NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts 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 includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- What is the current practice anticoagulation for the treatment of people with non-valvular atrial fibrillation? How does the CHA_2DS_2VASC score now used in clinical practice compare with $CHADS_2$ used in the clinical trial?
- What is the Committee's view on the generalisability of the ENGAGE AF-TIMI 48 trial to a UK setting? In particular, were the following characteristics of people in ENGAGE AF-TIMI 48 consistent with the UK population for whom edoxaban would be eligible:
  - Median age of 72 years

  - Proportion of people requiring dose adjustment at randomisation for any reason (25.4% in both treatment arms)
  - In the warfarin treatment arm, the median time in therapeutic range (INR 2-3) was 68.4% (mean 64.9%)
  - distribution of $CHADS_2$ scores (measure of stroke risk) 0, 1, 2, 3, 4, 5 and 6 of 0%, <0.1%, 47.4%, 31.0%, 16.0%, 5.7% and 1.2% respectively (people with a $CHADS_2$ score of 1 or 0 were excluded)?
- Given that the ENGAGE AF-TIMI 48 trial included people with a $CHADS_2$ score of 2 or more, can the efficacy of edoxaban can be generalised to a patient group with a $CHADS_2$=1?
- The only direct evidence available is the comparison with warfarin; edoxaban was non-inferior to warfarin for the primary composite endpoint of stroke of systemic embolism (hazard ratio 0.79. [97.5%CI 0.63 – 0.99, p<0.001}). Does the Committee consider these results to be robust?
- Does the network meta-analysis (NMA) provide a robust estimate of the relative effectiveness of edoxaban compared with other anticoagulants?
  - The company stated that the results should be interpreted with caution because of significant differences in patient characteristics and trial design that exist between the other trials comparing individual non-VKA oral anticoagulants with warfarin.
  - The company stated that the results from the network meta-analysis were generally consistent with the results of direct comparison of the non-VKA oral anticoagulants versus warfarin in the individual pivotal studies
  - The ERG highlighted that the violation of the proportional hazards assumption both within trials and across trials is an important limitation of the network meta-analyses and considered that these hazard ratio estimates should not be used to inform the company's economic model.
- The US Food and Drug Administration (FDA) assessed the benefit of edoxaban in people several subgroups and issued a warning that it is less effective in people with a creatinine clearance greater than 95 ml/min. Should special consideration be given to the impact of the following on treatment effect?
  - Time in therapeutic range

- Renal function
- Geographical location (Western Europe).

Cost effectiveness

- The company model was adapted from the apixaban technology appraisal (TA275). Is the model structure suitable?

- Does the Committee consider the following model inputs to be acceptable:

    - utility values; is consistency with those used in the appraisals of the other non-VKA anticoagulants important?

    - assumptions about treatment discontinuation after ischaemic or haemorrhagic stroke

- The company model assumes that for the cost of warfarin monitoring of £265.03 (weighted average assuming 66% seen in primary care (£323.10) with the remaining 34% were seen secondary care (£235.11)). Does the Committee consider the monitoring cost associated with warfarin treatment to be appropriate?

- Myocardial infarction was an endpoint in the ENGAGE AF-TIMI 48 trial, and was included in the model because the company stated that different interventions for stroke prevention in AF may also have an impact on the risk of myocardial infarction. Is this appropriate?

- Health-related quality of life (HRQL) data were collected in the ENGAGE trial but not used in the company's base-case cost-effectiveness analysis. During clarification the company provided HRQL data from a UK subgroup of the ENGAGE trial and using the standard UK population tariff of values. The mean values did not differ from those used in the company's base case analysis. The company also used data from a US study to adjust for the impact of increasing age on HRQL although when UK data was used it did not have a substantial effect once an error in the company model was corrected. Are these values reasonable?

- The results of the NMA are key drivers of the incremental results. The ERG considered that the results of the NMA may be unreliable due to violations of the proportional hazards assumption both within the ENGAGE trial, within trials of the other three non-VKA anticoagulants, and across the warfarin arms of the four trials included in the evidence network. How reliable is the comparison with other non-VKA oral anticoagulants?

- The incremental analysis (based on the NMA) reported small differences in QALYs and costs between the different treatments. What is the Committee's view on the reliability of an incremental analysis?

- The ERG had concerns about some of the data inputs included in the economic model. Analyses using the ERG's preferred input values (ERG scenario D) increases the deterministic pairwise ICER per QALY gained for the comparison of edoxaban with warfarin (Analysis D) from £12,881 to £16,008 (probabilistic analysis: £16,269 to £22,079).

- The additional analyses conducted by the ERG to explore alternative approaches to reconcile the model outputs with the ENGAGE trial and the age/gender distribution over time (ERG scenarios E and F) increased the pairwise ICERs compared with warfarin to approximately £21,700 and £23,600 in the probabilistic analysis and between £15,100 and £15,800 in the deterministic analysis.

- What is the Committee's view of the ERG scenario analyses?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of edoxaban tosylate within its marketing authorisation for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem	Comments from the	Comments from the ERG

		addressed in the submission	company	
Population	Adults with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism	As per NICE scope	None	People at lower risk of stroke, i.e. those with a $CHADS_2$=1, were not included in the ENGAGE trial, The ERG is uncertain whether the efficacy of edoxaban can be generalised to a patient group with a $CHADS_2$=1 is valid.
Intervention	Edoxaban tosylate	As per NICE scope	None	The ERG noted that the SPCs for rivaroxaban, dabigatran and apixaban state that treatment with can be continued during cardioversion. However, it is unclear whether treatment with edoxaban can be continued during cardioversion
Comparators	• Warfarin • Apixaban Dabigatran etexilate • Rivaroxaban	As per NICE scope	None	The company has only provided direct evidence for edoxaban versus warfarin (from the ENGAGE trial)
Outcomes.	▪ stroke ▪ systemic embolism, ▪ myocardial infarction, ▪ transient ischaemic attacks, ▪ mortality, ▪ adverse effects of treatment including haemorrhage ▪ health-related quality of life	As per NICE scope	None	All of the specified clinical effectiveness outcomes are addressed in the company's submission. Health-related quality of life, EQ-5D data were collected during the ENGAGE trial, and were made available in the clarification process. However, the results are only utilised in the sensitivity analyses of the cost effectiveness section.
Subgroups to be	If evidence allows, consideration will	As per NICE scope	None	The two subgroups specified in the NICE

considered	be given to subgroups defined by: • Time in therapeutic range on warfarin • Level of stroke/embolic risk			scope are considered in the company submission.

2 The technology and the treatment pathway

2.1 NICE clinical guideline 180 on the management of atrial fibrillation recommends that people with non-valvular atrial fibrillation with 1 or more risk factors for stroke or systemic embolism (that is a $CHADS_2$-VASc score of 1 or greater) should be offered anticoagulation with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist (VKA) such as warfarin. Anticoagulation may be inadvisable in people with atrial fibrillation at high risk of bleeding. The risk factors measured by the $CHADS_2$ scoring system are congestive heart failure (1 point allocated), hypertension (1 point), age as or over 75 years (1 point), diabetes mellitus (1 point), and previous stroke or TIA (2 points), while the CHA_2DS_2-VASc scoring algorithm includes additional stroke risks (i.e., presence of vascular disease (1 point), age 65-74 years (1 point), and female gender (1 point)) and an extra point is allocated to the risk factor “age as or over 75 years”.

2.2 The company anticipate that edoxaban would offer an alternative pharmacotherapy to warfarin and non-VKA oral anti-coagulants (NOACs) such as apixaban, dabigatran etexilate, rivaroxaban within the existing pathway for adult patients with non-valvular atrial fibrillation (NVAF) (see figure 1 reproduced from CG180).

2.3 Edoxaban tosylate (Lixiana, Daiichi Sankyo) is is a highly selective, direct and reversible inhibitor of factor Xa. Factor Xa is a key component in the

formation of blood clots. Inhibition of factor Xa in the coagulation cascade reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation. Edoxaban tosylate is administered orally. Edoxaban does not currently have a marketing authorisation in the UK for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. On 23rd April 2015 it received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) who have recommended edoxaban for the "prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)."

Figure 1. Stroke risk stratification algorithm

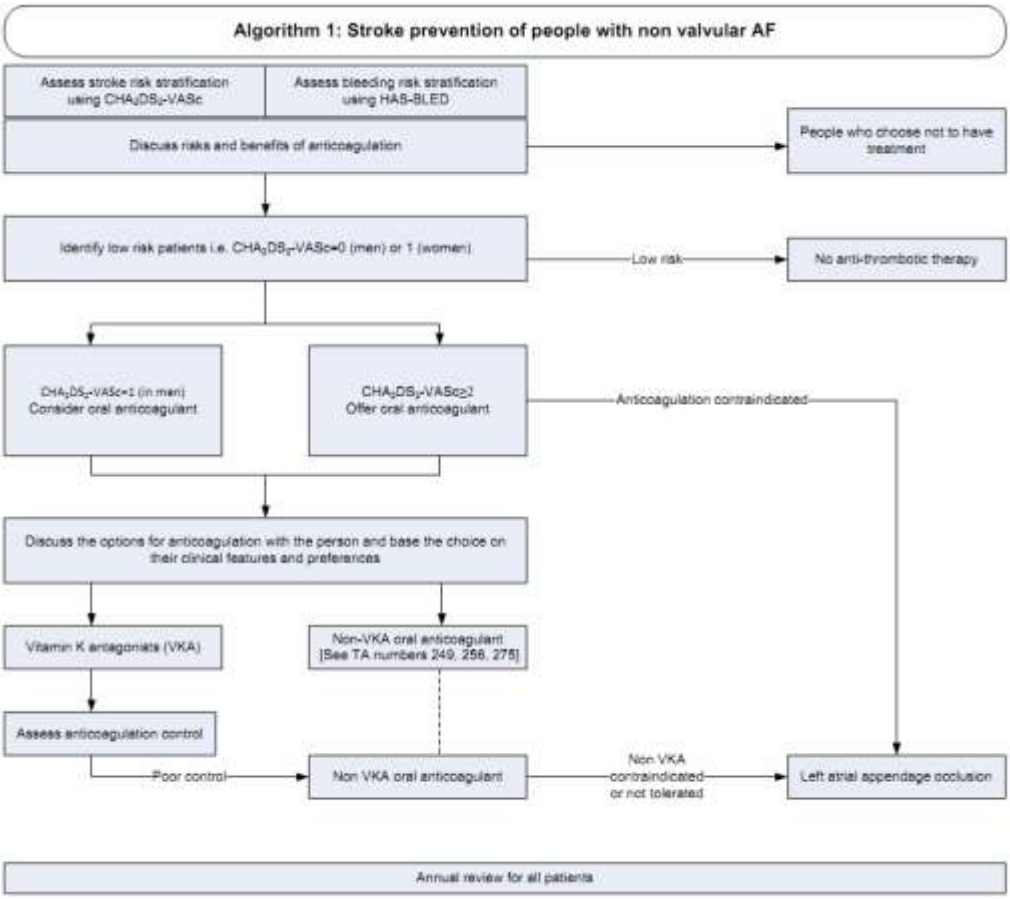


Table 2 Technology

	Edoxaban	Warfarin	Apixaban	Dabigatran etexilate	Rivaroxaban
Marketing authorisation	Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).	Prophylaxis of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation.	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
Administration method	Oral. No general need for monitoring of patients on edoxaban over and above usual clinical practice.	Oral. When warfarin is started using a standard dosing regimen the INR should be determined daily or on alternate days in the early days of treatment. Once the INR has stabilised in the target range the INR can be determined at longer intervals.	Oral. Does not require routine anticoagulant monitoring. However, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions.	Oral. Does not require routine anticoagulant monitoring. However, measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.	Oral. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2 of the SmPC).

