorter half-lives than warfarin, minor bleeding can resolve more quickly by stopping the drug but also means that missed doses are more likely to lead to a thrombotic event. Professional groups also highlighted that there is no reliable measure of the anticoagulant effect of apixaban and it is difficult to determine whether an individual is achieving an effective level of anticoagulation. Several

professional groups noted that the TTR of the trial population receiving warfarin (in ARISTOTLE) may be lower than what is typical in UK clinical practice, and 1 professional group suggested that the trial population was younger and had a lower level of non-steroidal anti-inflammatory drug and antibiotic use than in their practice. A lower TTR would be associated with more adverse outcomes in the warfarin arm and apixaban compared with well-controlled warfarin (TTR 75% or more) may not be superior in the long term.

5.2 Patient groups highlighted that people with atrial fibrillation who take warfarin find it difficult to live with and manage their treatment, stay in their therapeutic range, cope with day-to-day commitments such as work and family, and feel that their quality of life is affected. They estimated that almost 50% of patients who need oral anticoagulants are not receiving them and frequently, this is because of a fear of using warfarin, as well as low prescribing of dabigatran and rivaroxaban. The patient groups suggested that advantages of apixaban compared with warfarin were: a reduced risk of stroke, a reduced risk of bleeding as there is no need to keep the INR in a therapeutic range to prevent clotting or bleeding episodes, fewer side effects for the majority of patients, less interactions with medications and food, a reduced need to visit surgeries for INR monitoring, and reduced scarring through repeated blood tests. Additionally, the fixed dose of apixaban means simpler medicine management with reduced worry for patients, family members and carers about the monitoring and effectiveness of the medication, the side effects and travelling to or attending social events. The patient groups commented that apixaban offers almost immediate protection and they were not aware of any potential disadvantages.

6 Cost-effectiveness evidence

6.1 The manufacturer presented a deterministic base case for the warfarin-suitable and -unsuitable populations. In the population for whom warfarin was suitable, the ICER for apixaban compared with warfarin was £11,008 per QALY gained. The ERG's revised base case resulted in an ICER of £12,757 per QALY gained for apixaban compared with warfarin. The ERG also used the manufacturer's probabilistic sensitivity analysis to estimate the probabilistic incremental results. The equivalent probabilistic ICER for apixaban compared with warfarin was £16,852 per QALY gained. In both the deterministic and probabilistic incremental analyses for the warfarin-suitable population, dabigatran 110 mg was strictly dominated (was more costly and less effective) by the dabigatran blend (150 mg for people under 80 years, 110 mg for people over 80 years). Apixaban extendedly dominated rivaroxaban and the dabigatran blend (resulted in a lower ICER compared with warfarin despite having higher total QALYs and total costs than rivaroxaban and the dabigatran blend) (see table 4).

Table 4 Manufacturer's deterministic base-case incremental results and the probabilistic base-case incremental results estimated from the manufacturer's probabilistic sensitivity analysis.

Treatment	Total			Incremental[1]			ICER (£/QALY)	
	Costs (£)	LYG	QALY	Costs (£)	LYG	QALY	Versus warfarin	Incremental
Deterministic								
Warfarin	7,188	7.469	5.696	–	–	–	–	–
Dabigatran (150 or 110 mg)	8,437	7.537	5.788	1,248	0.068	0.091	13,648	Extendedly dominated
Dabigatran (110 mg)	8,684	7.503	5.756	247	-0.034	-0.032	25,308	Strictly dominated
Rivaroxaban	8,778	7.553	5.809	95	0.050	0.054	14,071	Extendedly dominated
Apixaban	8,983	7.614	5.860	205	0.06	0.05	11,008	11,008
Probabilistic (estimated from manufacturer probabilistic sensitivity analysis)								
Warfarin	5,331	6.869	5.303	–	–	–	–	–
Dabigatran (150 or 110 mg)	6,737	6.921	5.342	1,406	0.05	0.04	36,450	Extendedly dominated
Dabigatran (110 mg)	6,832	6.899	5.321	95	-0.02	-0.02	83,628	Strictly dominated
Rivaroxaban	7,070	6.943	5.366	237	0.04	0.05	27,565	Extendedly dominated
Apixaban	7,228	7.002	5.416	159	0.06	0.05	16,852	16,852

ICER, incremental cost-effectiveness ratio; LYG, life-year gained; mg, milligram; QALY, quality-adjusted life year

[1] Versus the next less costly technology

6.2 Although aspirin was not included as a comparator in the scope, the manufacturer compared apixaban with aspirin in a population for whom warfarin was unsuitable. In this population apixaban was associated with an ICER of £2903 per QALY gained compared with aspirin (see table 5).

