NICE National Institute for Health and Care Excellence

NICE guidance

Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance should be read in conjunction with NG196.

1 Recommendations

1.1 Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with non-valvular atrial fibrillation with 1 or more risk factors such as:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure.

1.2 Decide whether to start treatment with apixaban after an informed discussion with the person about its risks and benefits compared with warfarin, dabigatran etexilate, edoxaban and rivaroxaban. For people taking warfarin, consider the potential risks and benefits of switching to apixaban taking into account their level of international normalised ratio (INR) control.

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 5 mg twice daily and 2.5 mg twice daily has a European marketing authorisation for the 'prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with 1 or more risk factors, such as prior stroke or transient ischaemic attack, age 75 years or older, hypertension, diabetes mellitus, or symptomatic heart failure (New York Heart Association [NYHA] class 2 or higher)'.

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 manufacturer has stated that the cost per day for both doses (2.5 mg and 5 mg twice daily) of apixaban (excluding VAT) is £2.20, and the annual cost is £803. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of apixaban and a review of this submission by the Evidence Review Group (ERG).

3.1 The main clinical effectiveness evidence for apixaban came from 2 international, multicentre, double-blind, double-dummy, placebo-controlled, randomised controlled trials, which had investigated apixaban. ARISTOTLE (n=18,201) compared apixaban (5 mg twice daily; 2.5 mg twice daily in selected patients) with warfarin (in patients with an international normalised ratio [INR] target range of 2.0 to 3.0). AVERROES (n=5598) compared apixaban (5 mg twice daily; 2.5 mg twice daily in selected patients) with aspirin (81 mg to 324 mg once daily) in people 50 years or older with atrial fibrillation and at least 1 additional risk factor for stroke for whom treatment with warfarin had failed, or for whom warfarin was unsuitable or who were unwilling to take warfarin.

3.2 The primary objective of ARISTOTLE was to determine if apixaban was non-inferior to warfarin for the combined end point of stroke and systemic embolism. Stroke included both ischaemic stroke, caused by embolism from the heart, and haemorrhagic stroke, which can be a complication of anticoagulant treatment (although it may also occur spontaneously or as a result of secondary haemorrhage into an ischaemic stroke). 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). It enrolled patients from 39 countries; 40% of participants were from Europe and this included patients from 41 sites in the UK. The average age was 69 years and 65% of the population were male. The mean time in therapeutic range for patients in the warfarin arm was 62.2%, and the median time in therapeutic range was 66%. Approximately 4% of the study population received 2.5 mg apixaban (those who 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/100 ml [133 micromole/l] or more). The mean $CHADS_2$ score at baseline was 2.1 and approximately 65% of patients had a $CHADS_2$ score of 2 or more.

3.3 In the intention-to-treat 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), but the decrease for apixaban compared with warfarin in ischaemic or uncertain type stroke or systemic embolism was not statistically significant (ischaemic or uncertain type stroke HR 0.92, 95% CI 0.74 to 1.13, p=0.42; systemic embolism HR 0.87, 95% CI 0.44 to 1.75, p=0.70). The rates of myocardial infarction, and pulmonary embolism or deep vein thrombosis, were 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 fewer all-cause deaths than warfarin, which was of borderline statistical significance (3.52% and 3.94% respectively [HR 0.89, 95% CI 0.80 to 0.99, p=0.047]).

3.4 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 $\leq$1, 2 and $\geq$3). 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 consistently less than 1, but the confidence intervals of the $CHADS_2$ $\leq$1 and 2 groups crossed 1, meaning that that the difference between apixaban and warfarin was not statistically significant for these groups. The hazard ratios for stroke and systemic embolism in the groups of patients who received 5 mg and 2.5 mg apixaban were also both below 1 (the hazard ratios for $CHADS_2$ score subgroups and for the groups of patients who received 5 mg and 2.5 mg apixaban are commercial-in-confidence). The manufacturer also presented data for subgroups based on INR (international normalised

ratio) control using quartiles of centre time in therapeutic range (less than 58.0%, 58.0% to 65.7%, 65.7% to 72.2% and more than 72.2%). A centre's time in therapeutic range was calculated as the median of individual time in therapeutic ranges 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 (centre time in therapeutic range <58.0% [HR 0.77, 95% CI 0.56 to 1.06], centre time in therapeutic range 58.0% to 65.7% [HR 0.80, 95% CI 0.56 to 1.15], centre time in therapeutic range 65.7% to 72.2% [HR 0.79, 95% CI 0.54 to 1.13], centre time in therapeutic range >72.2% [HR 0.81, 95% CI 0.52 to 1.26]).

3.5 The adverse events and safety analyses were reported for the on-treatment population in ARISTOTLE (all patients 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<0.001). Apixaban resulted in significantly fewer bleeding events than warfarin for all of the major bleed types (intracranial major bleeding HR 0.42, 95% CI 0.30 to 0.58; other location major bleeding HR 0.79, 95% CI 0.68 to 0.93) and clinically relevant non-major bleeding events reported by the manufacturer apart from major gastrointestinal bleeding, for which the difference between apixaban and warfarin was not statistically significant (HR 0.89, 95% CI 0.70 to 1.15, p=0.37). There were similar proportions of patients who experienced adverse events with apixaban (81.5%) and warfarin (83.1%) and a lower proportion of patients who experienced bleeding adverse events with apixaban (25.2%) compared with warfarin (32.7%). Serious adverse events occurred in 35.0% of patients treated with apixaban and 36.5% of patients treated with warfarin. Fewer patients 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 patients in the apixaban arm and 8.4% of patients 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 (time in therapeutic range) and in patients who needed dose reduction.