Cost	£2.10 per tablet (15 mg, 30 mg, 60 mg) taken once daily and continued indefinitely. Provisional annual acquisition cost of £766.50 The recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: • Moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 mL/min) • Body weight ≤ 60 kg • Concomitant use of the following P-gp inhibitors: cyclosporine, dronedarone, erythromycin, ketoconazole	0.5 mg, 1 mg, 3 mg, 5 mg (28 tablet pack £1.66, £1.04, £1.07, and £1.08 respectively). Assuming an average daily dose of 4.5 mg, the annual cost is approximately £39.12. The company assumed that warfarin is associated with annual monitoring costs of £241.54.	5 mg (people over 80 years with body-weight ≤ 60 kg, 2.5 mg) twice daily 2.5 mg, 10-tab pack = £10.98, 20-tab pack = £21.96, 60-tab pack = £65.90; 5 mg, 56-tab pack = £61.50 The annual acquisition cost for either dose is approximately £803.	150 mg people over 80 years, or receiving concomitant treatment with verapamil, 110 mg) twice daily. Lower dose of 110 mg twice daily may be considered for patients aged 75–80 years, or with moderate renal impairment, or at increased risk of bleeding. 110 mg: 10-cap pack = £10.98, 60-cap pack = £65.90. 150 mg: 60-cap pack = £65.90. The annual acquisition cost is approximately £803.	20 mg once daily with food 10 mg, 10-tab pack = £21.00, 30-tab pack = £63.00, 100-tab pack = £210.00; 20 mg 28-tab pack = £58.80, 100-tab pack = £210.00 The annual acquisition cost is approximately £766.50.

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Clinical experts stated that the clinical management of NVAF is in line with the recommendations of NICE Clinical Guideline 180 (Management of atrial fibrillation). Individuals with AF should have an assessment of stroke (by $CHADS_2$-VASc score) and bleeding risks performed. Men with a $CHADS_2$-VASc score of 1 or more, and women with a $CHADS_2$-VASc score of 2 or more should be offered anticoagulation (taking the bleeding risk factors into account). Current anticoagulant therapies available are warfarin, apixaban, dabigatran etexilate, and rivaroxaban. Although there has been a significant uptake of the non-VKA oral anticoagulants (such as apixaban, dabigatran etexilate, rivaroxaban), access is variable across the UK, with most patients receiving warfarin to prevent stroke or systemic embolisation in AF. The reasons for this include unfamiliarity in the technologies, the maturity of local cardiac and anticoagulation networks, developing consensus in their introduction in primary and secondary care, clinician enthusiasm, and clinicians awaiting the now published updated NICE guidance.

3.2 People with atrial fibrillation who are poorly controlled on warfarin may benefit from treatment with edoxaban. However if the poor control is due to non-compliance, this may be problematic for edoxaban treatment which is not routinely monitored which could result in these patients being at risk of stroke. People who have difficulty with regular blood tests would also benefit from edoxaban, but caution is required for people with poor renal function.

3.3 Patient groups emphasised that the management of the medications for NVAF, symptoms and side effects can be a daily burden the individual's medical and 'life' needs are overlooked. The patient groups suggested that, despite guidance, access to therapies is restricted and variable around the country and welcomed an additional treatment option for

people with atrial fibrillation. Patient groups considered the main advantages of edoxaban to be the convenience of a once daily dose, reduced major bleeding rates compared to warfarin, no requirement for regular monitoring or dose adjustment. Patient groups and clinical experts commented that the lack of an effective proven antidote is a matter of concern in the event of bleeding or emergency surgery. In addition, the lack of a specific assay for the drug readily available in routine laboratories is an issue which may cause problems under these circumstances. Clinical experts also commented that increased rates of gastro-intestinal bleeding reported in the trials may be a concern.

4 Clinical-effectiveness evidence

Overview of the clinical trials

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 edoxaban and relevant comparators for stroke prevention in patients with NVAF. The systematic review identified 4 RCTs relevant to the edoxaban for the population specified in the scope. These were the ENGAGE AF-TIMI 48 (n=21,105), and the smaller phase 2 trials DU176b-C-J225 (n=536), DU176b-C-J226 (n=235) and DU176b-PRT018 (n=1,146) comparing edoxaban with warfarin.

4.2 The primary source of evidence was the ENGAGE AF-TIMI 48 international (46 countries, including 31 centres in the UK), double-blind, double-dummy, parallel-group, non-inferiority trial which compared safety and efficacy of edoxaban compared with warfarin. The company did not find any head-to-head studies comparing edoxaban with rivaroxaban, dabigatran or apixaban, so it conducted a network meta-analysis.

4.3 ENGAGE AF-TIMI 48 randomised a total of 21,105 people with moderate-to-high risk of stroke defined by a $CHADS_2$ (a scoring system measuring risk factors associated with congestive heart failure, hypertension, age,

diabetes and stroke) score of 2 or more were randomly assigned to the edoxaban 30 mg/15 mg dose-reduced (DR), edoxaban 60 mg /30 mg DR, or warfarin treatment groups (7034, 7035, and 7036 people in each treatment arm respectively). Patients in the control arm were well controlled with warfarin (international normalised ration [INR] of between 2 and 2.0 to 3.0) which was reflected by a median time in therapeutic range (TTR) of 68.4. Patients at increased risk of bleeding because of higher drug exposure, specifically those with body weight of 60 kg or less, creatinine clearance 30–50 mL/min, or concomitant treatment with selected P-gp inhibitors, had their dose reduced by 50% either at randomisation or during the study. To reflect the anticipated indication, only data from the arm (60 mg / or dose reduced 30 mg) were presented in the company submission. Randomisation was stratified by $CHADS_2$ risk score and edoxaban dose adjustment requirements. The company highlighted that because the trial was event-driven, the duration of treatment and follow-up of subjects in the study depended on the rate of accrual of events. The median duration of treatment exposure was 907 days, excluding interruptions and the median follow-up period was 1022 days (2.8 years) [range:1 days to 1541 days]. See table 7 of the company submission for further details.

4.4 Patient characteristics were similar between the treatment groups including age, gender, ethnicity, qualifying risk factors, $CHADS_2$ score, and renal function. Patients had a mean $CHADS_2$ score of 2.8 and approximately 53% of patients had a $CHADS_2$ score ≥3, which indicated the patient population was at moderate-to-high risk of stroke. Overall, the most people in the study were male (62%) with a median age of 72 years-old. See table 8 of the company submission for details of the baseline characteristics.

4.5 The trial included 4 analysis sets (intention-to-treat, modified intention to treat, per protocol analysis, and safety analysis) and 2 study periods (overall study period and on-treatment period). Definitions and a summary

of analysis sets in ENGAGE AF-TIMI 48 are presented in table 10 of the company's submission. The primary efficacy analyses were based on the modified intention to treat population for the on-treatment period, which included 7012 patients randomised to edoxaban (60 mg/30 mg DR) and 7012 randomised to warfarin.

4.6 The primary efficacy outcome was time to the first adjudicated stroke (ischaemic or haemorrhagic) or systemic embolic event (adjudicated by an independent clinical end-point committee, whose members were unaware of the study assignment). The efficacy analyses were performed within several analysis sets. All people in the trial were treated and followed until approximately 672 primary efficacy endpoint events were collected. The target number of events provided 87% power for confirming non-inferiority for each edoxaban regimen. A non-inferiority test using the modified intent-to-treat (mITT) population for the on-treatment period was pre-specified in the statistical analysis plan. If edoxaban was shown to be statistically significantly non-inferior to warfarin, a superiority test would be performed using the intent-to-treat (ITT) population and the overall study period.

4.7 Pre-specified secondary outcomes included:

- Time to first occurrence of:
  - Composite outcome of stroke, SEE and CV mortality
  - MACE (non-fatal, myocardial infarction, non-fatal stroke, non-fatal systemic embolism and death due to cardiovascular cause
  - Composite outcome of stroke, SEE and all-cause mortality
- Adjudicated composite endpoint of disabling stroke, SEE, life-threatening bleeds/ICH, and all-cause mortality
- Composite of adjudicated stroke, adjudicated SEE, and Investigator reported TIA, as well as each individual component
- Investigator reported VTE, including both PE and DVT, as well as each individual component
- Incidence of hospitalisation due to CV condition including hospitalisations for bleeding;
- Severity of strokes (modified Rankin scale performed 1 month following stroke onset);

4.8 Number of adjudicated and Investigator reported strokes and SEEs (1 subject can have multiple strokes and SEEs).Pre-planned subgroup analyses were performed for the subgroups of clinical interest including age (below and above 75 years), gender, $CHADS_2$ scores (≤ 3 versus, ≥ 4), dose-adjustment factor, VKA-naïve versus VKA-experienced, centre-level INR-TTR for warfarin subjects (for example, <60% versus ≥60%, <median versus ≥median), race and ethnicity. For full details of the pre-planned subgroup analyses, see section 6.3.7 of the company submission.

[redacted]

ERG comments

4.10 The ERG carried out a comprehensive search and no additional relevant papers were found.

4.11 The ERG considered the ENGAGE study to be well-designed and conducted. The ERG noted that the age and baseline characteristics of the people included in the ENGAGE trial were well-balanced across the treatment arms and matched the characteristics of people with NVAF in clinical practice in England and Wales. However people at lower risk of stroke (i.e. $CHADS_2$=1) were not included in the trial. It is also unclear whether patients with NVAF who are treated with edoxaban can continue their treatment whilst they undergo cardioversion.

4.12 During clarification the ERG asked for justification for the choice of modified ITT population and on-treatment period for the primary efficacy analysis which was conducted at the request of regulatory authorities. The

ERG agreed that the company had valid reasons for performing a modified ITT on-treatment analysis.