Table 5 Manufacturer's deterministic base case for the population for whom warfarin is unsuitable

Technologies	Total			Incremental†			ICER (£) versus aspirin	ICER (£) incremental
	Costs (£)	LYG	QALY	Costs (£)	LYG	QALY		
Aspirin	£7,916	7.063	5.354					
Dabigatran (150 or 110 mg)	£8,228	7.357	5.635	£312	0.294	0.281	£1,111	£1,111
Dabigatran (110 mg)	£8,531	7.311	5.592	£303	-0.046	-0.043	£2,587	Strictly dominated
Rivaroxaban	£8,608	7.367	5.651	£77	0.056	0.060	£2,326	£23,027
Apixaban	£8,870	7.410	5.683	£262	0.043	0.031	£2,903	£8,401

ICER, incremental cost-effectiveness ratio; LYG, life-year gained; mg, milligram; QALY, quality-adjusted life year

1 Versus the next least costly technology

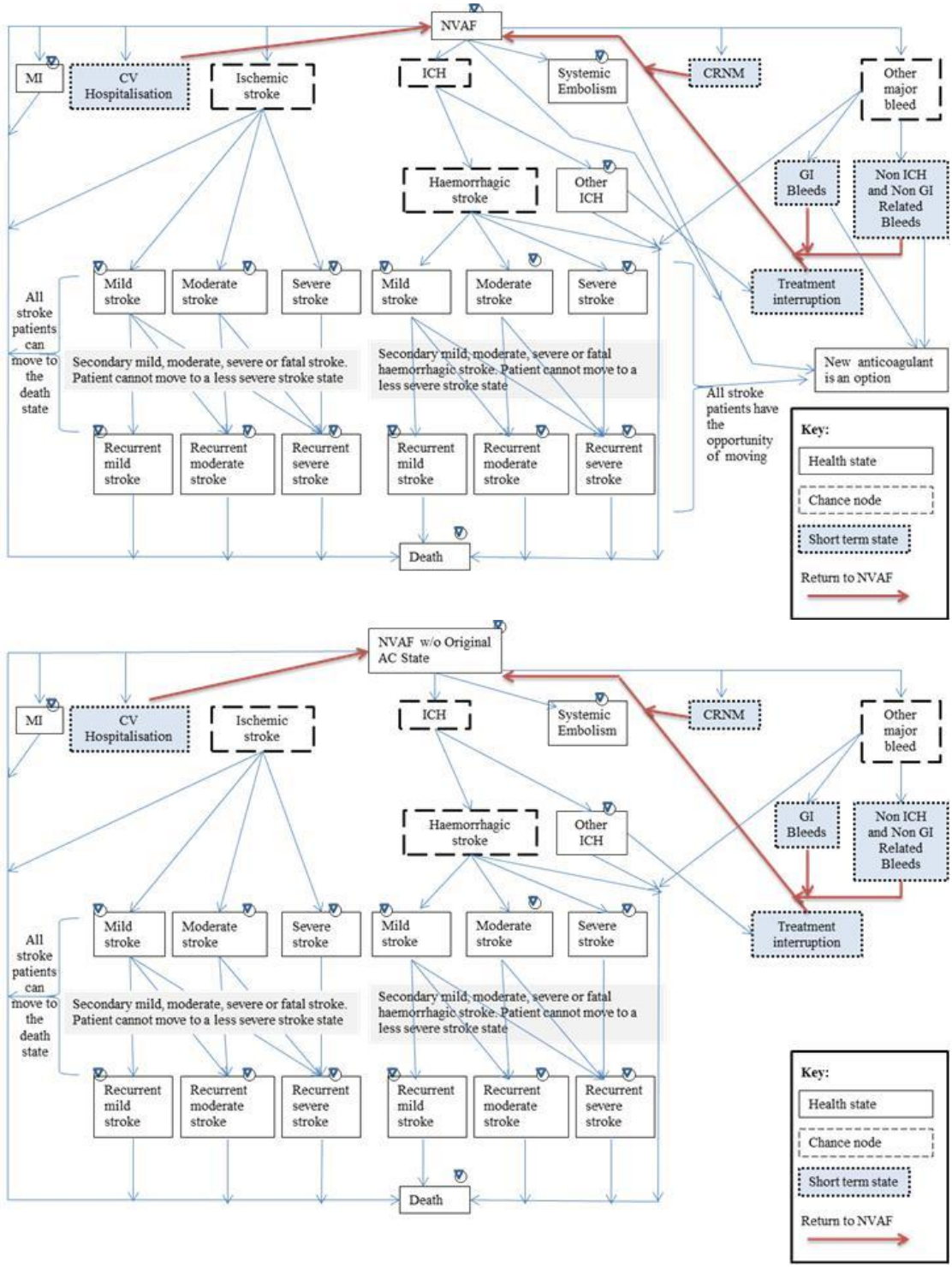
6.3 The manufacturer performed a systematic review to identify cost-effectiveness studies of interventions for the prevention of stroke or systemic embolism in adults with atrial fibrillation. The manufacturer identified 5 cost–utility studies. Of these studies, 3 used a Markov model, 1 used a semi-Markov model and 1 used a discrete event simulation. All of these evaluated the cost effectiveness of dabigatran, warfarin, aspirin, or aspirin plus clopidogrel in the prevention of stroke and systemic embolism in atrial fibrillation patients. The manufacturer also summarised the modelling approach used for the NICE single technology appraisals for dabigatran and rivaroxaban. Subsequent to the systematic review, a further cost–utility analysis was published that evaluated apixaban compared with aspirin in patients in whom warfarin was unsuitable. This analysis found that apixaban dominated aspirin (that is, apixaban was less costly and more effective).