3.6 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 in whom vitamin K antagonists were unsuitable. In the intention-to-treat population apixaban reduced the rate of stroke and systemic embolism compared with 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 patients who received apixaban compared with patients who received aspirin (HR 0.43, 95% CI 0.28 to 0.65). When considered as a separate outcome apixaban reduced the rates of ischaemic stroke compared with aspirin (HR 0.37, 95% CI 0.25 to 0.55) 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) and of major or clinically relevant non-major bleeding (HR 1.38, 95% CI 1.07 to 1.78). Although apixaban was associated with higher rates of major bleeding than aspirin, this was not statistically significant (HR 1.54, 95% CI 0.96 to 2.45, p=0.07).

3.7 No head-to-head data were available for apixaban compared with dabigatran etexilate (hereafter referred to as dabigatran) or rivaroxaban. The manufacturer used a Bayesian Markov chain Monte Carlo stimulation in WinBUGS to conduct 2 network meta-analyses using a fixed-effect model. The first meta-analysis included patients for whom vitamin K antagonist treatment was suitable and it compared apixaban, warfarin, dabigatran and rivaroxaban. The second meta-analysis was intended to assess a population of patients for whom vitamin K antagonists were unsuitable, comparing apixaban, dabigatran, rivaroxaban and aspirin.

3.8 The first meta-analysis included ARISTOTLE, RE-LY and ROCKET-AF trials. RE-LY compared dabigatran (150 mg and 110 mg twice daily) with warfarin. ROCKET-AF compared rivaroxaban (20 mg once daily) with warfarin. 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 $CHADS_2$ of 3.6 [ROCKET-AF], 2.1 [ARISTOTLE], 2.1 [RE-LY]) and the mean percentage time in therapeutic range was

lower in ROCKET-AF (55%) than in ARISTOTLE (62%) and RE-LY (64%). Where possible, the manufacturer used intention-to-treat data from each trial. However, the manufacturer highlighted that there was an absence of published intention-to-treat outcome data for some secondary outcomes from ROCKET-AF including fatal stroke, disabling stroke and non-disabling stroke. Therefore, data from the on-treatment population were also used. The second meta-analysis included ARISTOTLE, RE-LY, ROCKET-AF and AVERROES.

3.9 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 intention-to-treat 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.

3.10 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 twice daily). Apixaban was associated with a significantly lower incidence of all bleeding outcomes compared with rivaroxaban (intracranial haemorrhage, major bleeding, gastrointestinal bleeding, other major bleeding, clinically relevant non-major bleeding, any bleeding). Apixaban had a significantly lower incidence of all bleeding events except intracranial haemorrhage and clinically relevant non-major bleeding (which was not measured in RE-LY) than dabigatran 150 mg. Apixaban had a significantly lower incidence of any bleeding than dabigatran 110 mg. In addition, apixaban was associated with significantly fewer discontinuations compared with dabigatran 150 mg, dabigatran 110 mg and rivaroxaban. All of the hazard ratios from the first network meta-analysis are academic-in-confidence. 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 sections 3.3 and 3.5).

3.11 The manufacturer conducted 2 sensitivity analyses of its first network meta-analysis. 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 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. The second sensitivity analysis used the safety on-treatment dataset from ROCKET-AF rather than the intention-to-treat data from this trial, which was also generally consistent with the base case. The hazard ratios from the sensitivity analysis of the manufacturer's first network meta-analysis are academic-in-confidence.

3.12 The manufacturer commented that there were no data for rivaroxaban or dabigatran in the 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 patients for whom warfarin was suitable and unsuitable ('warfarin-suitable' and '-unsuitable' populations).

3.13 The manufacturer also used data from ARISTOTLE, RE-LY and ROCKET-AF to estimate the distribution of stroke severity and bleed type associated with apixaban, warfarin, rivaroxaban and dabigatran. Mild, moderate, severe and fatal stroke were classified by modified Rankin scores, with scores of 0 to 2 classed as a mild stroke, scores of 3 to 4 classed as a moderate stroke, a score of 5 classed as a severe stroke and a score of 6 classed as a fatal stroke. Data corresponding to these modified Rankin scores were available for apixaban and warfarin from ARISTOTLE, but ROCKET-AF and RE-LY grouped stroke severity scores differently. The manufacturer therefore estimated the proportion of patients that would be expected to have scores of 3 to 4 or 5 in the group of patients reported as having a stroke with a modified Rankin score of 3 to 5 with rivaroxaban or dabigatran in ROCKET-AF and RE-LY. The manufacturer based this estimate on the relative proportions of patients treated with apixaban who had these scores in ARISTOTLE. The

distribution of stroke severity across treatments in the population for whom a VKA antagonist was suitable is academic-in-confidence.