4.13 The ERG noted that the company planned to analyse all secondary endpoints using superiority tests for the ITT, mITT and per protocol (PP) analysis sets, for both the on-treatment and overall study periods. However, no adjustments were made for multiplicity. As each outcome was analysed using multiple populations and observation periods, generating a large number of p-values, the probability falsely rejecting the null hypothesis (of no difference between treatment groups) is likely to be high. The ERG considered that it would be more appropriate to pre-specify a single method of analysis to apply to all secondary outcomes.

Clinical trial results

4.14 The Company presented results for the primary efficacy analysis for non-inferiority using the modified intention-to-treat (on-treatment period) dataset, while the intention-to-treat dataset was used for the superiority tests. An overview of the number of patients in the different datasets is presented in table 16 of the company's submission.

4.15 For the primary efficacy endpoint (the prevention of stroke or SE) in the modified ITT analysis set (on-treatment and overall study period edoxaban (60 mg/30 mg DR) was non-inferior to well-controlled warfarin (median time in therapeutic range [TTR] = 68.4%). Stroke or SEE occurred in 182 people in the edoxaban 60 mg/30 mg DR group (1.18% per year) compared with 232 people in the warfarin group (1.50% per year, hazard ratio 0.79 (97.5% confidence interval [CI] 0.63-0.99, p<0.001 for non-inferiority). In the pre-specified superiority analysis which was performed in the ITT analysis set (overall study period), the annualised rate of stroke or SEE was 1.80% in the 1.57% in the edoxaban 60 mg/30 mg DR group with the warfarin group (HR versus warfarin, 0.87; 97.5% CI 0.73-1.04, p-value = 0.08 for superiority). Results for the mITT overall study period were consistent with those in the ITT overall study period.

Table 3 Primary efficacy results from ENGAGE AF-TIMI 48: Adjudicated Primary Endpoint – stroke or systemic embolic event (adapted from table 17 of the company's submission)

Stroke or SEE	**Edoxaban 60 mg / 30 mg DR, n (%/y)**	**Warfarin, n (%/y)**	**Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [97.5% CI]; p-value**
Stroke or SEE (mITT on-treatment period)	182 (1.18)	232 (1.50)	0.79 [0.63-0.99]; p<0.001 for non-inferiority; p=0.02 for superiority
Stroke or SEE (ITT overall study period)	296 (1.57)	337 (1.80)	0.87 [0.73-1.04]; p=0.08 for superiority
Stroke or SEE (mITT overall study period)	292 (1.55)	336 (1.80)	0.86 [0.72-1.03]; p<0.001 for non-inferiority

Abbreviations: ITT, intention-to-treat; mITT, modified intention-to-treat; SEE systemic embolic event.

4.16 The company presented results for the analyses of the components of the primary endpoint (stroke and systemic embolism) as well as subcomponents of stroke (ischaemic, haemorrhagic, fatal and disabling) for the modified ITT analysis set on-treatment period (table 18 of the company submission), the ITT analysis overall study period (table 19 of the company submission) and the modified ITT analysis set overall study period (table 20 of the company submission). The results presented here focus on the modified ITT overall study period because these were used for the company's network meta-analysis. For the modified ITT overall study period, edoxaban was shown to be superior to warfarin for haemorrhagic stroke (p=0.001).The results were similar for the modified ITT population, on-treatment period analysis and the ITT population analysis.

Table 4. Stroke and systemic embolism results from ENGAGE AF-TIMI 48 (mITT analysis set, overall study period)

Efficacy outcome	Edoxaban (N=7012) n (%/year)	Warfarin (N=7012) n (%/year)	Edoxaban vs warfarin HR (95% CI) p-value for superiority
Any stroke	278 (1.48)	316 (1.69)	0.87 (0.74 to 1.02) p=0.09
Haemorrhagic stroke	49 (0.26)	90 (0.48)	0.54 (0.38 to 0.77) p=0.001
Ischaemic stroke	233 (1.24)	234 (1.25)	0.99 (0.82 to 1.18) p=0.90
Disabling stroke	53 (0.28)	57 (0.30)	0.92 (0.64 to 1.34) p=0.67
Fatal stroke	79 (0.41)	86 (0.45)	0.91 (0.67 to 1.24) p=0.56
SEE	14 (0.07)	23 (0.12)	0.60 (0.31 to 1.17) p=0.14
First TIA	106 (0.56)	95 (0.50)	1.11 (0.84 to 1.47) p=0.45

SEE: Systemic embolic event, TIA: Transient ischaemic attack,

4.17 The company presented results of 3 composite analyses for the following secondary efficacy endpoints:

- stroke, SEE, and cardiovascular mortality;
- major adverse cardiovascular event (MACE, defined as a composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding); and
- stroke, SEE, and all-cause mortality.

In the modified ITT population for the overall study period edoxaban was found to be superior to warfarin in terms of the composite outcome of stroke, SE or death from cardiovascular cause (HR 0.86, 95% CI 0.78 to 0.95; p-value=0.004); MACE (HR 0.88, 95% CI 0.88 to 0.97; p-value=0.01); the composite outcome of stroke, SE or death (HR 0.89, 95% CI 0.82 to 0.98; p-value=0.01; and death from CV cause (HR 0.86, 95% CI 0.77 to 0.97; p-value=0.013. Similar trends were observed for the

mITT analysis set on treatment period and the ITT analysis set overall study period.

Table 5. Secondary efficacy results from the ENGAGE trial (mITT analysis set and overall study period)

Efficacy outcome	Warfarin (N=7012) n (%/year)	Edoxaban (N=7012) n (%/year)	Edoxaban vs warfarin, HR (95% CI) p-value for superiority
Stroke, SE or death from CV cause	828 (4.43)	723 (3.83)	0.86 (0.78 to 0.95) p=0.004
MACE	923 (4.98)	821 (4.39)	0.88 (0.80 to 0.97) p=0.01
Stroke, SE or death	1043 (5.58)	943 (4.99)	0.89 (0.82 to 0.98) p=0.01
All-cause death	836 (4.35)	769 (3.99)	0.91 (0.83 to 1.01) p=0.07
Death from CV cause	608 (3.16)	527 (2.73)	0.86 (0.77 to 0.97) p=0.013
Myocardial infarction	141 (0.75)	132 (0.70)	0.93 (0.74 to 1.18) p=0.56

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; mITT=modified intent-to-treat; MACE=major adverse cardiovascular event; SE=systemic embolism
Source: CS, Table 23

4.18 The company presented pre-specified subgroup analyses of the primary efficacy outcome using the modified ITT analysis set, overall study period which demonstrated the consistency of treatment effect across major subgroups.

4.19 The company analysed the primary efficacy results by study centre level time in therapeutic range (TTR) values to assess if the level of INR control achieved in a particular centre influenced the primary efficacy results. For the analysis comparing centre TTR above and below 60%, the p value for interaction was significant. The company stated this indicates that in centres with a TTR ≥60%, edoxaban has a similar effect versus warfarin

to that observed in the total study population, while there is a significant reduction in risk in the cTTR <60% subgroup. When the TTR data were examined by quartiles in the edoxaban 60 mg / 30 mg DR arm compared with warfarin, the hazard ratios for the primary endpoint in the first, second and third quartiles were 0.74, 0.88 and 0.82, respectively, and 1.08 for the fourth quartile, but the p-value for interaction was not significant (p=0.50). Further details of the results are presented in table 24 of the company submission.

4.20 For the subgroup analyses by risk of stroke (as defined by the $CHADS_2$ score), the company stated that the hazard ratio for edoxaban 60 mg / 30 mg DR vs. warfarin was stable and non-inferior across $CHADS_2$ scores 2 to 6 (see table 25 of the company submission for further details).

4.21 An analysis by renal function across 3 categories of creatinine clearance (CrCL: normal renal function [≥ 80 mL/min]; mild renal impairment [> 50 to < 80 mL/min] and moderate renal impairment [30 to 50 mL/min]) demonstrated a significant interaction for heterogeneity for the edoxaban 60 mg /30 mg DR regimen (p-value < 0.001). The HRs for the primary efficacy endpoint were 0.86 (95% CI 0.63 to 1.17) and 0.68 (95% CI 0.54 to 0.85) for high-dose edoxaban (60 mg / 30 mg DR) compared with warfarin for subgroups with creatinine clearance of 30 to ≤50 mL/min and >50 to <80 mL/min, respectively. In contrast, the relative risk of stroke or SEE was observed to be higher with edoxaban than with warfarin in the subgroup of people with normal renal function (CrCL ≥ 80 mL/min; HR 1.31 (95% CI 0.96 to 1.79)). The company highlighted that a variety of factors, an unusually low event rate in the warfarin group and potential imbalances between treatment groups due to randomization not being performed within subgroups, could have contributed to the observed HR for stroke or SEE compared with warfarin in the subgroup of people with normal renal function. The company highlighted that because of this the HR should be interpreted in the context of (1) a low absolute event rate for

stroke or SEE, and (2) the small absolute differences between treatment groups.

4.22 The company presented a post hoc analysis of patients from the European Economic Area plus Switzerland for the mITT overall study period which found that event rates were numerically lower for edoxaban 60 mg /30 mg DR (N=2423) than for warfarin (N=2474) for each of the efficacy endpoints, but with upper bounds of the confidence intervals crossing the line of unity:

- First stroke or SEE: 1.41%/year vs. 1.54%/year; HR 0.92 (95% CI 0.693 to 1.218)
- Ischaemic stroke: 1.10%/year vs. 1.19%/year; HR 0.93 (95% CI 0.676 to 1.281)
- Haemorrhagic stroke: 0.21%/year vs. 0.31%/year; HR 0.68 (95% CI 0.345 to 1.335)

Health related quality of life

4.23 Health-related quality of life data were collected during the ENGAGE trial using the EQ-5D questionnaire. Data were collected using the self-administered EQ-5D questionnaire at baseline and every 3 months, until the end of the study. Approximately 60% of patients participated in quality of life data collection, though a sizable proportion of those did not enrol in this sub-study until some time after baseline. In total, baseline utilities were calculated for 11,995 patients who participated in ENGAGE AF-TIMI 48. The country with the largest number of patients for whom baseline EQ5D data were available was the US, with 2,853 (approximately 24% of all respondents). Baseline EQ5D data were collected from a total of 164 patients from the UK.

ERG comments

4.24 The ERG was concerned about the large number of analyses performed for the components of the primary endpoints as there is no adjustment for multiplicity. Performing a large number of statistical tests increases the likelihood of significant results occurring by chance.

4.25 The ERG noted that the statistically significant result for non-inferiority in the ENGAGE trial was driven largely by a reduction in haemorrhagic stroke events in patients treated with edoxaban while there was no statistically significant difference between edoxaban and warfarin for any other listed component or subcomponent.