6.4 The manufacturer constructed a Markov model to evaluate the long- and medium-term consequences of apixaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. The model considered warfarin-suitable and -unsuitable populations separately. The baseline characteristics of both populations were considered to be equivalent to the characteristics of a cohort of patients with a diagnosis of atrial fibrillation from a UK GP based survey (Gallagher et al. 2011). The manufacturer noted that this cohort was on average older, had a lower proportion of men and a different distribution of $CHADS_2$ scores (there were more patients with a $CHADS_2$ of 0) than the apixaban trial populations. Data from both network meta-analyses were used to inform the clinical effectiveness of treatments in the warfarin suitable and unsuitable populations respectively and to derive the transition probabilities used in the model. The risk of stroke was adjusted for baseline $CHADS_2$ score distribution and the risks of stroke, intracranial haemorrhage, myocardial infarction, other major bleeds and CRNM bleeds were adjusted for age. The model had a lifetime time horizon. The intervention and comparators were implemented in the model according to their marketing authorisations. For dabigatran 150 mg it was assumed that people would switch to the 110 mg dose when they reached 80 years. The average daily dose of warfarin in the warfarin suitable population was assumed to be 4.5 mg once daily. The evaluation was undertaken from the perspective of the NHS and Personal Social Services in England and Wales, and costs and benefits were discounted at 3.5% per year after the first year.

6.5 The model had 18 health states, including death. Both event-related mortality and other-cause mortality were incorporated in the model. Patients transitioned between health states in cycles of

6 weeks with only 1 clinical event permitted per cycle. Patients entered the model in the nonvalvular atrial fibrillation ('NVAF') health state, and stayed in this state until they died or experienced one of the following permanent events: ischaemic stroke (mild, moderate, severe or fatal; severity levels based on modified Rankin scale [mRS]); haemorrhagic stroke (mild, moderate, severe or fatal); systemic embolism or myocardial infarction; or 1 of the following temporary events: other intracranial haemorrhage (that is not a haemorrhagic stroke); other major bleeds (gastrointestinal bleeds or other bleeds besides intracranial haemorrhage and gastrointestinal-related bleeds); CRNM bleeds; other cardiovascular hospitalisations (that is, cardiovascular hospitalisations unrelated to stroke or myocardial infarction). The model allowed a maximum of 2 lines of therapy. After a switch to second-line therapy, patients transitioned into the 'NVAF without original anticoagulant' health state and were at risk of the same events as patients in the 'NVAF' health state (with the exception of the switch to second-line therapy). See figure 1.

Figure 1 Diagram of manufacturer's model, where top panel shows structure for people who enter the model, and bottom panel shows structure for people on second-line treatment



6.6 The manufacturer classified the events as permanent or temporary. Patients who experienced a permanent event accrued both acute and long-term maintenance costs and were not assumed to recover to their previous level of health. After a permanent event, people in the model were not exposed to the risks of all events: people who had systemic embolism or myocardial infarction stayed in those health states until they died; people who had a non-fatal stroke could remain in that health state, have 1 recurrent stroke or die. Recurrent strokes were assumed to be of the same type as the initial event (ischaemic or haemorrhagic) but could be of different severity. The resource use and disutility associated with the second stroke was assumed to be equal to that of the most severe stroke experienced. After a temporary event, all patients were assumed to recover to their previous health status.

