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

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

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

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Abbreviations:

AC	Appraisal Committee
AE	adverse event
AF	atrial fibrillation
CEAC	cost effectiveness acceptability curve
CEAF	cost effectiveness acceptability frontier
$CHADS_2$	Algorithm used to assess risk of stroke: congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA
CHA_2DS_2-VASc	Algorithm used to assess risk of stroke: congestive heart failure, hypertension, age (65-74 years), age (≥75 years) diabetes mellitus, stroke/TIA, vascular disease
CI	confidence interval
CRNMB	clinically relevant non-major bleeding
CS	company submission
CSR	clinical study report
cTTR	centre level time in therapeutic range
CV	cardiovascular
CV-related	cardiovascular-related
DR	dose reduction
DVT	deep vein thrombosis
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
ENGAGE	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 trial
EPAR	European Public Assessment Report
ERG	Evidence Review Group
FDA	Food and Drug Administration
HRQoL	health-related quality of life
GI	gastrointestinal
HR	hazard ratio
HS	haemorrhagic stroke
ICH	intracranial haemorrhage
ICER	incremental cost effectiveness ratio
INR	international normalised ratio
IS	ischaemic stroke
ITT	intention to treat
IVRS	interactive voice recognition system
K-M	Kaplan-Meier
LY	life year
MACE	major adverse cardiac events: non-fatal MI, non-fatal stroke, non-fatal SE, and death due to CV cause or bleeding
MI	myocardial infarction
mITT	modified intention to treat
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
NOAC	new/novel oral anticoagulant
NVAF	non-valvular atrial fibrillation

PE	pulmonary embolism
PP	per protocol
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
RCT	randomised controlled trial
RR	relative risk
SA	sensitivity analysis
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SE	systemic embolism
SPC	summary of product characteristics
STA	single technology appraisal
TIA	transient ischaemic attack
ToT	time on treatment
TTR	time in therapeutic range
VKA	vitamin K antagonist

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence were submitted to NICE from Daiichi Sankyo in support of the use of edoxaban tosylate (Lixiana®) for preventing stroke and systemic embolism (SE) in people with non-valvular atrial fibrillation (NVAF).

Edoxaban tosylate (hereafter referred to as 'edoxaban') does not currently have a European marketing authorisation for any indication. The company submitted an application to the European Medicines Agency (EMA) in January 2014 for edoxaban to be licensed for two indications: the first (relevant to this appraisal) is for the prevention of stroke and SE in patients with NVAF and the second is for the treatment and prevention of venous thromboembolism. The company expected edoxaban to receive a positive opinion from the EMA Committee for Medicinal Products for Human Use in February 2015 and to be granted marketing authorisation in May 2015. At the time that this ERG report was submitted, the EMA had not published any decision regarding edoxaban.

The draft Summary of Product Characteristics (SPC) states that edoxaban is indicated for the prevention of stroke and SE in adult patients 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 (TIA).

1.2 Critique of the decision problem in the company submission

The population specified in the NICE scope is adults with NVAF who are at risk of stroke or SE. The company's main source of clinical evidence is the ENGAGE AF-TIMI 48 (ENGAGE) trial which provides data for the efficacy and safety of edoxaban versus warfarin in a cohort of patients with NVAF who are considered to be at moderate to high risk of stroke. (i.e. patients with a $CHADS_2$ ≥2).

The comparators specified in the NICE scope are: warfarin, apixaban, dabigatran etexilate (hereafter referred to as 'dabigatran') and rivaroxaban. The company has only provided direct evidence for edoxaban versus warfarin (from the ENGAGE trial). The ERG notes that the ENGAGE trial (edoxaban versus warfarin) and the ROCKET-AF trial (rivaroxaban versus warfarin) enrolled patients with $CHADS_2$ ≥2, whilst the RE-LY (dabigatran versus warfarin) and ARISTOTLE (apixaban versus warfarin) trials enrolled patients with $CHADS_2$ ≥1.

The outcomes specified in the final scope issued by NICE are: stroke, SE, myocardial infarction (MI), TIA, mortality, adverse effects (AEs) of treatment including haemorrhage and health-related quality of life (HRQoL). All of the specified clinical effectiveness outcomes are addressed in the company's submission (CS). EuroQol (EQ-5D) data were collected during the ENGAGE trial. However, the findings were not reported in the clinical effectiveness section of the CS, the results were only described in a cost effectiveness sensitivity analysis.

The two subgroups specified in the NICE scope (patients who are defined by their risk of stroke or SE, and patients who are defined by their time in therapeutic range (TTR) on warfarin) are considered in the CS.

1.3 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company has presented direct clinical evidence to support the use of edoxaban for preventing stroke and SE in people with NVAF from the ENGAGE trial. Approximately 7000 patients were recruited to the high dose edoxaban arm, with approximately 7000 more recruited to the warfarin arm of the trial. Only one patient was lost to follow-up. The whole trial included 254 patients from 31 UK centres and the trial data were fully mature.