4.26 The ERG commented that the estimate of treatment effect for the primary outcome may not be robust as the assumption of proportional hazards between treatment with edoxaban and treatment with warfarin for haemorrhagic stroke (one of the components of the primary outcome) because it appeared to be violated. The hazard trend in the warfarin arm changed sharply at 6 months in comparison with smooth hazard over time in the edoxaban arm.

4.27 For the subgroup analyses of the primary efficacy outcome, the ERG agreed that, for the majority of subgroups, the treatment effect appears to be consistent.

4.28 The ERG highlighted the reported lower efficacy of edoxaban in comparison to warfarin in the large subgroup of patients (37.5% and 37.2%, with normal renal function in the edoxaban and warfarin arms respectively). The ERG was aware that during the approval process for edoxaban in the US, the FDA raised concerns about the apparent lack of efficacy of edoxaban in patients with normal renal function. However, the ERG acknowledged that the company presented reasonable arguments that suggest that the detected subgroup differences may be spurious results. Therefore, the ERG suggested that the results of this subgroup analysis should be interpreted with caution.

4.29 The ERG noted that the results of the subgroup analysis suggested that the efficacy of edoxaban in comparison to warfarin is significantly greater for patients in the cTTR <60% subgroup than patients in the cTTR ≥60% subgroup (p=0.0361). This result was not consistent across all analysis sets; the p-value for interaction for subgroup differences between patients in cTTR <60% and cTTR ≥60% subgroups was non-significant when the analysis was conducted using the mITT population and on-treatment observation period. Furthermore, when the cTTR subgroup analyses were performed using different cut-off points (i.e. cTTR ≤66.4% versus cTTR >66.4%, or using quartiles), the subgroup differences were no longer found to be significant. Thus, the finding that cTTR may affect the efficacy of edoxaban in comparison to warfarin may be spurious.

4.30 The ERG considered that [redacted] the result in favour of edoxaban from the post-hoc analysis would have been more convincing if this analysis had been pre-specified. It is not possible to ascertain the extent to which exploratory analyses may have been performed to obtain a result that suggests that edoxaban is effective amongst Western European countries.

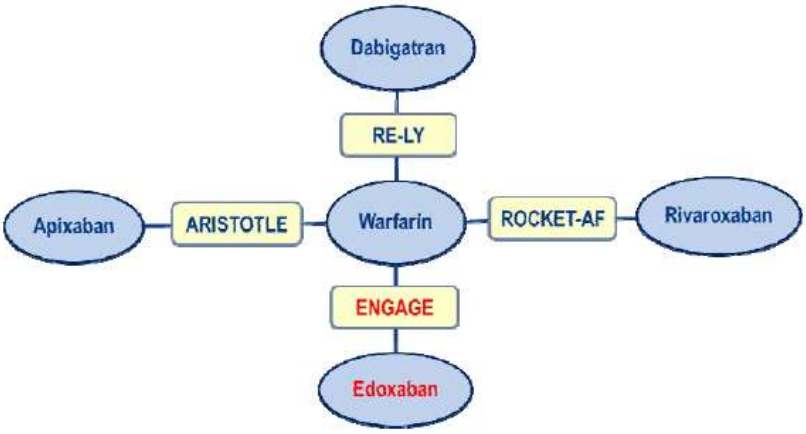
4.31 The ERG stated that the health-related quality of life data provided as part of the clarification process were difficult to interpret because of the low response rate and incomplete analysis. The ERG suggested that because of this it was difficult to draw any firm conclusions as to any difference in patients' experiences attributable to the choice of treatment

Network meta-analyses

4.32 The company identified 4 trials for inclusion in a network meta-analysis (NMA) to estimate the relative efficacy and safety of edoxaban (ENGAGE trial), compared with apixaban 5 mg twice daily (ARISTOTLE trial), dabigatran 150 mg twice or 110 mg twice daily (RE-LY trial)and rivaroxaban 20 mg once daily (ROCKET-AF trial)..All 4 RCTs compared

treatment with warfarin, creating a network of evidence (see figure 2). The company noted that the NMA data should be interpreted with caution because of significant differences in the patient characteristics and trial design between the 4 pivotal phase III trials. For example, ARISTOTLE and RE-LY trials included people with AF with a $CHADS_2$ score of 1 or more compared with 2 more for ENGAGE AF-TIMI48 and ROCKET-AF.

Figure 2. Network diagram of included studies



[redacted] Analyses were conducted for all patients with $CHADS_2 \geq 2$ [redacted]

4.34 [redacted]

Figure 3. Network meta-analyses Risk Ratios on Composite Primary Outcome of Stroke and Systemic Embolism, Baseline $CHADS_2$ ≥2 (from figure 9, company submission)

[redacted]

Table 6 Risk Ratios on other efficacy outcomes, Baseline CHADS2 ≥2 (RR; 95% CrI) – adapted from table 29 of the company submission

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.36 [redacted]

4.37 [redacted]

[redacted]

4.38 The company presented forest plots which presented findings from the [redacted]

Table 7. Network meta-analyses risk ratios, secondary analyses; RR (95% CrI) - see figures 12 to 17 of the company submission, and tables 25-27 of the ERG report

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with $CHADS_2$ score ≥3 at baseline					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with centre-level time in therapeutic range ≥60%					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients unrestricted by $CHADS_2$ score					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CrI=credible interval; RR=risk ratio; SE=systemic embolism
Source: Figures 12-17 of the company submission and table 25, 26 and 27 of the ERG report)

ERG comments

4.39 The ERG commented that the key characteristics of the trials (e.g. study population, design, outcome measures, and also effect modifiers [e.g. age, disease severity, duration of follow-up]) included in the network meta-analyses are sufficiently similar to justify combining the results. It

considered, the company's approach used annualised event rates and this approach minimised any potential biases resulting from differences in trial duration which ranged from 1.8 years in ARISTOTLE (apixaban) to 2.8 years in ENGAGE (edoxaban).

4.40 The ERG considered that the results of the NMA may be unreliable due to violations of the proportional hazards assumption both within the ENGAGE trial, within trials of the other three NOACs, and across the warfarin arms of the four trials included in the evidence network. [redacted].

4.41 [redacted] rendering the HRs unreliable.

Adverse effects of treatment

4.42 The company presented the results of the safety analyses which included all people who received at least 1 dose of randomised study drug for the on-treatment period in the ENGAGE AF-TIMI 48 trial. In the principal

safety analysis, the company stated that there was a significantly reduced rate of major bleeding in the edoxaban 60 mg/30 mg DR arm compared to the warfarin arm (HR 0.80, 95% CrI 0.71–0.91; p<0.001) and several secondary bleeding endpoints, including intracranial, fatal, clinically relevant non-major and life-threatening bleeds compared with the warfarin arm (p≤0.01 for all comparisons). A summary of the results are presented in table 8. Full results are presented in section 6.9.2 of the company submission).

Table 8. Adjudicated bleeding events during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period) - adapted from table 32 of the company submission

Bleeding Outcome	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value

Major bleeding	524 (3.43)	418 (2.75)	0.80 [0.71–0.91]; p<0.001
Fatal bleeding	59 (0.38)	32 (0.21)	0.55 [0.36–0.84]; p=0.006
Any intracranial bleeding	132 (0.85)	61 (0.39)	0.47 [0.34–0.63]; p<0.001
Fatal intracranial bleeding	42 (0.27)	24 (0.15)	0.58 [0.35–0.95]; p=0.03
Gastrointestinal bleeding	190 (1.23)	232 (1.51)	1.23 [1.02–1.50]; p=0.03
Bleeding at a critical organ	211 (1.36)	108 (0.70)	0.51 [0.41–0.65]; p<0.001
Overt bleeding with blood loss of ≥2 g/dLdL	327 (2.13)	317 (2.08)	0.98 [0.84–1.14]; p=0.7878
Minor bleeding	714 (4.89)	604 (4.12)	0.84 [0.76–0.94]; p=0.002
Any overt bleeding	2114 (16.40)	1865 (14.15)	0.87 [0.82–0.92]; p<0.001
Major or clinically relevant non-major bleeding	1761 (13.02)	1528 (11.10)	0.86 [0.80–0.92]; p<0.001
Clinically relevant non-major bleeding	1396 (10.15)	1214 (8.67)	0.86 [0.79–0.93]; p<0.001

4.43 The company submission stated that the five most frequent treatment-emergent adverse events reported by patients in the edoxaban or warfarin arms were urinary tract infections ([redacted] respectively), nasopharyngitis ([redacted]respectively), bronchitis ([redacted] respectively), dizziness ([redacted]respectively) and peripheral oedema ([redacted]respectively). See table 33 of the company submission. The company also presented subgroup analyses for the primary safety outcome by centre level TTR and by risk of stroke (as defined by $CHADS_2$). These are presented on pages 103-105 of the company's submission.

4.44 The company presented results for net clinical outcome from ENGAGE AF-TIMI and highlighted that edoxaban 60 mg / 30 mg DR was associated with significantly lower rates of all three composite outcomes than warfarin (p<0.01 for all comparisons; see table 35 of the company submission).

The company stated that this suggested edoxaban has a favourable risk-benefit profile compared with well-controlled warfarin for net clinical outcome, a composite of efficacy and safety events, including stroke, disabling stroke or SEE, major and life-threatening bleeding outcomes, as well as mortality.

ERG comments

4.45 The ERG commented that patients in the ENGAGE trial who were treated with edoxaban experienced statistically significantly fewer major bleeding events compared with patients receiving warfarin. However, statistically significantly greater numbers of gastrointestinal bleeding events were reported by patients treated with edoxaban compared to patients receiving warfarin. Similar numbers of patients in both arms discontinued treatment and similar numbers of patients in both arms experienced the most frequently reported adverse events

5 Cost-effectiveness evidence

5.1 The company identified 52 studies from the published literature related to cost-effectiveness and costing studies of interventions (non-VKA oral anticoagulants, warfarin) for the prevention of stroke and / or systemic embolism in adult patients with atrial fibrillation. As the company found no studies evaluating the cost-effectiveness of edoxaban for preventing stroke in people with non-valvular atrial fibrillation, it developed a new economic model.

5.2 In the cost-effectiveness analysis, the base case considered people with atrial fibrillation with a $CHADS_2$ score of 2 or more in line with the risk profile of people included in the ENGAGE AF-TIMI 48 study. The company acknowledged that this was similar to the rivaroxaban pivotal study (ROCKET-AF), but differed from the RE-LY (dabigatran) and ARISTOTLE (apixaban) studies where people were recruited with $CHADS_2$ score of 1 or more.