3.14 The manufacturer constructed a Markov model to evaluate the long- and medium-term consequences of apixaban for preventing 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). 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. The risks of stroke, intracranial haemorrhage, myocardial infarction, other major bleeds and clinically relevant non-major 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 patients would switch to the 110 mg dose when they reached 80 years in line with the marketing authorisation. The average dosage 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.

3.15 The model had 18 health states, including death. Both event-related mortality and other-cause mortality were incorporated in the model. Hypothetical patients transitioned between health states in cycles of 6 weeks with only 1 clinical event permitted per cycle. Patients entered the model in the non-valvular atrial fibrillation ('NVAF') health state, and stayed in this state until they died or experienced 1 of the following permanent events: ischaemic stroke (mild, moderate, severe or fatal); 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); clinically relevant non-

major bleeds; or 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).

3.16 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, patients in the model were not exposed to the risks of all events: patients who had systemic embolism or myocardial infarction stayed in those health states until they died; patients 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.

3.17 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. Patients could switch to aspirin or have no treatment. In the base case, anyone who discontinued treatment was assumed to receive aspirin as second-line treatment. Only a switch from first-line anticoagulation therapy to second-line therapy with aspirin altered patients' risk of subsequent clinical events. Patients who experienced certain permanent events also switched treatment: patients who had a myocardial infarction or haemorrhagic stroke were assumed to stop treatment, and patients receiving aspirin as second-line therapy switched to warfarin if they had an ischaemic stroke or systemic embolism. However, all other patients 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 after a permanent event was assumed to be

independent of treatment received, so switching did not affect their risk profile.

3.18 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 values. Values from 21 studies that presented EQ-5D data in a population with atrial fibrillation and 3 studies that reported EQ-5D values for a variety of chronic conditions after controlling for comorbidities were included. As there were some health states for which a utility value had not been identified, studies of a population with atrial fibrillation that reported utilities elicited by methods other than the 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's technology appraisal guidance 249 on dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation and
- NICE's technology appraisal guidance 256 on rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation.

3.19 The manufacturer used unit costs taken from NHS reference costs 2010/11 where possible. If available, Healthcare Resource Group codes specified in the costing report for atrial fibrillation from NICE's clinical guideline 36 on the management of atrial fibrillation 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, and a £3 renal monitoring cost for 19.4% of patients treated with dabigatran. The manufacturer used NHS reference costs for acute costs per episode for the temporary health states. The acute and long-term costs for systemic embolism and stroke were taken from a UK population-based assessment. 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 patients who had dyspepsia.

3.20 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. This represented a gain of 0.164 QALYs for an incremental cost of £1795. Dabigatran 110 mg twice daily was strictly dominated (was more costly and less effective) than the dabigatran blend (dabigatran used as per its marketing authorisation, that is, people who are younger than 80 years receive a 150 mg twice daily dose and people 80 years or older receive a 110 mg twice daily dose). 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).

3.21 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.

3.22 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. 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 per QALY gained. 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). 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.

3.23 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 sometimes used in clinical practice in the UK. 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 population for whom vitamin K antagonists were unsuitable because the majority of trials in the second network meta-analysis included patients for whom warfarin was suitable. The ERG therefore focused its critique on the ARISTOTLE trial and the first network meta-analysis which compared the safety and efficacy of apixaban with warfarin, rivaroxaban and dabigatran.

3.24 The ERG considered that the inclusion and exclusion criteria, 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 time in therapeutic range expected in a UK population, the mean time in therapeutic range 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. The ERG additionally considered that the distribution of $CHADS_2$ scores in ARISTOTLE was comparable to the UK population. However, 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.

3.25 The ERG noted that the results of the manufacturer's base case were generated deterministically rather than probabilistically. Therefore the ERG used the manufacturer's probabilistic sensitivity analysis to estimate the manufacturer's probabilistic base case. The ICER for apixaban compared with warfarin in the probabilistic base case was £16,852 per QALY gained. 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. The ERG considered whether certain outcomes would be expected to be dependent on the treatment a person received. It noted that 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. The ERG also noted that the within-trial rate of other-cause mortality was different 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 different risk of other-cause mortality.

3.26 The ERG noted that patients 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 patients in other health states. The ERG accepted the risk limitation applied to patients who experienced a stroke but that patients with systemic embolism or myocardial infarction would remain at risk of further events (in particular ischaemic stroke). The ERG considered that some people who stop therapy with apixaban, dabigatran or rivaroxaban may be eligible for treatment with warfarin or a different oral anticoagulant rather than aspirin which was the second-line treatment in the manufacturer's model. The ERG additionally commented that the risk profile of people on second-line therapy was not adjusted for characteristics such as age or $CHADS_2$ score in the manufacturer's model, but it accepted that adjusting for characteristics in second-line treatment may be beyond the reasonable scope of a Markov model.

3.27 The ERG commented that utilities were not age adjusted in the manufacturer's model, meaning that a person's quality of life would be affected by events experienced but not by increasing age. 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.

3.28 The ERG noted that the acute cost of systemic embolism in the

manufacturer's model (£4077.98) was approximately double the acute costs used in the submissions for 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.