The hazard ratio (HR) calculated from ENGAGE trial data for the primary composite endpoint of stroke and SE suggests that edoxaban is non-inferior, but not superior, to warfarin (HR=0.79; 95% CI 0.63 to 0.99, p<0.001). The non-inferiority of edoxaban is driven by a reduction in haemorrhagic stroke (HS) events. The non-inferiority of edoxaban, compared with warfarin, is consistent across a range of subgroup analyses, including the measure of time in therapeutic range (TTR) on warfarin (centre level TTR [cTTR] of ≥60%) and level of stroke or SE risk (across $CHADS_2$ 2 to 6).

Patients in the edoxaban arm of the ENGAGE trial experienced statistically significantly fewer major bleeding events than patients treated with warfarin (HR=0.80; 95% CI 0.71 to 0.91, p<0.001). However, there were statistically significantly greater numbers of gastrointestinal bleeding events in patients treated with edoxaban compared with patients treated with warfarin (HR=1.23; 95% CI 1.02 to 1.50 p=0.03).

The results of a post-hoc analysis of outcomes based on renal function indicate that edoxaban may be less effective than warfarin in preventing stroke or SE in patients with normal renal function. It is unclear whether this finding is a statistical anomaly.

[redacted] However, the estimate of treatment effect for the primary outcome from the post-hoc analysis for the European Economic Area plus Switzerland (which did not include Israel or Turkey) favoured edoxaban over warfarin (HR=0.92; 95% CI 0.69 to 1.22).

Indirect evidence

There is currently no direct clinical evidence comparing edoxaban with apixaban, dabigatran or rivaroxaban. Hence the company undertook a network meta-analysis (NMA). The results of the NMA for the [redacted]

[redacted]

[redacted]

[redacted]

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers the ENGAGE trial to be robust and of good quality. The key baseline characteristics of patients recruited to the ENGAGE trial match the characteristics of patients with NVAF who are treated in clinical practice in England and Wales, except in terms of risk of stroke. The trial only included patients who met the criteria for a $CHADS_2 \geq 2$. This means

that there are no clinical effectiveness data in the CS to support the use of edoxaban for patients at lower risk of stroke and SE ($CHADS_2$=1), a group who would be considered for anticoagulation treatment in the NHS in England and Wales. It is also unclear whether patients with NVAF who are treated with edoxaban can continue their treatment whilst they undergo cardioversion.

The ERG carried out an analysis of the three subcomponents of the ENGAGE trial primary composite endpoint. As a result, the ERG considers that the company's estimate of treatment effect may not be robust as the data show that, when HS is considered, the assumption of proportional hazards between the edoxaban and warfarin arms appears to be violated.

In addition, the ERG is of the opinion that the results of the company's NMA are unreliable as the ERG is able to demonstrate that the assumption of proportional hazards is violated both within the ENGAGE trial (HS events) and across the warfarin arms of the included trials (primary composite endpoint in all four included trials, and principal safety endpoint in the edoxaban and apixaban trials). Furthermore, examination of published results for the key trials that compare the other three NOACs with warfarin show, in each case, evidence that, in terms of the primary outcome, there is a statistically significant violation of the proportional hazards assumption. The HRs generated by the NMA should, therefore, be considered with caution.

Where HR values were required to populate the economic model, and where it was not possible to generate these for patients with $CHADS_2$ ≥2, the NMA incorporated two additional working assumptions, namely, using data from all patients and, where such data were not available, assuming a HR of 1. The result of this strategy is that there are differences between the outcomes reported in the clinical effectiveness section of the ERG report and outputs generated by the cost effectiveness model.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo Markov cohort model to evaluate the cost effectiveness of edoxaban compared to warfarin, dabigatran 110mg, dabigatran 150mg, apixaban and rivaroxaban. The model structure is largely based on that submitted to NICE for the STA of apixaban for the prevention of stroke or SE in people with NVAF (TA275). It has been developed in Microsoft Excel using a 1-month cycle length. The characteristics of the population modelled are based on those reported in the ENGAGE trial, including a $CHADS_2$ ≥2 and a starting age of 71 years. It includes a half-cycle correction and the time horizon is set to patient lifetime (i.e. a maximum follow-up of 30 years). As recommended by NICE, a

discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in quality adjusted life years (QALYs). The model perspective is that of the UK NHS. Resource use, costs and utilities were estimated based on information from the ENGAGE trial, the results of the company's NMA, published sources and clinical expert views.

The model comprises 18 health states; stable AF, stroke (HS and IS), SE, myocardial infarction (MI) and dead. Stroke events (HS and ischaemic [IS]) are divided into mild, moderate and severe categories. Health states (IS, HS, SE and MI) are further divided into acute events and long-term impacts. On entering the model all patients have stable AF. Annual event rates for first non-fatal clinical events for patients treated with either edoxaban or warfarin were derived from the edoxaban arm of the ENGAGE trial and converted into monthly probabilities. Event rates for dabigatran, rivaroxaban and apixaban were obtained by applying the HRs from the company's NMA, and event rates for warfarin based on applying the HRs from the ENGAGE trial, to the baseline edoxaban data.