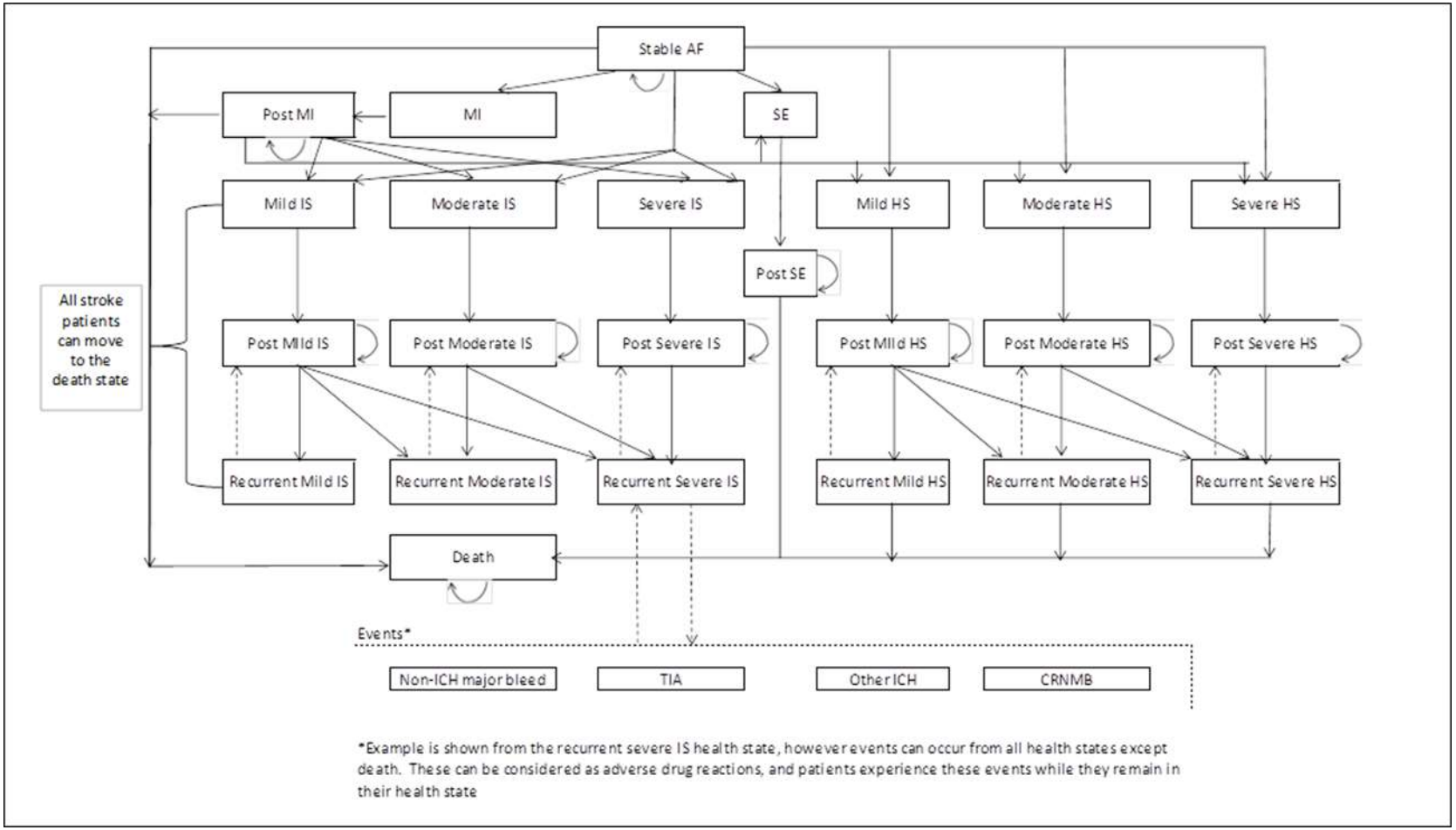
Model structure

5.3 The company developed a Markov cohort model to compare edoxaban with warfarin, apixaban, rivaroxaban and dabigatran for preventing stroke and systemic embolism in people with NVAF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack and a $CHADS_2$ index score of at least 2 (the baseline characteristics of the ENGAGE trial). The model consisted of 18 health states (patients entering the model with 'stable AF'), with one-month cycles and a 30-year (remaining lifetime) time horizon from a starting age of 71 years. The company conducted the analysis from the perspective of the NHS and Personal Social Services, and discounted costs and health effects at an annual rate of 3.5%. A half-cycle correction was applied to both costs and QALYs (with the exception of drug costs).

5.4 The health states in the company's model were defined by the clinical events considered to have a permanent impact on patients, and were assumed to have an initial impact, as well a long-term impact on costs, quality of life and mortality. The health states captured the main thrombotic events and adverse events of treatment included haemorrhagic and ischaemic stroke (HS and IS), systemic embolism (SE) and myocardial infarction (MI) events. Health states were further subdivided into an initial health state where costs and quality of life associated with the acute event and the case fatality rate were applied in the month after the initial event, and a long-term health state, where ongoing event costs, quality of life and mortality were applied per monthly cycle. Events considered to have no long-term impact in the model were other intracranial haemorrhage (ICH), non-ICH major bleeds, clinically relevant non-major bleeds (CRNMBs), and transient ischaemic attack (TIA). In the model, these events incurred costs and a disutility for the length of the event.

5.5 In the model, people were at risk of experiencing an event whilst in each (initial and post-event) health state of the model (except death), and the monthly probability of each event was applied in each cycle of the model to these patients. Upon entering an initial health state, people could also experience an event in the same model cycle (that is, two events can be experienced in the same model cycle, one having a temporary impact, and the other having a more permanent impact on the patient). In addition, people in the model were able to experience any clinical outcome more than once (henceforth referred to as recurrent events), or more than one type of clinical outcome over the timeframe of the model. It was assumed that people were only able to move to a health state considered to be more severe than their previous health state.

Figure 4. Model structure (see figure 22 of company submission)



ERG comments

5.6 The ERG commented that the model structure was largely based on the models submitted for previous appraisal of apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (NICE technology appraisal 275). The ERG noted that the company model included data from other sources in addition to the ENGAGE trial to inform its estimates of survival, including the company's NMA, several articles from the literature and clinical assumptions. The ERG highlighted that the company did not fully justify the selection of some of these sources and did not provide a reason for the difference between trial and model estimates. The ERG identified that, in terms of overall survival, the company's model was not able to accurately reproduce ENGAGE trial data. The ERG suggested that the lack of ability to replicate a key trial outcome and the absence of a justification for this casts doubt on the reliability of all results generated by the company's model. The ERG carried out a number of adjustments to try to resolve this issue. However, the Markov model structure used by the company did not directly measure important outcomes in a format that was easily verifiable and it was difficult to trace which parameter was causing which effect.

5.7 The ERG considered that the perspective and time horizon adopted in the model are appropriate, and consistent with the NICE reference case. The ERG noted that the discount rate of 3.5% was applied monthly in the company's model. The NICE reference case recommends that discounting should be carried out annually. The ERG suggested that this methodological error was likely to have only a minor impact on model results.

Model details

Clinical effectiveness

5.8 The monthly probability of each clinical outcome for edoxaban was estimated from annual event rates from the ENGAGE AF-TIMI 48 trial (the

method for estimating monthly probabilities are outlined in section 7.3.2 of the company's submission). The monthly probability of each event was assumed to be distributed according to a beta distribution. The transition probabilities for the remaining interventions were obtained by applying the hazard ratio from the network meta-analysis for the intervention to the baseline probability (see section 5.14 and table 10 below).

5.9 In the model, people could permanently discontinue or switch treatment following an ischaemic stroke or a haemorrhagic stroke. Following discontinuation and switching to a new therapy, the transition probability (of health state and event) does not change to reflect the new therapy. The company assumed that people could not discontinue or switch treatment for any other reason because there would be no difference between treatment groups. Assumptions around event-related discontinuation are presented in table 9.

Table 9. Event-related discontinuation (adapted from table 57 of the company's submission)

Event	Assumption
Ischaemic stroke	All warfarin patients discontinue treatment, and resume treatment with a NOAC (specifically, edoxaban). 50% of NOAC patients will permanently discontinue, and 50% will continue on the same therapy.
Haemorrhagic stroke	Warfarin patients discontinue treatment, and resume treatment with: 20% restart on anti-platelet (aspirin); 20% restart on NOAC (edoxaban); 60% restart on warfarin. 50% of NOAC patients will permanently discontinue, and 50% will continue on the same therapy.

NOAC= Non-VKA Oral Anticoagulants

Table 10. Event rates for edoxaban ($CHADS_2 \geq 2$ population) - adapted from table 49 of the company submission

Event	Monthly probability	Distribution	Monthly probability
IS ($CHADS_2$ 2 to 3)	[redacted]	Beta (shape parameters [redacted]	[redacted]
IS ($CHADS_2$ ≥4)	[redacted]	Beta (shape parameters [redacted]	[redacted]
HS ($CHADS_2$ 2 to 3)	[redacted]	Beta (shape parameters [redacted]	[redacted]
HS ($CHADS_2$ ≥4)	[redacted]	Beta shape parameters [redacted]	[redacted]
SE	[redacted]	Beta (shape parameters [redacted]	[redacted]
MI	[redacted]	Beta (shape parameters [redacted]	[redacted]
Other ICH	[redacted]	Beta (shape parameters [redacted]	[redacted]
TIA	[redacted]	Beta (shape parameters [redacted])	[redacted]
Non-ICH major bleed	[redacted]	Beta (shape parameters [redacted])	[redacted]
CRNMB	[redacted]	Beta (shape parameters [redacted]	[redacted]

CRNMB=clinically relevant non-major bleeding; HS=haemorrhagic stroke; ICH=intracranial haemorrhage; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism; TIA=transient ischaemic attack

5.10 The risk of each clinical event was assumed to increase with age; therefore the company included a per-decade risk-adjustment factor in the model. To allow for a continuously increasing risk in each cycle, the per-decade adjustment factor was converted to a monthly adjustment factor (described in Section 7.2.2 of the company's submission) and applied to the baseline probability of the event (table 50 of the company's submission).

5.11 Hazard ratios were used in the economic model to represent the relative treatment effect of each comparator compared with edoxaban. The base case analysis used hazard ratios from the network meta-analysis of patients with CHADS2 ≥ 2. Since ROCKET-AF and ENGAGE AF-TIMI 48 enrolled patients with $CHADS_2 \geq 2$, whereas RE-LY and ARISTOTLE enrolled patients with $CHADS_2 \geq 1$, only data from patients with $CHADS_2 \geq 2$ in RE-LY and ARISTOTLE were used in the base case network meta-analyses. Where there were no available data for a clinical outcome, it was assumed that the hazard ratio was equivalent to the hazard ratio estimated in the "all patients" analysis. Where there were also no available data in the "all patients" analysis, the hazard ratio was assumed to be 1. Hazard ratios for warfarin were extracted from ENGAGE AF-TIMI 48 trial data, and hazard ratios for the other NOACs were obtained from the network meta-analysis.