3.29 For its revised base case the ERG changed some of the assumptions used in the manufacturer's model. The ERG assumed that other-cause mortality, stroke severity and bleed type were independent of the type of anticoagulant treatment received. The ERG adjusted utility for increasing age by -0.00029 per year. The ERG assumed that people who had myocardial infarction or systemic embolism were at risk of recurrent stroke, and used the same acute costs for systemic embolism as in NICE technology appraisal guidance 256, as this was the most conservative cost used in the submissions for NICE technology appraisal guidance 256 and 249. The ERG also assumed the time horizon was 26 years.

3.30 The ERG noted that after these amendments, dabigatran 110 mg continued to be strictly dominated by the dabigatran blend and rivaroxaban and the dabigatran blend remained extendedly dominated by apixaban. The ICER for apixaban compared with warfarin for each individual amendment was relatively consistent with the manufacturer's base-case ICER. The ERG noted that assuming stroke severity was independent of treatment increased the ICER of apixaban compared with warfarin to £12,277 per QALY gained, whereas assuming bleed type was independent of treatment decreased this ICER to £9771 per QALY gained. When all of the amendments were combined to form the ERG's revised base case, this resulted in an ICER for apixaban compared with warfarin of £12,757 per QALY gained. This represented an incremental cost of £1823 compared with warfarin for an additional 0.14 QALY.

3.31 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 people on second-line therapy, using the same risk adjustment factors as for people 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 the manufacturer's base case of £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.

3.32 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of apixaban, having considered evidence on the nature of non-valvular atrial fibrillation and the value placed on the benefits of apixaban by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee heard from clinical specialists and patient experts that the current standard treatment for people with non-valvular atrial fibrillation who need anticoagulation is warfarin or the newer oral anticoagulants rivaroxaban or dabigatran. The clinical specialists explained that the majority of people receiving an anticoagulant currently receive warfarin. In addition, some people who meet criteria for anticoagulation are currently receiving the antiplatelet agent aspirin inappropriately because of clinical reluctance to prescribe warfarin. The Committee heard that warfarin is an effective treatment but that it is associated with a number of problems. The patient experts explained that repeated INR monitoring tests with warfarin can cause pain and scarring and limit a person's choice of leisure or other activities and that warfarin can have a greater impact on a person's quality of life than atrial fibrillation itself. They also highlighted that warfarin has multiple interactions with food, alcohol and drugs that can cause further inconvenience that make adherence to treatment difficult. Overall, the patient experts considered that making the day-to-day choices about lifestyle needed in order to take and monitor warfarin appropriately has a substantial impact on a person's quality of life. The Committee accepted the limitations of warfarin therapy and the considerable effect it may have on the people who take it, and recognised the potential benefits of apixaban for people with atrial fibrillation.

4.3 The Committee considered the clinical-effectiveness data from the ARISTOTLE trial comparing apixaban with warfarin. It considered that the ARISTOTLE trial was of good quality and it discussed whether the results were generalisable to people diagnosed with atrial fibrillation in the NHS. The Committee noted that the mean time in therapeutic range for those

in the warfarin arm was 62.2% (the median was 66%) and asked the clinical specialists whether this was representative of what would be achieved in clinical practice in the UK. The clinical specialists explained that there is variation in time in therapeutic range achieved between centres. One clinical specialist quoted a benchmarking study using a computerised dose adjustment system in which a mean time in therapeutic range of over 70% was achieved. Another clinical specialist stated that the time in therapeutic range observed in ARISTOTLE reflected what is generally seen in the UK, not what is observed in centres achieving the best time in therapeutic range, and that centres should aim for a time in therapeutic range for each individual of 70% and above. One clinical specialist also highlighted that in their experience people treated for atrial fibrillation tended to be older and more likely to be on non-steroidal anti-inflammatory drugs (NSAIDS), which can impact on bleeding complications, than the ARISTOTLE population. The Committee noted the potential differences between the trial population and people treated for atrial fibrillation in the UK but concluded that the characteristics of the people who participated in ARISTOTLE were broadly generalisable to the UK population.

4.4 The Committee considered the results of the ARISTOTLE trial. It noted that apixaban was more effective than warfarin in reducing the primary efficacy outcome of all stroke (ischaemic and haemorrhagic), and systemic embolism. The Committee noted that the primary efficacy outcome was a composite of the effectiveness outcomes (ischaemic stroke and systemic embolism) and a bleeding outcome (haemorrhagic stroke). The Committee heard from the clinical specialists that there is debate about the primary outcomes to use in trials of anticoagulants for atrial fibrillation, but that it is common to use composite outcomes, such as the primary efficacy outcome in ARISTOTLE. The Committee considered the individual components of the composite outcome. It heard from the clinical specialists that once an embolus leaves the heart it is a matter of chance whether it flows to the brain, resulting in ischaemic stroke, or to the rest of the body, causing systemic embolism. The proportion of each was therefore not a treatment effect. The Committee also heard from the clinical specialists that a particular benefit conferred by the new anticoagulants compared with warfarin was the reduction in haemorrhagic strokes. This was also shown in the

ARISTOTLE trial, in which there was a statistically significant reduction in haemorrhagic stroke with apixaban compared with warfarin, whereas for the other individual components of the composite end points (ischaemic stroke and systemic embolism) there was no statistically significant difference. The Committee concluded that apixaban was more clinically effective than warfarin for the primary efficacy outcome of reducing stroke and systemic embolism.