The incremental cost effectiveness ratio (ICER) for the comparison of edoxaban versus warfarin is estimated to be £12,881 per QALY gained; edoxaban is more expensive (£2544) and offers more QALYs (+0.2) than warfarin. When compared with either dabigatran (110mg) or rivaroxaban, edoxaban is shown to be cheaper (-£117 and -£787 respectively) and to offer more QALY gains (+0.001 and +0.08 respectively). When compared with apixaban or dabigatran 150mg, edoxaban treatment is shown to be slightly more expensive (+£17 and +£394 respectively), and leads to fewer QALY benefits (of -0.07 and -0.08 respectively). In summary, the costs and benefits of the four NOACs do not differ substantially. However, the results of the company's full incremental analysis show that edoxaban, dabigatran 110mg, apixaban and rivaroxaban are strictly dominated by dabigatran 150mg and that when compared to warfarin, dabigatran 150mg has an ICER of £7678 per QALY gained.

The company carried out a wide range of deterministic and probabilistic sensitivity analyses (PSA). The deterministic results show that the company's conclusions (i.e. that dabigatran 150mg dominates all NOACs and is cost effective compared to warfarin) are robust to the alternative model inputs used in the analyses. The results from the PSA show that edoxaban has a 2.9% (3.4%) probability of being cost effective at a willingness to pay threshold of £20,000 (£30,000) per QALY gained.

ERG Interpretation of the company's base case results

Edoxaban is dominated (less effective and more costly) by another NOAC in both the deterministic and probabilistic base case incremental analyses. There are differences in the

results of the probabilistic and deterministic analyses as to which NOAC is cost effective; these are driven by very small and uncertain differences between two of the NOACs (apixaban and dabigatran 150mg). In the deterministic analysis, dabigatran 150mg dominates other NOACs and has an ICER of £7645 per QALY gained compared to warfarin. In the probabilistic incremental analysis, apixaban dominates or extendedly dominates other NOACs and has an ICER of £13,036 per QALY gained compared to warfarin. In the incremental analyses, the differences in costs and QALYs between edoxaban and the other NOACs are small, but the finding that edoxaban is more costly and less effective than apixaban and dabigatran 150mg is consistent across all but one of the sensitivity analyses conducted by the company.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

Cost effectiveness not claimed

The economic evaluation provided by the company is consistent with the NICE scope and largely meets the NICE reference case. The company model was adapted from a model previously assessed by NICE in a technology appraisal of apixaban. The ERG notes that the company's model does not show edoxaban to be the most cost effective anticoagulant option available.

The NMA

Whilst the differences in costs and QALYs between the NOACs are small, the finding that edoxaban is less effective and more costly than apixaban and dabigatran 150mg appears to be robust to a ranage of assumptions. These incremental analyses are, however, driven by the results of the NMA conducted by the company. The ERG notes differences in patient populations in the trials used in the analysis that generated model inputs; specifically, the inclusion of patients with a $CHADS_2$=1 in the trials of apixaban and dabigatran, but not in the trials of edoxaban and rivaroxaban. The ERG questions the validity of the results as their analyses have shown that the assumption of proportionality required for the NMA is violated within the key NOAC trials, and also across the warfarin arms of these trials. Therefore, the ERG has serious concerns about the robustness of the results of the incremental analyses presented.

Age-related utility decrements

The ERG identified a number of inconsistencies in the model and has concerns about some of the sources of data used in the analysis. However, the majority of these were found to have only minor impacts on results in analyses conducted by the ERG using the ERG's preferred values. An important exception was the use of data from a US rather than UK

population to reflect a deterioration in HRQoL with age. The use of UK data had a substantial impact on the cost effectiveness results in the pairwise comparison between edoxaban and warfarin, with the ICER increasing to £32,129 per QALY gained in the probabilistic analysis and £34,008 per QALY gained in the deterministic analysis.

Overall survival

The ERG has identified that the estimates of OS predicted by the company's model are different from those observed in the ENGAGE trial. Several parameters used to inform the estimates of OS in the model are not sourced from the trial; for example, the rates of acute stroke mortality. The magnitude of the difference between the observed (trial) and predicted (model) estimates casts some doubt on the credibility of the model.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

Clinical effectiveness

- The company provided a detailed submission. The ERG's requests for further clinical information were fulfilled promptly and to a good standard
- The key clinical evidence is derived from a completed (median follow-up of 2.8 years), good quality randomised controlled trial that recruited substantial numbers of patients, none of whom crossed over to receive alternative treatments and very few of whom were lost to follow-up
- The submission fulfilled the majority of the requirements set out in the decision problem

Cost effectiveness

- The economic evaluation presented in the CS was consistent with the NICE scope.
- The ERG's requests for clarification were fulfilled promptly
- The company attempted to address concerns raised by NICE Appraisal Committees regarding the design and functionality of the models submitted in previous appraisals of NOACs
- The results from the model are robust to the sensitivity analyses conducted in the CS