Table 11. Clinical outcome hazard ratios used in the company's economic model, all relative to edoxaban (see table 51 of the company's submission)

CHADS2 ≥ 2 (base case population)	**IS**	**HS**	**SE**	**MI**	**Other ICH**	**TIA**	**Non-ICH major bleed**	**CRNMB**
HRs reported as used in the model in company submission, Table 51								
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran 110mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR for warfarin from ENGAGE trial (used in company's base case)*								
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR for warfarin from NMA (programmed in model for possible sensitivity analysis)								
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A value greater than 1 favours edoxaban regarding that event.
*The company submission included HR estimates that differed to those used in the model
CRNMB=clinically relevant non-major bleeding; HS=haemorrhagic stroke; ICH=intracranial haemorrhage; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism; TIA=transient ischaemic attack
Source: Company submission, Table 51 and the company's Excel model

5.12 Ischaemic stroke and haemorrhagic stroke were separated into mild, moderate and severe to ensure a more accurate view of the costs and health consequences of stroke events, given the wide variation in the severity of stroke. The definitions of mild, moderate and severe stroke used in the model were based on the modified Rankin scale. Mild stroke (Rankin scale 0–2) was defined as resulting in minimum residual sequalae, patients able to return to independent living; moderate stroke (Rankin scale) 3–4 was described as requirement for some assistance with walking and bodily needs; severe stroke (Rankin scale 5–6) was described as requiring inpatient rehabilitation after stabilisation and with residual sequelae that prevents patients from returning to independent living. The distribution of mild, moderate and severe strokes for the model was obtained by pooling ischaemic and haemorrhagic stroke events for the high dose edoxaban (60 mg / 30 mg DR) and warfarin arms in the mITT analysis set overall study period in the ENGAGE AF-TIMI 48 trial. The proportions of people experiencing strokes of each severity category were as follows: Mild, 42.89%; Moderate, 16.48% and Severe, 40.63% (see table 53 of the company's submission).

5.13 In the company's model, people in the haemorrhagic and ischaemic stroke health states were assumed to be at increased risk of stroke based on 10 year estimates of recurrent stroke obtained from a South London Stroke Registry. The risk of recurrent stroke was adjusted for age. The number of strokes that a patient could experience over the course of the model was limited to the number of cycles in the model (since the number of events a patient can experience per cycle is limited to one event). The distribution of stroke severity for edoxaban was then applied to all patients who had a recurrent stroke event. Table 12 shows the monthly probabilities used in the company's model.

Table 12. Risk of stroke following prior clinical events (table 54 of the company submission)

Event	10-year cumulative risk	95% CI (distribution)	Monthly probability	Source
Stroke after MI	41.1%	29.1% to 55.8% (beta)	0.44%	Mohan *et al.* 2009
Recurrent IS	25.7%	21.9% to 29.9% (beta)	0.25%	Mohan *et al.* 2009
Recurrent HS	27.0%*	16.6% to 45.5% (beta)	0.26%	Mohan *et al.* 2009

*Includes primary intracerebral haemorrhage and subarachnoid haemorrhage

HS=haemorrhagic stroke; IS=ischaemic stroke; MI=myocardial infarction.

5.14 The company's model included death as a result of clinical events and all-cause mortality. The probability of death for each health state was estimated using various sources. People experiencing an event are also at risk of death in the model. These acute event-related mortality rates are presented in table 13.

Table 13 Acute event-related mortality (table 55 of the company's submission)

Health state	Probability of death	95% CI (distribution)	Source
Health states			
Mild IS	0%	-	Clinical assumption from advisory board (Company submission, Section **Error! Reference source not found.**)
Moderate IS	16.8%	13.9% to 20.1% (beta)	Janes *et al.* 2013
Severe IS	16.8%	13.9% to 20.1% (beta)	Janes *et al.* 2013
Mild HS	0%	-	Clinical assumption
Moderate HS	31.6%	22.7% to 42.8% (beta)	Janes *et al.* 2013
Severe HS	31.6%	22.7% to 42.8% (beta)	Janes *et al.* 2013
SE	0%	-	ENGAGE AF-TIMI 48 trial
MI	13.2% (10.8 for males and 15.6% for females)	NR in source	Scarborough *et al.* 2010
Events			
Other ICH	31.6%	22.7% to 42.8% (beta)	Janes *et al.* 2013
TIA	0%	-	Clinical assumption from ad hoc advice (Company submission Section **Error! Reference source not found.**)
Non-ICH major bleed	0%	-	Clinical assumption from ad hoc advice (Company submission Section **Error!**

Health state	Probability of death	95% CI (distribution)	Source
			Reference source not found.)
CRNMB	0%	-	Clinical assumption from ad hoc advice (Company submission Section **Error! Reference source not found.**)

CRNMB=clinically relevant non-major bleeding; HS=haemorrhagic stroke; ICH=intracranial haemorrhage; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism; NR=not reported.

5.15 For people who have previously experienced and survived a clinical event and are in the post-event health state, the company applied an event-specific hazard ratio to background general mortality. The company assumed that there was no long-term impact on mortality for bleeding and transient ischaemic attack. Hazard ratios for mortality associated with key clinical outcomes were sourced from published literature. There were no published data on the long-term mortality following a systemic embolism, so this was estimated from ENGAGE AF-TIMI 48 trial data. The hazard ratio for mortality due to systemic embolism was estimated from mortality observed in the ENGAGE AF-TIMI 48 trial and general population mortality. The long-term mortality hazard ratios used in the model are presented in table 14.

Table 14 Long-term mortality for event survivors (see table 56 of the company submission)

Health states	Hazard ratio* (distribution)	Source
IS		
Mild	3.18 (lognormal)	Bronnum-Hansen *et al.* 2001
Moderate	5.84 (lognormal)	Henriksson *et al.* 2010
Severe	15.75 (lognormal)	Huybrechts *et al.* 2008
HS		
Mild	3.18 (lognormal)	Bronnum-Hansen *et al.* 2001
Moderate	5.84 (lognormal)	Henriksson *et al.* 2010
Severe	15.75 (lognormal)	Huybrechts *et al.* 2008
SE	4.27 (lognormal)	Estimated from UK Life Tables and ENGAGE AF-TIMI 48 trial data
MI	3.36 (lognormal)	Bronnum-Hansen *et al.* 2001 [87]

HS=haemorrhagic stroke; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism.

ERG comments

5.16 With regard to the treatment effectiveness assumptions used in the company's model, the ERG highlighted (see also sections 4.25, 4.37 and 4.38) that for the primary outcome, the assumption of proportionality, required for the NMA, has been shown to be violated both within and between trials. Therefore, the results of the NMA should be interpreted with caution. The company provided the ERG with data from Kaplan–Meier analyses for a variety of outcomes from the ENGAGE trial. On reviewing the data provided by the company, the ERG noted that [redacted]

[redacted] The impact of this exploratory analysis is presented in section 5.40 (scenario R16).

5.17 Although the ERG agreed with the assumption in the company submission that patients experiencing a mild stroke are at a low, or no, risk of stroke-related mortality in the acute stage, it was not implemented correctly in the model since the model does not allow for any stroke-related mortality in the first cycle. In addition, the model predicts that, of a cohort of 1000 people with NVAF in receipt of warfarin, there will be 157 stroke events. Using the company's approach to applying the risk of acute-stroke mortality, approximately 15 (9.6%) of these would be fatal, which is substantially less than the 16.8% reported in the study by Janes. Substantial structural amendments to the model would be required to fully correct this error, however the ERG did assess the impact of applying the acute mortality rates reported by Janes to all patients experiencing a stroke (IS and HS separately) (see section 5.40, scenario R11).

5.18 The ERG noted that there was no rationale for not using acute mortality data from the ENGAGE trial. The ERG's preferred option is to use the ENGAGE trial data in the model. As part of its exploratory analyses, the ERG extracted acute mortality data relating to ischaemic stroke and haemorrhagic stroke from the clinical study report (CSR50, page 132) and pooled it across both the warfarin and edoxaban arms of the trial (see scenario R12 in section 5.40).

5.19 The ERG was unable to identify the long term mortality estimates from the sources referenced by the company and was therefore unable to replicate the calculations because of insufficient information in the company submission.

5.20 The ERG did not consider the company's assumption that, after an ischaemic stroke or haemorrhagic stroke, 50% of patients taking a NOAC permanently discontinue treatment and 50% continue on the same therapy to reflect of NHS clinical practice. The ERG asked the company to provide the results of additional sensitivity analyses with 1) all patients restarting on anticoagulation therapy following an ischaemic stroke and 2) all patients discontinuing therapy following a haemorrhagic stroke. The impact of this was explored in the ERG's exploratory analyses (scenario R10)

5.21 The ERG noted that the company had assumed that after patients switch to a new therapy, transition probabilities do not change to reflect the new treatment. Clinical advice to the ERG suggested that this assumption was reasonable.

5.22 The ERG highlighted that the comparison of overall survival from the model and the ENGAGE trial shows that the model overestimates overall survival for both arms compared to the trial, and potentially underestimates the relative effectiveness of edoxaban compared to warfarin. The ERG considered that the magnitude of these differences raised some concerns about the validity of the model.

Utility values

5.23 In the company model, baseline quality of life in the model refers to the health state of stable AF, where patients on treatment have not yet experienced a clinical event. The baseline quality of life assumed in this analysis was 0.78, which was estimated from the baseline utility as reported in Khan (2004), a study of AF patients receiving warfarin in the UK. An alternative baseline utility value based on the health related

quality of life data from ENGAGE AF-TIMI48 was used as an alternative baseline utility in the sensitivity analyses. This alternative value was 0.836. The company assumed that patients who have a stroke, myocardial infarction and systemic embolism experience a permanent decrement to their health-related quality of life. Health related quality of life was not assumed to be constant over time as adjustments were made for cohort aging (-0.00029 per year) to reflect the impact of age and thrombotic events on a patient's quality of life. Utility estimates for mild, moderate and severe stroke (0.76, 0.39, and 0.11 respectively) derived from Gage (1996) were adjusted to reflect that quality of life is lower following a stroke (0.68, 0.31 and 0.03 respectively). See table 15 for a summary of the quality of life values used in the company's model.

5.24 The adverse events that were considered in the company's model were the clinical outcomes modelled as events, namely non-ICH major bleed, clinically relevant non-major bleeds, other ICH, and transient ischaemic attack. Based on clinical advice to the company, these were assumed to reduce a patient's health-related quality of life for a limited time period and not permanently.