4.5 The Committee considered the results of the manufacturer's subgroup analyses from ARISTOTLE. It noted that the subgroup analysis by $CHADS_2$ score comprised 3 groups: people with a $CHADS_2$ score of 1 or less, people with a $CHADS_2$ score of 2 and people with a $CHADS_2$ score of 3 or over. The Committee was aware that the ERG had concerns that because people with $CHADS_2$ scores of 3 to 6 had been grouped together, it was not possible to comment on potential variation in treatment effect for these subgroups. The Committee concluded that there was no biologically plausible reason to indicate that the relative treatment effect would be dependent on baseline risk and that the mean $CHADS_2$ score of 2.1 in the trial was a reasonable reflection of the UK population currently on anticoagulant therapy.

4.6 The Committee noted that the manufacturer presented data for subgroups based on INR control using quartiles of centre time in therapeutic range. It further noted that there was a numerically lower rate of stroke or systemic embolism with apixaban compared with warfarin in all analyses broken down by centre time in therapeutic range, but that ARISTOTLE was not statistically powered to demonstrate superiority across subgroups. The Committee concluded that the evidence from subgroups based on centre time in therapeutic range was not sufficiently robust to use to formulate guidance based on an individual's time in therapeutic range.

4.7 The Committee considered the adverse events reported in ARISTOTLE. The Committee noted that for the primary safety outcome of major bleeding (using the International Society on Thrombosis and Haemostasis definition), treatment with apixaban resulted in fewer bleeding events than warfarin, including a reduced rate of intracranial bleeding. The Committee recognised that this has a high mortality rate

and a large impact on a person's quality of life, and is the most feared bleeding outcome for people taking any type of anticoagulant. The Committee noted however that there were no statistically significant differences in the rates of gastrointestinal bleeding between apixaban and warfarin. The Committee concluded that apixaban resulted in fewer bleeds than warfarin and it recognised the particular importance of the effects of apixaban in reducing the risk of intracranial bleeding for people with atrial fibrillation when compared with warfarin.

4.8 The Committee noted that all anticoagulants are associated with a risk of bleeding and discussed the management of atrial fibrillation in people who experience a bleed while taking warfarin or apixaban. The Committee heard from the clinical specialists that people taking warfarin who experience a bleed may be given vitamin K to reverse the effects of warfarin. However, there are no standard treatments to reverse the effects of apixaban (or the other newer oral anticoagulants rivaroxaban and dabigatran) and that this is an area of ongoing research. Current clinical opinion is that the newer oral anticoagulants have moderate half-lives and that people who have bleeds while taking these drugs should stop treatment. The Committee also heard from the patient experts and the clinical specialists that reversing the effect of warfarin with vitamin K may take several hours, but that there are other approaches, such as using a prothrombin concentrate, that are fast-acting. The Committee concluded that there is a standard approach to reverse significant bleeding for a person taking warfarin, but that there is uncertainty about the most effective way to stop active bleeding when a person is taking apixaban.

4.9 The Committee noted that the manufacturer had included evidence on the efficacy of apixaban compared with aspirin for people for whom vitamin K antagonist treatment was unsuitable, but that this was not part of the scope issued by NICE. The Committee understood that the manufacturer's rationale for including aspirin as an additional comparator reflected the recommendation in NICE clinical guideline 36 that people who need anticoagulation but for whom warfarin is unsuitable should be offered aspirin. The Committee was also aware that aspirin had not been included as a comparator in the apixaban scope because, since the publication of NICE clinical guideline 36, dabigatran and rivaroxaban had

been recommended for use by NICE and these were now alternative treatments to warfarin. The Committee heard from the clinical specialists that aspirin is a less effective treatment than the anticoagulants but is still being prescribed for some people with atrial fibrillation despite publication of NICE technology appraisal guidance 249 and 256. The Committee further heard that although AVERROES was a useful trial, the population for whom warfarin was unsuitable was very mixed, including people for whom warfarin was clinically unsuitable and those who were unwilling to take it. The Committee noted that the ERG did not consider that AVERROES met the inclusion criteria for this appraisal and had focused its critique on ARISTOTLE. The Committee agreed that the comparators defined in the final scope were appropriate and that the key trial for this appraisal was ARISTOTLE. However, it noted with interest that the evidence presented in AVERROES showed that apixaban was associated with a reduced rate of stroke or systemic embolism compared with aspirin and an increased rate of bleeding events overall, but not an increased rate of major bleeds.