1.7.2 Weaknesses and areas of uncertainty

Clinical effectiveness

- At the time this ERG report was submitted, the EMA had not issued a positive opinion for edoxaban and therefore the EPAR was unavailable. This means that the exact clinical indication for edoxaban is uncertain
- There are no clinical trial data describing the clinical effectiveness of edoxaban versus warfarin in patients with a $CHADS_2$=1. In clinical practice in England and Wales these patients would be considered for anticoagulation treatment

- It is unclear whether patients with NVAF who are treated with edoxaban can continue their treatment whilst they undergo cardioversion
- Health-related quality of life (HRQoL) data were collected within the ENGAGE trial using EQ-5D and provided to the ERG on request. However, for the UK population of patients, response rates were low and the data are not fully analysed. It is therefore difficult to draw any firm conclusions as to any difference in patients' experiences attributable to the choice of treatment
- In the absence of direct evidence comparing edoxaban with apixaban, dabigatran and rivaroxaban, the company conducted a NMA. The ERG considers 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

Cost effectiveness

- Results from the company's model do not show edoxaban to be the cost effective compared with other approved anticoagulant treatments
- The results of the NMA are key drivers of the incremental results. Due to violations of the proportional hazards assumption, both within each of the four clinical trials in the network, and across the warfarin arms of the four trials, the ERG has serious concerns about the validity of NMA results used in the model
- The economic model uses data from a US population study to inform a deterioration in HRQoL with increasing age. These estimates are significantly lower than those from UK population studies. The use of data from a UK population in the model substantially increases the ICER for edoxaban compared to warfarin.
- A 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 considers that the magnitude of these differences raises some concerns about the validity of the model
- Limited data were available to the company to fully inform the subgroup analyses presented and, therefore, the results of these are highly uncertain
- In addition the ERG has a number of data related concerns:
    - A wide range of sources were used in the model to inform treatment effectiveness and extrapolation including the NMA, ITT and mITT analyses of the ENGAGE trial, several articles from the literature and clinical assumptions
    - Some of the data sources used to inform the model and assumptions regarding clinical practice (e.g. discontinuation rates following HS) are of concern to the ERG; however, these are not expected to significantly impact upon the results.
    - Various estimates used in the model were incorrectly reported in the CS and the ERG was not able to verify all estimates used in the model from the stated sources

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has carried out the following alterations to the company's base case model:

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

R2. An alternative utility estimate for the SE state

R3. HRs in the incremental analysis for warfarin from the company's NMA rather than HR from the ENGAGE trial data.

R4. An alternative utility estimate for the MI state

R5. An alternative utility estimate for the TIA state

R6. Utility values for the three stroke states unadjusted for respondents' own health

R7. An alternative utility values for stroke states

R8. Patients receiving dabigatran 150mg switch to dabigatron 110mg at age 80 years

R9. All patients discontinue treatment following HS

R10. Introduction of acute mild stroke case fatality rate (16.8% for IS and 31.6% for HS)

R11. Case fatality rates for the three stroke states sourced from ENGAGE trial data

R12. Amended age adjusted utility decrement per year

R13. Warfarin daily cost estimated using data from the eMIT database

R14. Amendments to reflect a distribution of different starting ages, each with different gender distribution

R15. ENGAGE trial hazard rates for HS

R16. Reconciliation of OS estimates

The ERG also carried out a number of analyses in which multiple parameters were changed.

- Analysis C: Combining alternative utility data (R2, R4, R5, R7) and warfarin hazard ratios from NMA (R3) (in the incremental analysis only).
- Analysis D: As for analysis plus the age-adjustement to utilities, the costs of warfarin, the HR for HS and assumptions regarding dose reduction for dabigatran treatment discontinuation after HS, and (R8, R9, R12, R13, R15).
- Analysis E: All the amendments introduced in analysis D plus applying the amendment to the probabilities of acute stroke fatality from the trial (R15)
- Analysis F: All the amendments introduced in analysis D plus applying the amendment to reconcile the model and ENGAGE trial OS estimates (R16) and the age/gender distribution over time (R14).

Individually, most of the ERG amendments to the company model had only minor impacts on the ICERs per QALY gained in the pairwise analyses with warfarin. The exception was the amendment to the age-adjustment to utilities which increased the ICER to £37,129 per QALY gained in the probabilistic analysis and £34,008 per QALY gained in the deterministic analysis. Cumulatively, this amendment and the further amendments to cost and utility data (Analysis D) increased the ICERs for edoxaban compared to warfarin to £60,940 (probabilistic analysis) and £49,305 (deterministic analysis) per QALY gained. Two approaches to reconciling the trial and model data for OS were undertaken. These increased the ICERs per QALY gained for edoxaban compared to warfarin to approximately £45,000 and £60,000 in the probabilistic analysis (£37,000 and £50,000 in the deterministic analysis).

In the incremental analyses, the result that edoxaban was dominated (more costly and less effective) by at least one other NOAC was consistent across all ERG amendments, and consistent between the probabilistic and deterministic analyses.