6.7 A variety of treatment switches were permitted in the model. A switch from first-line to second-line therapy was permitted after discontinuation because of a clinical event (intracranial haemorrhage or other major bleed) or after discontinuation because of other causes. People could switch to aspirin or have no treatment. In the base case, anyone who discontinued treatment was assumed to receive aspirin second-line. Only a switch from first-line anticoagulation therapy to second-line therapy with aspirin altered people's risk of subsequent clinical events. People who experienced certain permanent events also switched treatment: people who had a myocardial infarction or haemorrhagic stroke were assumed to discontinue treatment, people receiving aspirin as second-line therapy switched to warfarin if they had an ischaemic stroke or systemic embolism. However, all other people who had ischaemic stroke or systemic embolism were assumed to remain on their original treatment in the base case. The risk of subsequent

events for patients in permanent clinical event health states was assumed to be independent of treatment received, so switching did not affect their risk profile.

6.8 The manufacturer conducted a systematic review of health-state utility value studies relevant to the health states considered in the model, focusing on studies that reported EQ-5D health-state utility values. Values from 21 studies that presented EQ-5D data in an atrial fibrillation population and 3 studies that reported EQ-5D values for a variety of chronic conditions after controlling for comorbidities were included. As there were still some health states for which a utility value had not been identified, studies that reported utilities in an atrial fibrillation population elicited by methods other than EQ-5D were screened, and data from a further 8 studies were included. One further study was identified from the reference list from the submissions for NICE technology appraisal guidance 249 and 256 (see table 6 for the utilities used).

Table 6 Utility values for health states and treatments used in the manufacturer's model

Health state		Utility value
'NVAF' or 'NVAF without original anticoagulant'		0.7800
Stroke (ischaemic or haemorrhagic)	Mild	0.7600
	Moderate	0.3900
	Severe	0.1100
Systemic embolism		0.6795
Myocardial infarction		0.6830
Temporary health events		
Other intracranial haemorrhage (applied upon occurrence for a duration of 6 weeks)		-0.1070
Other major bleeds (applied upon occurrence for a duration of 2 weeks)		-0.1070
CRNM bleed (applied upon occurrence for a duration of 2 days)		-0.0582
Other cardiovascular hospitalisation (applied upon occurrence for a duration of 6 days)		-0.0970
Treatment		
Apixaban		-0.0020
Aspirin		-0.0020
Aspirin (second-line)		-0.0020
Warfarin		-0.0130
Dabigatran (110 mg)		-0.0020
Dabigatran (150 mg)		-0.0020
Rivaroxaban		-0.0020
CRNM, clinically relevant non-major		

6.9 The manufacturer used unit costs taken from NHS reference costs 2010/11 where possible, and where available, Healthcare Resource Group codes specified in the costing report for atrial fibrillation from NICE clinical guideline 36 were used. The average daily drug acquisition costs were £2.20 for apixaban, £2.20 for dabigatran (either dose), £2.10 for rivaroxaban and £0.12 for warfarin (4.5 mg average daily dose). The manufacturer's model included intervention costs such as an annual INR monitoring cost of £248 which was an inflated estimate of the ERG's calculation in

technology appraisal guidance 249 (dabigatran etexilate), and a £3 renal monitoring cost for 19.4% of people treated with dabigatran. The acute costs per episode for the temporary health states were £3010 for other intracranial haemorrhage; £1494 for gastrointestinal bleeds; £3948 for other major bleeds; £1134 for CRNM bleeds and £1571 for cardiovascular hospitalisations. Permanent health states accrued acute and long-term costs. The acute cost associated with a myocardial infarction episode was £2019 with an additional long-term cost of £7 per month. The costs of stroke or systemic embolism were taken from a population-based study. The acute costs for systemic embolism were £4078 with long-term costs of £184 per month. The acute costs associated with ischaemic stroke in the model ranged from £3516 for a mild stroke to £25,051 for a severe stroke, with the long-term costs ranging from £184 to £545 per month. The acute costs of haemorrhagic stroke ranged from £10,237 for a mild stroke to £44,487 for a severe stroke. The long-term costs per month were the same as those for ischaemic stroke. Fatal ischaemic and haemorrhagic strokes were associated with a cost of £3162 and £1,636 respectively. Dyspepsia was the only adverse event that was not explicitly modelled as a health state, and a yearly cost of £27.60 was applied to all people who had dyspepsia.