4.10 The Committee discussed the indirect clinical-effectiveness evidence for apixaban compared with dabigatran (both the 110 mg twice daily dose and 150 mg twice daily dose) and rivaroxaban. The Committee noted that the manufacturer presented 2 network meta-analyses for vitamin K antagonist-suitable and -unsuitable populations (which included aspirin) respectively. The Committee noted that the ERG considered the second meta-analysis to be flawed as there were no specific data available for rivaroxaban or dabigatran for a warfarin-unsuitable population and the network meta-analysis included a mixed population including people for whom warfarin was suitable and unsuitable. The Committee considered that only the first network meta-analysis, relating to the warfarin-suitable population, was appropriate to the decision problem. The Committee noted that the population in the study comparing rivaroxaban with warfarin (ROCKET-AF) had a higher mean baseline $CHADS_2$ score than the population in the study comparing dabigatran with warfarin (RE-LY) or ARISTOTLE. The Committee additionally noted that the mean time in therapeutic range in the warfarin arm was lower in ROCKET-AF than in RE-LY or ARISTOTLE. The Committee considered that the differences in baseline characteristics between the study populations meant that there was uncertainty surrounding the results of the network meta-analysis.

The Committee noted that the network meta-analysis did not detect any difference between apixaban, rivaroxaban and dabigatran in the rate of stroke or systemic embolism; showed a lower rate of all bleeding outcomes with apixaban compared with rivaroxaban and of all bleeding outcomes except intracranial haemorrhage and clinically relevant non-major bleeding (which was not measured in RE-LY) compared with dabigatran 150 mg; a lower rate of 'any bleeding' compared with dabigatran 110 mg; and a lower rate of myocardial infarction with apixaban compared with dabigatran (both doses). The Committee noted that the network meta-analysis had shown broadly similar outcomes and some differences between apixaban, rivaroxaban and dabigatran, but because of differences in the trial populations the results of the network meta-analysis should be viewed with caution. It also noted that some of the criteria in the network meta-analysis were in fact not a direct treatment effect, such as the proportion of ischaemic stroke compared with systemic embolism, and evidence was lacking that the severity of an ischaemic or haemorrhagic stroke was treatment specific for the new agents. The Committee concluded that the network meta-analysis results should be interpreted in the light of these uncertainties and were not sufficiently robust to reliably differentiate between apixaban, rivaroxaban and dabigatran.

4.11 The Committee considered the manufacturer's economic model and the exploratory analyses performed by the ERG. It agreed with the ERG that the general modelling approach was reasonable and consistent with other analyses of atrial fibrillation treatments. The Committee noted the discussion on the proportion of ischaemic stroke compared with systemic embolism being unrelated to the treatment (see 4.4). It also questioned whether the severity of an ischaemic or haemorrhagic stroke was treatment specific (see 3.13). In a previous appraisal the Committee had heard from experts that it was plausible and that there is evidence that strokes on warfarin were likely to be more severe than on dabigatran, but the clinical specialists for the appraisal of apixaban did not put forward any evidence that this had been substantiated and were of the opinion that at least for the newer agents, there was no biologically plausible reason or evidence that the severity of strokes would differ between apixaban, rivaroxaban and dabigatran. The Committee concluded that although the general modelling approach was

appropriate, weaknesses included the assumption that whether a person experienced an ischaemic stroke or systemic embolism was treatment related, and that there is currently insufficient evidence to support the assumption in the model that the severity of an ischaemic or haemorrhagic stroke was dependent on the specific anticoagulant agent they had received.

4.12 The Committee considered the utility values used in the model. The Committee noted that ARISTOTLE had not assessed health-related quality of life and that the utility values used in the manufacturer's model were identified through a systematic review. The Committee questioned whether the manufacturer's assumption of a permanent utility decrement following a myocardial infarction was appropriate. However, it accepted the views of the clinical specialists that disutility following a myocardial infarction would not be expected to change substantially after 6 months. The Committee concluded that the utilities used in the model were appropriate.

4.13 The Committee considered the costs used in the model. It noted that the estimates for stroke and systemic embolism were based on a cohort study of a population living in the Oxford area of the UK and that the costs for ischaemic stroke were lower than those for haemorrhagic stroke. The Committee questioned whether the study had been able to estimate haemorrhagic stroke costs accurately given the lower incidence of this event than ischaemic stroke in the population, and whether the higher haemorrhagic stroke costs assumed in the model could have driven the cost-effectiveness results. The Committee heard from the ERG that the haemorrhagic stroke costs were consistent with those used in NICE technology appraisal guidance 249 and 256 and that, as a small proportion of people had a haemorrhagic stroke in the model, other factors such as discontinuation rates drove the cost-effectiveness results to a greater extent than the cost of haemorrhagic stroke. The Committee also noted that an INR monitoring cost of £248 was assumed by the manufacturer, and that this was consistent with the monitoring costs used in NICE technology appraisal guidance 249 (and was updated for inflation). The Committee concluded that the costs used in the model were appropriate.

4.14 The Committee considered the results of the economic model. It noted that the manufacturer's base-case deterministic and probabilistic ICERs for apixaban compared with warfarin were £11,000 and £16,900 per QALY gained respectively, and that the ERG's revised deterministic base case, (see 3.30) resulted in an ICER of £12,800 per QALY gained. The Committee noted that only one of the sensitivity analyses performed by the ERG (in which alternative second-line treatments rather than aspirin were considered, see 3.31) influenced the results substantially. The Committee accepted the ERG's comment that this analysis should be interpreted with caution because the main driver of the ICER was discontinuation rates on first-line treatment. The Committee noted that the ERG's sensitivity analysis assuming stroke severity was independent of treatment had a modest effect on the ICER compared with warfarin (the ICER increased to £12,300 per QALY gained when stroke severity was assumed to be the same for all of the anticoagulants). The Committee concluded that apixaban had been shown to be cost effective compared with warfarin, the most plausible ICER being less than £20,000 per QALY gained, and could be recommended as an option for preventing stroke and systemic embolism for people with non-valvular atrial fibrillation who have 1 or more risk factors for stroke.