1.9 ERG conclusions

The company has presented direct clinical evidence to support the use of edoxaban for preventing stroke and SE in people with NVAF from the ENGAGE trial. The ERG considers this trial, which is complete, to be robust and of good quality. Results from the ENGAGE trial suggest that, based on the primary composite endpoint of stroke and SE, edoxaban is non-inferior, but not superior, to warfarin.

The cost effectiveness analysis presented by the company shows that edoxaban is dominated (more costly and less effective) by at least one other treatment option in both the deterministic and probabilistic analyses. These results are robust to a range of alternative assumptions and sources of data.

However, the ERG has concerns about the reliability of the company's estimates. Firstly the results of the incremental analyses are driven by the HRs estimated by the company's NMA; the ERG notes that the assumption of proportionality underpinning this analysis is violated. Secondly, the ERG considers that the data used to inform the age-adjustment of utilities is inappropriate, and notes that the results are sensitive to this. Finally the differences between the OS predicted by the model and the ENGAGE trial raises some concerns as to the validity of the model.

The ERG carried out a number of amendments to the company's model. Analyses using the ERG's preferred input values increases the deterministic pairwise ICER per QALY gained for the comparison of edoxaban with warfarin (Analysis D) from £12,720 to £34,008 (probabilistic analysis: £16,269 to £32,129). Further amendments to address the differences in OS estimates, and the age/gender distribution increase the ICERs per QALY gained to between approximately £45,000 and £60,000 in the probabilistic analysis and between £37,000 and £50,000 in the deterministic analysis.

2 BACKGROUND

Clinical and economic evidence were submitted to NICE from Daiichi Sankyo in support of the use of edoxaban tosylate (Lixiana®) for preventing stroke and systemic embolism (SE) in people with non-valvular atrial fibrillation (NVAF).

2.1 Critique of company's description of underlying health problem

The context section (Section 2) of the company submission (CS[1]) presents the key issues relating to the underlying health problem, including clinical features, prognosis and prevalence. This information is summarised in Box 1. The Evidence Review Group (ERG) considers the company's description of the underlying health problem to be relevant and appropriate.

Box 1 Pathophysiology and prevalence of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia caused by irregular electrical signals generated throughout the atria of the heart.[2] Non-valvular AF (NVAF) is defined by international guidelines as cases in which the rhythm disturbance occurs in the absence of rheumatic mitral stenosis or a prosthetic heart valve.[3] NVAF is the most frequently diagnosed type of AF in the UK.[4]

AF is characterised by loss of synchronous atrial mechanical activity that can have adverse consequences related to a reduction in cardiac output (possibly resulting in symptoms) and to left atrial appendage thrombus formation (resulting in an increased risk of stroke and peripheral embolisation).[2] AF is known to progress from short episodes to longer more frequent attacks and sustained forms of arrhythmia, ultimately progressing to final expression as an irreversible cardiac arrhythmia.[2] The longer AF persists, the more difficult it is to restore and maintain sinus rhythm.[2]

The European Society for Cardiology (ESC) distinguishes five types of AF, based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF.[5]

AF is often asymptomatic and may be diagnosed only during routine physical examination. The most common symptoms of AF are palpitations, fatigue, dyspnoea, effort intolerance, and light-headedness.[6] In some patients with persistently elevated ventricular rates, cardiomyopathy may occur, leading to heart failure as the prominent manifestation of AF. Patients with AF can also present with an acute ischaemic stroke, TIA, or systemic embolism.[3]

Prevalence of AF in patients with associated cardiovascular disease (CVD) is higher compared to that in the overall population.[7] These conditions are responsible for structural and electrophysiological changes in the heart, which can lead to development of AF.[8,9] The presence of underlying CVD, both chronic and acute has a substantial effect on the prevalence and incidence of AF.[5]

The prevalence of AF was estimated at 1.76% in England according to the GRASP-AF registry[10] and 1.85% in Wales according to data from the National Health Service (NHS) Quality and Outcomes Framework for 2012/2013.[11] AF occurs more frequently in men than in women and rarely affects people aged less than 50 years. However it increases to almost 1% in people aged 55-64 and 11% at 85 years according to data from the General Practice Research Database.[12,13] The prevalence of AF is estimated to at least double in the next 50 years as the average age of populations within Europe increases.[14]

The company describes the risk of stroke associated with atrial fibrillation (AF) (Box 2) and notes that anticoagulation therapy is routinely used to prevent strokes in patients who have been diagnosed with AF. The company outlines two risk assessment tools, $CHADS_2$[15] and CHA_2DS_2-VASc[16] (Box 3); these tools enable clinicians to quantify the risk of stroke in patients with NVAF and thereby identify patients who may benefit from anticoagulation treatment. The ERG considers the company's information describing risk of stroke in the CS to be appropriate.