6.10 The manufacturer assessed the univariate sensitivity of the model to 117 parameters using deterministic sensitivity analyses. In the warfarin-suitable population, parameters that had the most influential effect on the ICER for apixaban compared with warfarin were disutility associated with warfarin use, the hazard ratios for intracranial haemorrhage , ischaemic stroke or other-cause mortality during the trial, the cost of INR monitoring visit and the discount rate applied to QALYs (see figure 2). For apixaban

compared with rivaroxaban or dabigatran, the most influential parameters were the hazard ratios associated with stroke, intracranial haemorrhage and other-cause mortality during the trial for these comparators compared with apixaban, the absolute stroke risk for apixaban, and the second-line stroke risk for aspirin. All of the ICERs calculated in the manufacturer's deterministic sensitivity analysis for apixaban compared with the comparator drugs were below £20,000. In addition, the manufacturer carried out 19 scenario analyses. The majority of the scenario analyses decreased the base-case ICER (for apixaban compared with comparator) (see table 7). The probabilistic sensitivity analysis indicated that the probability that apixaban was cost effective at £20,000 and £30,000 per QALY gained was 80% and 87% respectively. For the dabigatran blend, rivaroxaban and warfarin the probabilities of being cost effective at £20,000 were 10%, 9% and 1% respectively. At £30,000 these were 5%, 7% and 0% respectively.

Figure 2. Tornedo diagram demonstrating the effect on the ICER for apixaban versus warfarin of varying parameter inputs in the warfarin suitable population

Table 7 Scenarios assessed by manufacturer (modified from table 83, page 169, manufacturer's submission)

Scenario description	ICER versus warfarin	ICER versus rivaroxaban	ICER versus dabigatran blend
Recurrent stroke (ischaemic and haemorrhagic) switched off	£11,062	£4,313	£7,467
Trial specific other-cause mortality switched off (adjusted UK life-table data used for full-model time horizon)	£12,830	£4,096	£7,644
Long-term mortality based on general public (atrial fibrillation correction switched off, HR=1)	£10,118	£3,764	£6,684
Other-cause discontinuation set equal to apixaban for all comparators	£11,472	£3,451	£6,919
Discontinuation rates set the same as apixaban	£11,203	£3,243	£7,906
Discount costs and benefits at 6% and 1.5% respectively	£8,914	£2,949	£5,585
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic), systemic embolism cost and long-term maintenance costs equal to Youman et al. (2002) (inflated to 2010/11 costs)*	£11,453	£3,804	£8,066
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and systemic embolism cost equal to NHS reference cost of stroke (estimated as £2952 based on weighted average of AA04A, AA04B, A10A, AA10B, AA16A, AA16B,AA22A, AA22B, AA23A, AA23B; cost of fatal stroke cost is £0)	£12,152	£4,968	£8,545
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and systemic embolism cost equal to PBR Tariff costs of stroke (estimated as £4231 based on weighted average of AA04Z, AA10Z, AA16Z, AA22Z, AA23Z, cost of fatal stroke is £0)	£12,096	£4,821	£8,526
Reduce health-state utility decrements for other ICH, other major bleeds and CRNM bleeds by 25%	£11,011	£4,095	£7,637
Reduce utility values for ischaemic and haemorrhagic stroke and systemic embolism health states by 25%	£10,955	£3,822	£8,064
Assume same (apixaban) stroke severity	£11,608	£1,637	£8,421

Scenario description	ICER versus warfarin	ICER versus rivaroxaban	ICER versus dabigatran blend
distribution for all interventions (mild, moderate, severe and fatal)			
Age is 80, risks calculated using cTTR specific data, 100% of patients have cTTR >76.51%, all drugs have same stroke severity distribution, trial mortality off, no cost for fatal strokes, NHS reference costs used for stroke and systemic embolism, utility decrements associated with bleeding reduced by 25%	£16,124	£2,799	£3,891
Age is 70, risks calculated using cTTR specific data, 100% of patients have cTTR <52.38%, costs of stroke and systemic embolism inflated by 15%	£5,137	£2,862	£7,725
Apply warfarin disutility of 0.013 to all NOACs	£15,152	£4,999	£8,834
Apply disutility of 0.0 to all anticoagulants	£14,530	£4,105	£7,697
Gallagher et al. (2008)†) baseline characteristics	£11,894	£4,236	£6,135
Treatment choice post other ICH or other major bleeds: no treatment	£10,573	£2,073	£3,898
Treatment choice post other ICH or other major bleeds: warfarin	-	£8,745	£28,695
HR, hazard ratio; ICH, intracranial haemorrhage; NOAC, new oral anti-coagulant; PBR, payment by results * Reference not provided, † Gallagher et al., (2008) Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? J Thromb Haemost Sep; 6(9): 1500-6.			