4.15 The Committee noted that in the manufacturer's model dabigatran and rivaroxaban had higher ICERs compared with warfarin than the ICER for apixaban compared with warfarin. In addition, in the incremental analysis dabigatran 110 mg twice daily was dominated by the dabigatran blend and the dabigatran blend and rivaroxaban were extendedly dominated by apixaban. However, the Committee was concerned that there was considerable uncertainty about the relative treatment effects and cost effectiveness of apixaban, rivaroxaban and dabigatran arising from differences in the baseline characteristics of the people included in the trials and the relative treatment effects attributed to the individual anticoagulants that informed the network meta-analysis. The Committee concluded that there was insufficient evidence to distinguish between the cost effectiveness of apixaban, dabigatran and rivaroxaban at this time.

4.16 Finally, the Committee concluded that the decision about whether to start treatment with apixaban should be made after an informed

discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of INR control.

Summary of Appraisal Committee's key conclusions

Key conclusion

1.1 Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation.

1.2 The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate or rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control.

4.4 The Committee concluded that apixaban was more clinically effective than warfarin for the primary efficacy outcome of reducing stroke and systemic embolism.

4.7 The Committee concluded that apixaban resulted in fewer bleeds than warfarin and it recognised the particular importance of the effects of apixaban in reducing the risk of intracranial bleeding for people with atrial fibrillation when compared with warfarin.

4.14 The Committee concluded that apixaban had been shown to be cost effective compared with warfarin, the most plausible ICER being less than £20,000 per QALY gained, and could be recommended as an option for preventing stroke and systemic embolism for people with non-valvular atrial fibrillation who have 1 or more risk factors for stroke.

Current practice

Clinical need of patients, including the availability of alternative treatments

4.2 The Committee heard from clinical specialists and patient experts that the current

standard treatment for people with non-valvular atrial fibrillation who need anticoagulation is warfarin or the newer oral anticoagulants rivaroxaban or dabigatran. The clinical specialists explained that the majority of people receiving an anticoagulant currently receive warfarin. The clinical specialists said that some people who meet criteria for anticoagulation are currently receiving the antiplatelet agent aspirin inappropriately because of clinical reluctance to prescribe warfarin.

The technology

Proposed benefits of the technology: How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

4.2 The Committee accepted the limitations of warfarin therapy (for example, the inconvenience, pain and scarring associated with INR monitoring, and the multiple interactions with food, alcohol and drugs) and the considerable effect it may have on the people who take it, and recognised the potential benefits of apixaban for people with atrial fibrillation.

What is the position of the treatment in the pathway of care for the condition?

2.1 Apixaban is used as an alternative to warfarin, rivaroxaban and dabigatran and is an anticoagulant treatment for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation with 1 or more risk factors for stroke.

Adverse reactions

4.7 The Committee concluded that apixaban resulted in fewer bleeds than warfarin and it recognised the particular importance of the effects of apixaban in reducing the risk of intracranial bleeding for people with atrial fibrillation when compared with warfarin.

Evidence for clinical effectiveness

Availability, nature and quality of evidence

4.3 The Committee considered the clinical-effectiveness data from the ARISTOTLE trial comparing apixaban with warfarin.

4.9 The Committee noted that the manufacturer had included evidence on the efficacy of apixaban compared with aspirin for people for whom vitamin K antagonist treatment was unsuitable, which was not part of the scope issued by NICE. The Committee agreed that the comparators defined in the final scope (warfarin, rivaroxaban and dabigatran etexilate) were appropriate and that the key trial for this appraisal was ARISTOTLE.

Relevance to general clinical practice in the NHS

4.3 The Committee concluded that the characteristics of the people who participated in ARISTOTLE were broadly generalisable to the UK population.

Uncertainties generated by the evidence

4.10 The Committee concluded that the network meta-analysis results should be interpreted with caution (for example, because of the differences in baseline characteristics between the study populations) and were not sufficiently robust to reliably differentiate between apixaban, rivaroxaban and dabigatran.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

4.5 The Committee concluded that the evidence from subgroups based on centre time in therapeutic range was not sufficiently robust to use to formulate guidance based on an individual's time in therapeutic range.

4.6 The Committee concluded that there was no biologically plausible reason to indicate that the relative treatment effect would be dependent on baseline risk.

Estimate of the size of the clinical effectiveness including strength of supporting evidence

4.4 The Committee concluded that apixaban was more clinically effective than warfarin for the primary efficacy outcome of reducing stroke and systemic embolism.

Evidence for cost effectiveness

Availability and nature of evidence

4.11 The Committee agreed with the ERG that the general modelling approach was reasonable and consistent with other analyses of atrial fibrillation treatments.