Box 2 Stroke risk associated with atrial fibrillation

Patients with AF have a risk of stroke and systemic thromboembolism that is five times greater than that of age-matched people in sinus rhythm.[17] The level of risk depends on comorbidities and demographic factors, and ranges from less than 1% to more than 20% per year.[17] The important independent prognostic factors for an increased risk of AF-related stroke are age, history of TIA or stroke, hypertension, diabetes mellitus, and evidence of moderate to severe left ventricular systolic dysfunction. In 90% of cases, AF occurs in patients with underlying heart disease.[18] The majority of patients with AF have hypertension.[18]

At least 15% to 20% of all ischaemic strokes occur in patients with AF, and the risk of ischaemic stroke increases with age.[19] The risk of stroke recurrence is greater for patients with AF compared to patients without AF.[20] Strokes are significantly more severe, and more likely to be fatal, in patients with AF compared with those without AF.[20-22] Death related to stroke is recorded as 11% in AF patients compared to 4% in non-AF patients.[22] Moreover, in non-fatal cases, strokes in AF patients are associated with greater functional disability compared to non-AF patients.[20-22]

Oral anticoagulants, including vitamin K antagonists (VKAs) and the new oral anticoagulants (NOACs) are the mainstay of stroke prevention in AF.[23]

Box 3 $CHADS_2$ and CHA_2DS_2-VASc risk assessment

The risk factors measured by the $CHADS_2$ scoring system are:

- congestive heart failure (1 point)
- hypertension (1 point)
- age at or over 75 years (1 point)
- diabetes mellitus (1 point)
- previous stroke or TIA (2 points)

The CHA_2DS_2-VASc scoring algorithm includes additional stroke risks:

- congestive heart failure (1 point)
- hypertension (1 point)
- age 65-74 years (1 point)
- age ≥75 years (2 point)
- diabetes mellitus (1 point)
- previous stroke/TIA/thromboembolism (2 points)
- vascular disease (1 point)
- female (1 point)

The company states that NICE's clinical guideline[24] published in 2014 recommends the use of the CHA_2DS_2-VASc tool to assess the risk of stroke in patients with NVAF. The CHA_2DS_2-VASc tool takes into account more risk factors than $CHADS_2$ and enables clinicians to differentiate between patients who are at very low risk of stroke from patients who are at a greater risk and who, therefore, require anticoagulation treatment. When patients are assessed using the $CHADS_2$ tool, patients who score 0 or 1 may be at greater risk of stroke than their score suggests due to factors not included in the assessment (e.g. female gender or vascular disease).

The ERG notes that recent clinical trials[25-28] evaluating the new oral anticoagulants (NOACs), (i.e. apixaban, dabigatran, edoxaban and rivaroxaban), use the $CHADS_2$ tool to stratify patients in terms of stroke risk. The ERG considers that the use of $CHADS_2$ in these clinical trials is reasonable, since $CHADS_2$ was routinely used for assessment purposes when the clinical trials were designed.

The ERG is aware that there is no means of directly mapping the scores from a $CHADS_2$ assessment to the scores from a CHA_2DS_2-VASc assessment.

2.2 Critique of company's overview of current service provision

The company's overview of current service provision is presented in Sections 2.4 and 2.5 of the CS. An overview of the current NICE guideline (CG180[24]) and a summary of NICE guidance (TA249,[29] TA256,[30] TA275[31]) relevant to this appraisal are also included in the CS and summaries of this information are presented in Box 4 and Box 5 respectively.

Box 4 NICE clinical guideline CG180

NICE has recently published new guidelines for the management of atrial fibrillation, (CG180[24]), including recommendations about the treatment of AF with anticoagulants:

- Anticoagulation therapy may be achieved with apixaban, dabigatran etexilate, rivaroxaban or VKAs. It recommends that the options for anticoagulation should be discussed with the patient and the choice based on their clinical features and preferences. The NICE guideline makes no recommendations for using one anticoagulant over another.
- Anticoagulation should be considered for men with a CHA_2DS_2-VASc score of 1 and offered to men and women with a CHA_2DS_2-VASc score of 2 or above, taking their bleeding risk into account.
- Anticoagulation should be reassessed for a person with poor anticoagulation control with VKAs shown by any of the following:
  i. Two International Normalised Ratio (INR) values higher than 5 or one INR value higher than 8 within the past 6 months,
  ii. Two INR values less than 1.5 within the past 6 months,
  iii. Time in Therapeutic Range (TTR) less than 65% (the calculation is over a maintenance period of at least 6 months).
  iv. If poor anticoagulation control with VKAs cannot be improved, the clinician should evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the patient.

This guideline supersedes the previous NICE guideline on the management of atrial fibrillation and recommends that aspirin monotherapy should not be prescribed to people with atrial fibrillation solely on account of stroke prevention.

Box 5 NICE guidance

Dabigatran etexilate was recommended in March 2012 (TA249[29]) as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischaemic attack or systemic embolism,
- left ventricular ejection fraction below 40% symptomatic heart failure of New York Heart Association class 2 or above,
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

Rivaroxaban was recommended in May 2012 (TA256[30]) as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more risk factors such as:

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

Apixaban was recommended in January 2013 (TA275[31]) as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with non-valvular atrial fibrillation with one or more risk factors such as:

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

The clinical pathway for stroke prevention in patients with NVAF in clinical practice in England and Wales is included in the CS and reproduced in Figure 1. The company states that the expected place of edoxaban in the treatment pathway is as an additional alternative NOAC therapy. The ERG considers the clinical pathway presented in the CS is accurate and agrees that edoxaban is an additional alternative NOAC therapy.