6.11 The manufacturer carried out subgroup analyses by level of INR control; this was limited to the comparison of apixaban with warfarin in the warfarin-suitable population. The manufacturer highlighted that the ICER for apixaban compared with warfarin for the subgroup of people with the highest mean cTTR was more favourable than the base-case ICER (£9889 per QALY gained). This result was driven by the lower number of ischaemic and

haemorrhagic strokes experienced by patients on both medications resulting in a better incremental QALY gain for patients on apixaban compared with warfarin. The cost-effectiveness results from the manufacturer's subgroup analysis by $CHADS_2$ score categories did not vary substantially from the base-case results.

6.12 The ERG considered that the manufacturer had presented a robust and predominantly conservative (direction of bias more likely to be against rather than towards apixaban) economic evaluation of apixaban compared with warfarin, dabigatran 110 mg, dabigatran blend and rivaroxaban in the warfarin suitable population. However, the ERG commented on the plausibility of some of the assumptions and inputs used in the manufacturer's model:

- Severity of stroke event and bleed type was assumed to be dependent on the treatment received. The ERG considered that this may not be clinically appropriate and that there may be limitations to the data that informed these assumptions. Stroke severity was not a pre-specified outcome in the apixaban, dabigatran or rivaroxaban trials and stroke severity distributions in the model were based on secondary analysis of ARISTOTLE data and weighting of the data reported in RE-LY and ROCKET-AF.
- People who had a stroke (haemorrhagic or ischaemic), systemic embolism or myocardial infarction were assumed to be at risk of fewer types of subsequent clinical events than people in other health states The ERG accepted the risk limitation applied to patients who experienced a stroke but said that people with systemic embolism or myocardial infarction would remain at risk of further events (in particular ischaemic stroke).
- The within trial rate of other-cause mortality was [redacted] for patients treated with warfarin than apixaban, dabigatran or

rivaroxaban. Although patients treated with warfarin may be at a higher risk of event-specific death, the ERG did not expect that they would be at a [redacted] risk of other-cause mortality.

- The ERG commented that utilities were not age-adjusted in the manufacturer's model, meaning that a patient's quality of life would be affected by events experienced but not by increasing age.
- The ERG considered that the time horizon in which patients were modelled for 49 years was not appropriate, as more than 99% of people in the model had died after 26 years (by 100 years).
- The acute cost of systemic embolism in the manufacturer's model (£4077.98) was approximately double the acute costs used in the submissions in NICE technology appraisal guidance 249 (dabigatran £2772 [fatal and non-fatal acute costs]) and NICE technology appraisal guidance 256 (rivaroxaban £1658). These submissions had used NHS reference costs.
- All patients who stopped treatment switched to second-line aspirin. The ERG considered that some patients who stop therapy with apixaban, dabigatran or rivaroxaban may be eligible for treatment with warfarin or a different oral anticoagulant.
- The ERG considered that the assumption of equivalent disutility between the apixaban, rivaroxaban and dabigatran may not be robust but that any resultant bias was likely to be against apixaban.
- The ERG commented that the risk profile of patients on second-line therapy was not adjusted for patient characteristics such as age or $CHADS_2$ score, but it accepted that adjusting for patient characteristics in second-line treatment may be beyond a reasonable scope of a Markov model.

6.13 The ERG carried out a sensitivity analysis in response to the points raised in section 6.12. The following sensitivity analyses were combined to form a revised ERG base case:

- other-cause mortality was assumed to be independent of treatment received
- utility adjusted for age (upon request, the manufacturer provided an updated model during clarification with an adjustment of -0.00029 per year)
- stroke severity distribution was assumed to be independent of treatment received
- bleed type was assumed to be independent of treatment received
- systemic embolism patients were assumed to be at risk of recurrent stroke
- myocardial infarction patients were assumed to be at risk of recurrent stroke
- the acute cost of systemic embolism was assumed to be equal to the cost used in the NICE technology appraisal guidance 256 rivaroxaban submission (chosen over the dabigatran appraisal as the more conservative cost)
- the time horizon was assumed to be 26 years.