Table 15. Summary of quality-of-life values for cost-effectiveness analysis (source: table 60 of the company submission)

Health state / event	Utility value / decrement	CI (distribution)	Reference in submission	Justification
Stable AF	0.780 (Base case) 0.74 education group 0.82 education and self-monitoring group	SE 0.0427	Khan *et al.* 2004	The only EQ-5D utility from UK based study
	0.836		ENGAGE AF-TIMI 48	Based on US patients
Age-adjustment disutility per year	-0.00029	-0.00059 to 0.0000129 (beta)	Sullivan *et al*. 2011	Most recent and relevant source identified
Health states				
Mild IS Moderate IS Severe IS	0.68 0.31 0.03	0.14 to 1.0 0.0 to 0.99 0.0 to 0.51 (90% CI, beta)	Gage *et al*. 1996	It is the only study reporting stroke severity for mild, moderate and severe
Mild HS Moderate HS Severe HS	0.68 0.31 0.03	0.14 to 1.0 0.0 to 0.99 0.0 to 0.51 (90% CI, beta)	Gage *et al*. 1996	It is the only study reporting stroke severity for mild, moderate and severe
SE	0.680	NA**	Sullivan *et al*. 2011	Only source identified
MI	0.683	SD: 0.233 (beta)	Lacey *et al*. 2003	It is the only UK-based study using EQ 5D identified via the systematic review
Events				
Other ICH disutility	-0.107	NR	Thomson *et al*. 2000	Only source identified
	6 weeks	-	Apixaban STA (TA275)	
TIA disutility	-0.103**	-0.088 to -0.119 (beta)	Sullivan *et al*. 2006	Only source identified
	NA	-	-	
Non-ICH major bleed disutility	-0.107	NR	Thomson *et al*. 2000	Only source identified
	2 weeks	-	Apixaban STA	

Health state / event	Utility value / decrement	CI (distribution)	Reference in submission	Justification
			(TA275)	
CRNMB disutility	-0.0582	NR	Sullivan *et al*. 2011	Only source identified
	2 days	-	Apixaban STA (TA275)	

CRNMB=clinically relevant non-major bleeding; HS=haemorrhagic stroke; ICH=intracranial haemorrhage; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism; NR=not reported

ERG comments

5.25 The ERG highlighted that the estimate for the age-related utility decrement in the model (-0.00029 per annum) was based on self-reported health status of a US population, although the UK tariff of values had been applied to these figures they may not be generalisable to a UK population. The ERG commented that data from a UK population have previously been used to estimate an age-related utility decrement in a NICE appraisal of aflibercept for the treatment of metastatic colorectal cancer (TA307). The ERG used EQ-5D data from the Health Survey for England and an analysis using these data yielded an estimated annual utility decrement of -0.00646 which had little effect on the cost-effectiveness results (see ERG's exploratory analyses in section 5.40, scenario R13).

5.26 The ERG did not consider the base case utility value for stable atrial fibrillation health state which had been derived from a UK study by Khan (which had a modest sample size of 125 patients, with a low response rate) and was designed to assess the effectiveness of an anticoagulation education programme and self-monitoring of patients with atrial fibrillation taking warfarin) to be representative of a general atrial fibrillation population. The ERG preferred the use of EQ-5D data collected as part of the ENGAGE trial.

Resource use

5.27 The company used the British National Formulary 68 (July 2014) to obtain drug costs in the model. All costs for the IS, HS, and SE health states were based on the Oxford Vascular study (OXVASC, 2013), a large study of healthcare costs after stroke in patients with AF in the Oxfordshire region. Costs associated with myocardial infarction were based on NHS reference costs. Post-myocardial infarction costs were based on the Electronic Drug Tariff/British National Formulary 68 (July 2014) respectively. The costs associated with each health state, as well as costs associated with adverse advents are presented in table 16.

5.28 The monitoring costs for warfarin patients were adapted from the unit cost of anticoagulation monitoring used in the NHS Costing Template for dabigatran, which was also used in the apixaban technology appraisal. These costs were inflated to 2013 costs using the PSSRU Hospital and Community Services Health Index (HCHS). The model assumed that 34% of patients will be seen in a secondary care setting (£235.11) with the remaining 66% seen in primary care (£323.10) giving a weighted average annual cost of £265.03 (see tables 62 and 63 of the company submission).

Table 16 List of health states and associated costs in the company's economic model – adapted from table 64 in the company submission

Health states	Value (Standard error)	Duration	Reference
Mild IS	£3,683 (£1,080)	Acute, one off cost	Luengo-Fernandez
Post Mild IS	£193 (£41)	Monthly	
Moderate IS	£19,212 (£2,654)	Acute, one off cost	
Post Moderate IS	£376 (£91)	Monthly	
Severe IS	£26,240 (£4,273)	Acute, one off cost	
Post Severe IS	£571 (£388)	Monthly	
Mild HS	£10,723 (£2,184)	Acute, one off cost	
Post Mild HS	£193 (£41)	Monthly	
Moderate HS	£27,548 (£6,023)	Acute, one off cost	
Post Moderate HS	£376 (£91)	Monthly	
Severe HS	£46,598 (Not reported)	Acute, one off cost	
Post Severe HS	£571 (£388)	Monthly	
SE	£4,285 (Not reported)	Acute, one off cost	
Post SE	£193 (£41)	Monthly	
MI	£2,446 (Not reported)	Acute, one off cost	NHS Reference Costs 2012-13
Post MI	£3.86 (Not reported)	Monthly	Electronic Drug Tariff, BNF68
Death	£2,902 (Not reported)	One off cost	Luengo-Fernandez
Adverse events	Value	Duration	Reference
Other ICH	£2,589	Acute, one off cost	NHS Reference Costs 2012-13
Transient ischaemic attack	£938	Acute, one off cost	
Non-ICH major bleed	£1,803	Acute, one off cost	
CRNMB	£883	Acute, one off cost	

ERG comments

5.29 The ERG noted that the cost of warfarin used in the company's model (£0.11 per day) was estimated using the list prices reported in the BNF. However, the ERG highlighted that warfarin is widely available to the NHS at discounted prices. The ERG carried out an exploratory analysis using the warfarin cost estimated from figures reported in the Department of Health's eMit database (£0.0375). This is summarised in section 5.43 (ERG's exploratory analysis, scenario R14).

Company's base-case results and sensitivity analysis

5.30 In the deterministic base case analysis (based on people with $CHADS_2$ ≥2), edoxaban, dabigatran 110mg, apixaban and rivaroxaban were strictly dominated (less effective and more costly) by dabigatran 150mg, which had an ICER of £7645 per additional QALY gained compared to the remaining comparator in the analysis, warfarin. These results are summarised in table 17. For probabilistic ICERs, see the ERG comments below and table 18).

Table 17. Company incremental base case (deterministic results) – adapted from table 79 of the company submission

Technology	Total costs	Total QALYs*	Inc costs	Inc QALYs	ICER vs warfarin (QALYs)	ICER per QALY gained (£)
Warfarin	£13,413	6.32	-	-	-	-
Dabigatran 150mg	£15,563	6.60	£2,150	0.28	£7,645	£7645
Apixaban	£15,940	6.59	£377	-0.01	£9,383	Strictly dominated
Edoxaban	£15,957	6.52	£17	-0.07	£12,881	Strictly dominated
Dabigatran 110mg	£16,074	6.51	£117	0.00	£13.565	Strictly dominated

Rivaroxaban	£16,744	6.44	£670	-0.08	£28,180	Strictly dominated

5.31 The company presented cost effectiveness acceptability curves for the incremental analysis that showed that the probability of edoxaban being cost effective was 2.9% at a threshold of £20,000 per QALY gained and 3.4% at a threshold of £30,000 per QALY gained. Warfarin had the highest probability (36.8%) of being the most cost effective option given a cost effectiveness threshold of £20,000 per QALY gained but that, at a cost effectiveness threshold of £30,000 per QALY gained, apixaban has the highest probability of being the most cost effective option (32.6%). In the pairwise comparison of edoxaban compared to warfarin, at a threshold of £20,000 edoxaban has a 47.1% probability of being cost effective and at £30,000 a probability of 57.1%.

5.32 The company conducted 14 pair-wise deterministic sensitivity analyses, each varied one of the following parameters: starting age, risk adjustment factor per decade, other-cause mortality adjustment factor, acute mortality risk for all events, post-outcome mortality hazard ratio for all events, intervention cost per month for each drug, monitoring cost per month for each drug, acute cost of each event, post-outcome monthly cost of each event, cost of death, stable atrial fibrillation utility, acute disutility and post-outcome utility for each event and other cause discontinuation rates. The analyses estimated the effect on net monetary benefit and the ICERs per QALY; however, only changes in net monetary benefit are reported in the company submission. The company highlighted that the variables that had the most impact on the deterministic base case results were patients' starting age (lower limit 52.1 years, upper limit 89.1 years), cost of treatment and the addition of a monitoring cost for patients treated with edoxaban (baseline £0, upper limit £26.50). Utility values in the model had limited effect on the results with the utility of stable AF and post-event utility of myocardial infarction and haemorrhagic stroke being in the top 10 variables.

5.33 The company presented results for subgroup analysis for people with a $CHADS_2$ score of 3 or more (table 87 of the company submission) and a centre level time in therapeutic range of 60% or more (table 88 of the company submission) in accordance with the final scope. Edoxaban, dabigatran 110 mg, and rivaroxaban were strictly dominated (less effective and more costly) by apixaban and dabigatran 150 mg in people with a CHADS score of 3 or more. For the subgroup of people with a centre level time in therapeutic range of 60% or more, edoxaban, dabigatran 110mg, apixaban and rivaroxaban were strictly dominated (less effective and more costly) by dabigatran 150mg, which had an ICER of £11,738 per additional QALY gained compared to the remaining comparator in the analysis, warfarin.

ERG comments

5.34 Although the results from the base case probabilistic analysis were not explicitly included in the company submission the ERG calculated and presented this in table 18. Based on the probabilistic analysis, edoxaban, dabigatran 110mg and rivaroxaban are strictly dominated (less effective and more costly) by dabigatran 150mg and apixaban extendedly dominated dabigatran 150mg (was it was more effective and had a lower ICER) with an ICER of £13,036 per QALY gained compared to warfarin.

Table 18 Company's probabilistic base case results (ERG extracted results of the pairwise comparison from the company's model – table 43 of the ERG report)

	Costs	QALYs	Incremental Cost	Incremental QALY	ICER
Warfarin	£12,868	6.56	-	-	-
Rivaroxaban	£16,313	6.65	-	-	Dominated
Dabigatran 110mg	£15,732	6.66	-	-	Dominated
Edoxaban	£15,451	6.72	-	-	Dominated
Dabigatran 150mg	£15,293	6.75	£2,425	0.185	Extendedly Dominated
Apixaban	£15,531	6.77	£2,662	0.204	£13,036

5.35 The ERG noted that the differences, in terms of costs and QALYs, between all the anticoagulants considered in this appraisal, are very small. The biggest difference in lifetime (30 years) costs was between rivaroxaban and warfarin (£3455) and the biggest difference in lifetime QALYs was between apixaban and warfarin (0.205, i.e. 75 days).