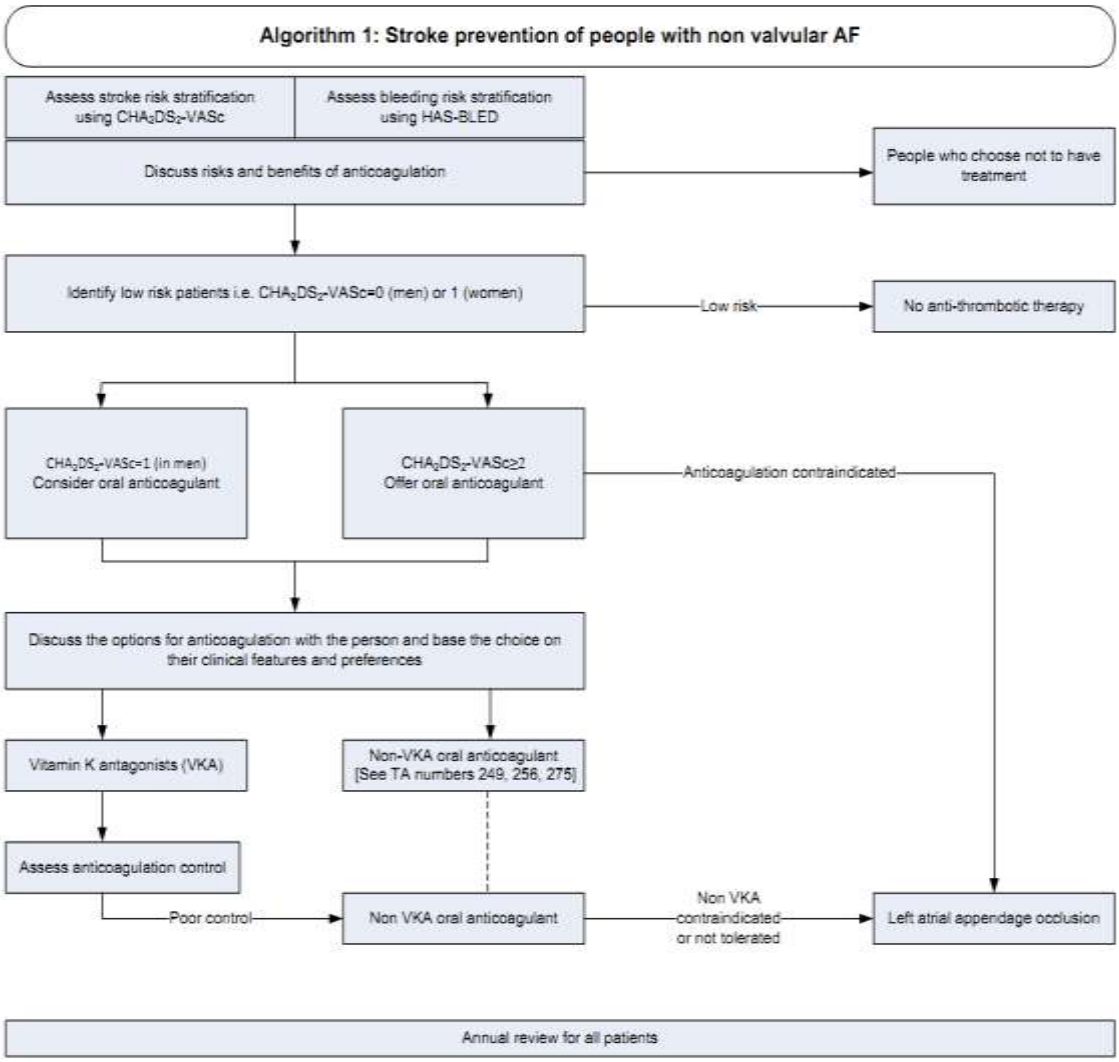

Figure 1 Stroke prevention pathway for patients with NVAF

Source: CS, Figure 2

2.3 Issues related to clinical practice

A number of issues relating to anticoagulation treatment for patients with NVAF in current clinical practice are reported in the CS. These are summarised in

Box 6.

The ERG notes that NVAF requires lifelong anticoagulation treatment. Patients who are treated with warfarin are required to undergo frequent blood tests to assess the efficacy of warfarin in preventing blood clots, as measured against the international normalised ratio (INR) level. If the INR level is too high, the patient is at risk of bleeding; if the INR level is too

low, the patient is at inadequately protected against stroke. Warfarin doses are adjusted to keep patients' INR levels between 2.0 and 3.0.[32]

Box 6 Issues related to anticoagulation treatment

Use of VKAs such as warfarin can be challenging in clinical practice due to their narrow therapeutic window, the requirement for routine monitoring and dose adjustments, their unpredictable dose response, the slow onset of action, and the risk of bleeding.