The ERG commented that the incremental cost-effectiveness results were unaffected by any of the above amendments (both individual and combined amendments), that is, dabigatran 110 mg continued to be strictly dominated by dabigatran blend, and rivaroxaban and dabigatran blend remained extendedly dominated by apixaban. The ERG's revised base-case analysis resulted in an ICER for apixaban compared with warfarin of £12,757 per QALY gained (see table 8).

Table 8 Incremental impact of ERG's revised base-case amendments (page 148, ERG report)

Analysis	Tx	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Inc. ICER (£/QALYs)	Cumulative ICER (£/QALYs)
Manufacturer's base case	**Warfarin**	**7,188.49**	**5.70**	**–**	**–**	**–**	**11,007.68**
	Apixaban	**8,983.07**	**5.86**	**1,794.58**	**0.163**	**11,007.68**	
Other-cause mortality assumed to be independent of Tx	Warfarin	7,166.80	5.68	–	–	–	12,829.47
	Apixaban	8,917.83	5.82	1,751.02	0.14	12,829.47	
Utility adjusted for age	Warfarin	7,188.49	5.59	–	–	–	13,081.07
	Apixaban	8,983.07	5.75	1,794.58	0.16	11,226.73	
Stroke severity assumed to be independent of Tx	Warfarin	6,576.61	5.73	–	–	–	14,788.43
	Apixaban	8,485.48	5.89	1,908.87	0.16	12,276.64	
Bleed type assumed to be independent of Tx	Warfarin	7,264.28	5.67	–	–	–	12,805.14
	Apixaban	9,018.76	5.85	1,754.48	0.18	9,771.15	
SE patients assumed to be at risk of stroke	Warfarin	7,201.36	5.69	–	–	–	12,774.04
	Apixaban	8,994.67	5.85	1,793.31	0.16	10,982.25	
MI patients assumed to be at risk of stroke	Warfarin	7,310.59	5.69	–	–	–	12,739.74
	Apixaban	9,104.35	5.86	1,793.76	0.16	10,981.19	
Acute SE costs from rivaroxaban HTA submissionused	Warfarin	7,152.47	5.70	–	–	–	12,748.90
	Apixaban	8,948.37	5.86	1,795.90	0.163	11,015.79	
26 year time horizon	Warfarin	7,185.87	5.70	–	–	–	12,757.14
	Apixaban	8,980.27	5.86	1,794.40	0.163	11,013.85	
Event-risk on second-line Tx adjusted for patient characteristic	Impact unknown, however analysis of impact from age adjustment of second-line treatment event risks suggested that impact may favour apixaban						

s							
ERG revised base case	Warfarin	**6,733.32**	**5.57**	**–**	**–**	**–**	**12,757.14**
	Apixaban	**8,556.42**	**5.71**	**1,823.17**	**0.14**	**12,757.14**	
ERG, Evidence Review Group; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALY, quality-adjusted life year; SE, systemic embolism; Tx, treatment							

6.14 The ERG carried out 3 further exploratory analyses that were not included in its revised base case. These were:

- Age adjustment of event risks for patients on second-line therapy, using the same risk adjustment factors as for patients receiving first-line therapy. Dabigatran blend and rivaroxaban continued to be extendedly dominated by apixaban. The ICER for apixaban compared with warfarin fell slightly from £11,008 to £10,779 per QALY gained.
- Removal of treatment-related disutility. Dabigatran blend and rivaroxaban continued to be extendedly dominated by apixaban but the ICER for apixaban compared with warfarin increased from £11,008 to £14,530 per QALY gained.
- Changes to the treatment sequence to allow second-line treatment with warfarin, apixaban, rivaroxaban or dabigatran. The results of these analyses were highly variable with ICERs for apixaban varying between £287 per QALY gained (compared with warfarin when dabigatran 110 mg was the second-line treatment) and £60,366 per QALY gained (compared with dabigatran blend when rivaroxaban was the second-line treatment). However, the ERG commented that the results of this analysis should be interpreted with caution because the main driver of the ICERs was discontinuation rates associated with first-line therapy and, consequently, treatments with higher discontinuation rates such as dabigatran appeared more effective than in the manufacturer's base case.