5.36 The ERG highlighted that the company's results from the probabilistic analyses carried out by the company differ somewhat from those generated by the deterministic analyses. In both sets of analyses edoxaban is dominated (less effective and more costly than at least one alternative treatment). However, the conclusions for dabigatran 150mg and apixaban differed between the probabilistic and deterministic analyses. In the deterministic analysis dabigatran 150mg was less costly and more effective than the other non-VKA oral anticoagulants, whereas in the probabilistic analysis apixaban dominated dabigatran 150mg. The ERG considers that this was due to the very small differences in QALYs between dabigatran 150mg and apixaban in all analyses. In addition the results of the probabilistic analysis were not completely stable (repeated runs of the same analyses give slightly different results). Ideally the model would be set up to conduct more than 1000 runs.

5.37 The ERG noted various discrepancies between the probabilistic distributions used in the model and those reported in the company submission (Appendix 10.7 of the company submission). However, using the values reported in the company submission did not change the results of the probabilistic base case analysis. In addition, the ERG had concerns with the method used in the sensitivity analysis to evaluate the impact of changing the starting age in the model. In this analysis only the starting age was amended and not the time horizon. As a result, for younger ages, the model no longer reflected a lifetime horizon and so underestimated the lifetime costs and benefits. For example, as the model runs for only 30 years, amending the starting age to 40 years will only estimate costs and QALYs up to a maximum age of 70 years.

5.38 The ERG considered the subgroup analysis for patients with $CHADS_2 \geq 3$ and another based on centre time in therapeutic range (cTTR≥60%) to be based on very limited data and, as a consequence, the analyses mostly used data from the base case analyses for the $CHADS_2 \geq 2$ and $CHADS_2 \geq 1$ populations. Therefore, the extent to which these results are truly representative of effect on the subgroup identified in the scope was unclear.

5.39 The ERG concluded that the results generated by the company's model should be considered with caution. The main reasons for this were:

- The incremental analysis being based upon the company's network meta-analyses. Analysis by the ERG suggested that the assumptions of proportional hazards required for this analysis do not hold. The results of the incremental analysis are therefore highly uncertain
- The source of data used to adjust utilities to reflect a reduction of health-related quality of life with increasing age were based on data from a US population and significantly underestimate this impact when compared with data from a UK population
- The model overestimated overall survival when the outputs were compared with data from the ENGAGE trial.
- The company conducted sub-group analyses as requested in the NICE scope was based on limited data.

Company scenarios

5.40 Scenario analyses were undertaken by the company around hazard ratios for transient ischaemic attack and clinically relevant non-major bleeds. The base case analysis assumes values of 1 where data were not available; in the scenario analysis, all values of 1 were changed to 0.93 or 0.72 for transient ischaemic attack and 1.19 or 1.25 for clinically relevant non-major bleeds. Changing the hazard ratio for transient ischaemic

attack had little impact on the ICER. When a value of 0.93 or 0.72 was used there was no difference to the overall results, that is, treatment options were in the same order as the company's base case results.

ERG exploratory analyses

5.41 After the ERG report was finalised, the ERG identified an error in the company model that had a large impact on the application of one of the ERG's scenarios (R12 in the ERG report, R13 in the ERG addendum). The ERG corrected this error (scenario R2 of the addendum) and updated its exploratory analyses in an addendum which superseded the exploratory analyses in the ERG report. The updated exploratory analyses are presented below.

5.42 The ERG carried out 17 individual exploratory analyses. The details of each parameter are presented in section 6 of the ERG report and have been updated in the ERG's addendum (R1 to R17 on page 9 of the addendum to the ERG report). These analyses use the ERG's preferred alternative parameter values or formulae:

R1. Correcting an error in the cell reference for the utility estimate for post-SE

R2. Corrected implementation of age-related disutility

R3. An alternative utility estimate for the SE state

R4. HRs in the incremental analysis for warfarin from the company's NMA rather than HR from the ENGAGE trial data.

R5. An alternative utility estimate for the MI state

R6. An alternative utility estimate for the TIA state

R7. Utility values for the three stroke states unadjusted for respondents' own health

R8. An alternative utility values for stroke states

R9. Patients receiving dabigatran 150mg switch to dabigatran 110mg at age 80 years

R10. All patients discontinue treatment following HS

R11. Applying the acute stroke fatality rate to all stroke events (16.8% for IS and 31.6% for HS)

R12. Used trial data on acute stroke case fatality rates for all IS and HS stroke

R13. Amended age adjusted utility decrement per year

R14. Warfarin daily cost estimated using data from the eMIT database

R15. Amendments to reflect a distribution of different starting ages, each with different gender distribution

R16. ENGAGE trial hazard rates for HS

R17. Reconciliation of OS estimates

These are presented in table 19 below. In addition, the ERG carried out four analyses in which multiple parameters were changed. These amendments are labelled C, D, E and F and refer to the following:

- Analysis C: Combining alternative utility data (R2, R3, R5, R6, R8) and warfarin hazard ratios from NMA (R4) (in the incremental analysis only).
- Analysis D: As for analysis C plus the age-adjustment to utilities, the costs of warfarin, the HR for HS and assumptions regarding dose reduction for dabigatran treatment discontinuation after HS (R9, R10, R13, R14, R16)

- Analysis E: All the amendments introduced in analysis D plus applying an amendment to the probabilities of acute stroke fatality from the trial (R12)

- Analysis F: All the amendments introduced in analysis D plus applying the amendment to reconcile the model and ENGAGE trial OS estimates (R17) and the age/gender distribution over time (R15).

5.43 The ERG noted that the economic model appeared to be robust to any sensitivity analysis carried out by the company and most of the analyses carried out by the ERG. None of the ERG's amendments to the company's model changed the result that edoxaban was more expensive and less effective that at least one of the alternative treatments when full incremental analyses are carried out (see tables 47 and 48 of the ERG addendum for the deterministic and probabilistic results). When all of the ERG's preferred values were used in the model (scenario D) the pairwise deterministic (probabilistic) ICERs for the comparison of edoxaban with warfarin were £16,008 (£22,079). Including additional alternative amendments to attempt to reconcile the model survival outputs with the trial data and to reflect the changing age/gender distribution over time changed the deterministic pairwise ICERs to between approximately £15,100 and £15,800, and the probabilistic results to between £21,700 and £23,600 per QALY gained.

Table 19 ERG exploratory analyses - pairwise deterministic results, edoxaban versus warfarin - (table 49 of ERG addendum)

Scenario	Description	Edoxaban		Warfarin		Incremental		
		Total cost	Total QALY	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
A	Company deterministic base case	£15,957	6.52	£13,413	6.32	£2,544	0.20	£12,881
R1	Company base case-corrected utility for SE*	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R2	Company base case – corrected implementation of age-related disutility	£15,957	6.71	£13,413	6.51	£2,544	0.20	£12,454
R3	Alternative utility value for SE	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R4	HR for warfarin from NMA	£15,957	6.51	£13,403	6.32	£2,554	0.19	£13,287
R5	Alternative utility value for MI	£15,957	6.51	£13,413	6.31	£2,554	0.20	£12,818
R6	Alternative utility value for TIA	£15,957	6.51	£13,413	6.32	£2,554	0.20	£12,823
R7	Corrected utility values for mild, moderate and severe stroke	£15,957	6.53	£13,413	6.34	£2,554	0.20	£12,951
R8	Alternative utility values for acute mild, moderate and severe	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,809

	stroke and post stroke states							
R9	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R10	Discontinuation rate medication following HS 100%	£15,927	6.51	£13,385	6.32	£2,542	0.20	£12,813
R11	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	£15,726	6.47	£13,110	6.27	£2,616	0.21	£12,644
R12	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	£15,556	6.46	£12,871	6.25	£2,685	0.21	£12,649
R13	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	£15,957	2.34	£13,413	2.27	£2,544	0.07	£34,008
R2+R13	Amendments to age-adjusted utility: implementation and value (0.00646)	£15,957	6.65	£13,413	6.45	£2,544	0.20	£12,555
R14	Warfarin daily cost sourced from eMIT as per NICE	£15,957	6.51	£13,203	6.32	£2,754	0.20	£13,883

	reference case							
R15	Change in age and gender distribution over time	£18,365	6.92	£15,806	6.66	£2,558	0.26	£10,010
R16	Apply ENGAGE trial hazard rates for HS	£15,957	6.51	£13,078	6.35	£2,879	0.17	£17,137
R17	Reconcile OS estimates-amend other cause mortality adjustment factor value to 1.54165	£15,335	6.24	£12,904	6.06	£2,430	0.18	£13,735
C	R2+R3+R4+R5+R8	£15,957	6.70	£13,403	6.51	£2,544	0.20	£12,912
D	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R16**	**£15,927**	**6.65**	**£13,010**	**6.47**	**£2,917**	**0.18**	**£16,008**
E	**R2+R3+R4+R5+R6+R8+R9+R10+R12+R13+R14+R16**	**£15,539**	**6.60**	**£12,520**	**6.41**	**£3,019**	**0.19**	**£15,807**
F	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R15+R16+R17**	**£17,735**	**6.77**	**£14,675**	**6.56**	**£3,060**	**0.20**	**£15,176**
	Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio							

Innovation

5.44 The company considered edoxaban tosylate to be innovative for the following reasons:

- Use of edoxaban may result in potential convenience benefits, since INR monitoring is not required, as is the case with VKAs. Poor

compliance may eventually lead to undesired health outcomes such as stroke/recurrence

- Edoxaban may also lead to improved health-related benefits due to the absence of lifestyle limitations on account of the absence of significant drug-drug or drug-food interactions, and its ease of use as a once-daily medication. Once daily regimens of medication enhance patient adherence and compliance to therapy
- For reasons presented above (monitoring, compliance, lifestyle changes), warfarin has been shown to have an impact on quality-of-life which has not been taken into consideration in the QALY benefits in the base case model. A study has estimated that warfarin was associated with a disutility of 0.012, compared with NOACs
- The administration of a 4-factor prothrombin complex concentrate (PCC) has been shown to reverse the effects of edoxaban in the case of uncontrolled bleeding. Edoxaban is currently the only NOAC to include such guidance in its SmPC based on clinical data.

6 Equality issues

6.1 No equality issues have been identified in the evidence submission or during the scoping exercise. During the scope consultation it was suggested that a subgroup of ‘very elderly’ people (defined by consultees at the scoping workshop as people over about 80 years) should be specified in the scope. Attendees at the scoping workshop noted that there may be little evidence on the effectiveness of edoxaban tosylate in this subgroup. Attendees also advised that factors other than age (such as fitness) can also guide the choice of treatment. During the workshop the technical team explained that, to avoid discrimination, NICE prefers not to make recommendations based solely on age unless there is

compelling clinical evidence to support that recommendation. Attendees agreed it was not necessary to consider a subgroup defined by

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Appendix A: Clinical efficacy section of the draft European public assessment report

Not available