Uncertainties around and plausibility of assumptions and inputs in the economic model

4.11 The Committee concluded that although the general modelling approach was appropriate, weaknesses included the assumption that whether a person experienced a ischaemic stroke or systemic embolism was treatment related, and there is currently insufficient evidence to support the assumption in the model that the severity of an ischaemic or haemorrhagic stroke was dependent on the specific anticoagulant agent they had received.

4.15 The Committee was concerned that there was considerable uncertainty surrounding the relative treatment effects and cost-effectiveness of apixaban, rivaroxaban and dabigatran arising from differences in the baseline characteristics of the people included in the trials and the relative treatment effects attributed to the individual anticoagulants that informed the network meta-analysis. The Committee concluded that there was insufficient evidence to distinguish between the cost effectiveness of apixaban, dabigatran and rivaroxaban at this time.

Incorporation of health-related quality-of-life benefits and utility values

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

4.12 The Committee noted that ARISTOTLE had not assessed health-related quality of life and that the utility values used in the manufacturer's model were identified through a systematic review. The Committee questioned whether the manufacturer's assumption of a permanent utility decrement following a myocardial infarction was appropriate. However, it accepted the views of the clinical specialists that disutility following a myocardial infarction would not be expected to change substantially after 6 months. The Committee concluded that the utilities used in the model were appropriate.

No health-related benefits were identified that were not included in the economic model.

Are there specific groups of people for whom the technology is particularly

cost effective?

Apixaban is recommended as an option for all people with non-valvular atrial fibrillation within its marketing authorisation. No specific groups of people for whom the technology is particularly cost effective were identified.

What are the key drivers of cost effectiveness?

4.14 The Committee noted that only one of the sensitivity analyses performed by the ERG (in which alternative second-line treatments rather than aspirin were considered, see 3.31) influenced the results substantially. The Committee accepted the ERG's comment that this analysis should be interpreted with caution because the main driver of the ICER was discontinuation rates on first-line treatment.

Most likely cost-effectiveness estimate (given as an ICER)

4.14 The Committee concluded that apixaban had been shown to be cost-effective compared with warfarin, the most plausible ICER being less than £20,000 per QALY gained.

Additional factors taken into account

- Patient access schemes (PPRS) - not applicable.
- End-of-life considerations - not applicable.
- Equalities considerations and social value judgements - no equalities issues were identified.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has non-valvular atrial fibrillation and the doctor responsible for their care thinks that apixaban is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 During this appraisal it was noted that there is a need for additional research on the management of bleeds that occur while people are receiving apixaban, rivaroxaban or dabigatran etexilate, as there are no antidotes or established treatments to stop active bleeding for these agents.

Appendix A: Appraisal Committee members, and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Professor A E Ades
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant
General Practitioner, Heartwood Medical Centre, Derbyshire

Mr Andrew England
Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool

Professor Jonathan Grigg
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Brian Hawkins
Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont
Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin
Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth
Reader in Health Economics, HERG, Brunel University

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Dr Alec Miners
Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Ms Sarah Parry
CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees
Lay Member

Dr Ann Richardson
Lay Member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Ms Ellen Rule
Programme Director, NHS Bristol

Dr Peter Sims
General Practitioner, Devon

Mr David Thomson
Lay Member

Dr John Watkins
Clinical Senior Lecturer / Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Olivia Wu
Reader in Health Economics, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Mary Hughes
Technical Lead

Zoe Charles
Technical Adviser

Bijal Joshi
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Technology Assessment Group (BMJ-TAG):

- Edwards SJ, Hamilton V, Trevor N et al. Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation: A Single Technology Appraisal. BMJ-TAG, 2012.

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on apixaban by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor

- Bristol-Myers Squibb and Pfizer (apixaban)

II Professional/specialist and patient/carer groups:

- AntiCoagulation Europe (ACE)
- Anticoagulation Specialist Association (ASA)
- Arrhythmia Alliance (AFA Affiliated)
- Association of British Neurologists
- Atrial Fibrillation Association (AFA)
- British Association of Stroke Physicians
- British Heart Foundation
- British Society for Haematology

- Clinical Leaders of Thrombosis (CLOT)
- Heart Rhythm UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III Other consultees:

- Berkshire PCT Cluster
- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Bayer (rivaroxaban)
- BMJ – TAG
- Boehringer Ingelheim (dabigatran etexilate)
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- MRC Clinical Trials Unit
- National Clinical Guidelines Centre
- National Institute for Health Research Health Technology Assessment Programme

C The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on apixaban by providing oral evidence to the Committee.

- Professor Gregory YH Lip, Consultant Cardiologist & Professor of Cardiovascular Medicine, nominated by Bristol-Myers Squibb and Pfizer – clinical specialist
- Dr Francis Murgatroyd, Director of Cardiac Electrophysiology, nominated by Heart Rhythm UK – clinical specialist
- Dr Eric Watts, Hon Consulting Haematologist, nominated by the Royal College of Pathologists and the British Society for Haematology – clinical specialist
- Mrs Jo Jerrome, Assistant Director, nominated by Atrial Fibrillation Association (AFA) – patient expert
- Mrs Diane Eaton, Project Development Manager, nominated by AntiCoagulation Europe (ACE) – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bristol-Myers Squibb and Pfizer

Update information

June 2021: Recommendation 1.2 updated to include the other anticoagulants approved by NICE.

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Accreditation