6.15 The ERG additionally produced a summary of the QALYs and costs gained for each treatment disaggregated by health state (see tables 9 and 10).

Table 9 ERG's summary of QALYs gained by health state

Health state	Total QALYs				
	Apixaban	**Warfarin**	**Rivaroxaban**	**Dabigatran (150 mg or 110 mg)**	**Dabigatran (110 mg)**
NVAF	5.458	5.282	5.388	5.363	5.317
Ischaemic stroke					
Mild	0.151	0.143	0.151	0.136	0.146
Moderate	0.040	0.045	0.041	0.045	0.049
Severe	0.002	0.002	0.002	0.002	0.002
Recurrent stroke*	0.015	0.014	0.015	0.014	0.015
Haemorrhagic stroke					
Mild	0.010	0.015	0.023	0.007	0.008
Moderate	0.005	0.005	0.004	0.002	0.003
Severe	0.000	0.001	0.000	0.000	0.000
Recurrent stroke*	0.000	0.000	0.001	0.000	0.000
Other events					
SE	0.059	0.061	0.060	0.063	0.063
MI	0.122	0.129	0.127	0.157	0.154
Other temporary events**	-0.001	-0.002	-0.002	-0.002	-0.001
Total QALYs	**5.860**	**5.696**	**5.809**	**5.788**	**5.756**

*Mild, moderate and severe recurrent stroke health states have been aggregated as QALY numbers were small and recurrent stroke is independent of treatment.

**Other temporary events includes (other ICH, other major bleeds, CRNM bleeds and CV hospitalisation).

CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; mg, milligram; MI, myocardial infarction; NVAF, nonvalvular atrial fibrillation; SE, systemic embolism; QALY, quality-adjusted life year

Table 10 ERG's summary of costs accrued by health state

Health state	Total costs (£)				
	Apixaban	Warfarin	Rivaroxaban	Dabigatran (150 mg or 110 mg)	Dabigatran (110 mg)
Anticoagulation	3,347	252	2,891	2,657	2,716
Routine care	0	0	0	0	0
Monitoring	72	977	80	90	88
Ischaemic stroke					
Mild	651	620	652	594	631
Moderate	1341	1487	1394	1522	1627
Severe	605	648	618	683	722
Fatal	61	58	74	75	78
Recurrent stroke*	195	201	200	194	210
Haemorrhagic stroke					
Mild	63	98	144	44	49
Moderate	195	175	143	94	113
Severe	143	230	128	115	122
Fatal	12	25	11	8	8
Recurrent stroke*	19	24	28	10	13
Other events					
SE	251	263	257	271	268
MI	114	120	119	142	140
Other temporary events**	1,912	2,013	2,040	1,929	1,891
Total costs	**8,983**	**7,188**	**8,778**	**8,437**	**8,684**

*Mild, moderate and severe recurrent stroke health states have been aggregated as QALY numbers were small and recurrent stroke is independent of treatment.

**Other temporary events includes (other ICH, other major bleeds, CRNM bleeds, CV hospitalisation and dyspepsia).

CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; mg, milligram; MI, myocardial infarction; SE, systemic embolism; QALY, quality-adjusted life year

7 Equalities issues

7.1 During consultation on the scope, consultees commented that availability of therapy should not be restricted by a patient's age.

The manufacturer noted that there were no equalities issues in their submission. One professional group said that patients with atrial fibrillation and mental impairments that affect their ability to make decisions about treatment options should not be denied or refused access to a treatment that could reduce their risk of stroke and systemic embolism. No other potential equity issues were raised in the submissions.

8 Innovation

8.1 The manufacturer commented that, as apixaban provides a similar level or stroke prevention to dabigatran and rivaroxaban but with significantly lower rates of bleeding and treatment discontinuations, apixaban will afford the NHS and patients with atrial fibrillation a new standard of stroke prevention care.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE technology appraisal guidance 249 (2012). Available from www.nice.org.uk/guidance/TA249
- Rivaroxaban for the prevention of stroke in atrial fibrillation. NICE technology appraisal guidance 256 (2012). Available from www.nice.org.uk/guidance/TA256
- Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/guidance/CG36
- Thoracoscopic exclusion of the left atrial appendage in atrial fibrillation (with or without other cardiac surgery) for the prevention of thromboembolism. NICE interventional procedure guidance 400 (2011). Available from www.nice.org.uk/guidance/IPG400
- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 349 (2010). Available from www.nice.org.uk/guidance/IPG349