- VKA dosing must be guided by INR monitoring
- Only 61% of patients spent their time within the therapeutic range (INR 2-3)
- INR monitoring is a burden for the patient and impacts patient's quality of life
- The requirement for dose adjustment may increase the risk of accidental overdose. This makes it extremely challenging for physicians to maintain patients in the recommended therapeutic range, and equally cumbersome for patients with the need for frequent monitoring
- Warfarin has 40-fold variability in dose (doses range from 0.5 to 20 mg a day) in different patients to reach the same effect, and food interactions, drug-drug interactions, and genetic factors contribute to this variability.
- The underuse of VKAs in clinical practice is driven by safety and convenience issues associated with the use of VKAs
- NOACs have proven efficacy and safety in large clinical trials and are indicated for use in NVAF, however the level of uptake is low and there is still a significant proportion of patients requiring anticoagulation that are not receiving it.

The ERG agrees generally with the points made by the company (

Box 6). However, the ERG is aware that warfarin is the standard anticoagulation treatment used in the NHS and that its efficacy and safety are well-documented. In comparison, the use of NOACs in the NHS is relatively new and, as the company reports, (Box 6), the current level of use of NOACs in the NHS is low. For these reasons, the ERG considers that the long-term safety of NOAC treatment is not as well established as it is for warfarin. The ERG is also aware that there are patients who manage treatment with warfarin very well.

2.4 Main comparators identified in the company submission

The main comparators to edoxaban are correctly identified in the CS as: vitamin K antagonists (VKAs – usually warfarin) and the non-VKA oral anticoagulants i.e. apixaban, dabigatran and rivaroxaban. The ERG has summarised the current treatment options in Table 1.

Table 1 Main comparators

Treatment	Dose	Schedule
Warfarin	Tailored to patient	Once daily
Apixaban	5mg 2.5mg (if at least two of the following criteria ≥80years, body weight ≤60kg, serum creatinine ≥1.5mg/dL [133 micromole/L])	Twice daily
Dabigatran	150mg 110mg (if ≥80yrs or concurrent verapamil*	Twice daily
Rivaroxaban	20mg	Once daily

*verapamil is a calcium channel blocker

2.5 Number of patients eligible for treatment with edoxaban

The company anticipates that all patients with NVAF who are at risk of stroke and SE will be eligible for treatment with edoxaban and estimates that the number of patients in England and Wales likely to be eligible for treatment each year is 617,358. The company's calculations and the ERG's calculations are presented in Table 2.

Table 2 Company and ERG estimates of number of patients eligible for treatment with edoxaban

	Rate	England	Wales	Total
Company estimate				
AF patients		985,813	58,787	1,044,600
NVAF patients	75%[33]	739,360	44.090	783,450
NVAF patients at risk of stroke (i.e. $CHADS_2 \geq 1$)	78.8%[34]	582,615	34,743	**617,358**
ERG estimate				
AF patients		985,813	58,787	1,044,600
NVAF patients	90%[4,35] (and clinical advice to ERG)			940,140
NVAF patients at risk of stroke (i.e. $CHADS_2 \geq 1$)	78.8%[34]			**740,830**
NVAF patients considered for treatment in England and Wales CHA_2DS_2-VASc ≥1 (males) CHA_2DS_2-VASc ≥2 (females)	80%[4]			**752,112**

AF-atrial fibrillation; NVAF=non-valvular atrial fibrillation
Source: CS, Table 2

The overall number of AF patients in England is calculated using data from the GRASP-AF[10] registry and applying an AF prevalence rate of 1.76% to a population of 56,012,096 patients registered in GP practices.[10] This calculation yields 985,813 patients with AF.

The company's source of information pertaining to the number of patients in Wales with AF is unclear. The reference cited in the CS relates to the Quality and Outcomes Framework for

England[36] produced by the Health and Social Care Information Centre; however, this report does not appear to contain data specific to Wales.

The company estimates that 75% of patients from the overall population of patients with AF have NVAF. The figure of 75% is derived from data from the REALISE-AF[33] registry, an international database (26 countries) of 10,000 patients with AF who were enrolled between October 2009 and May 2010. However, data from the European-based PREFER[4] registry (patient enrolment Jan 2012 to Jan 2013) and cited by the company in Section 2.1 and in Table 42 of the CS, suggest that 98.1% of patients in the UK with AF have NVAF. Also, the results of a national audit for Scotland[35] (2012) demonstrate that 93.3% of patients with AF have NVAF. Clinical advice to the ERG is that the European and UK data are local and recent and are therefore more relevant. Further clinical advice is that valvular AF is rare in the UK and 90% to 95% of patients in clinical practice have NVAF.

The company's estimate that 78.8% of patients in clinical practice have a $CHADS_2$ ≥1 (and therefore may be considered for anticoagulant treatment) is derived from a paper published in 2014.[34] The paper describes a population-based study that examined the outcomes of a cohort of 16,513 patients in the UK who were registered with the UK Clinical Practice Research Datalink and who were diagnosed with AF between 2005 and 2010. The ERG considers that the company's estimate that 78.8% of NVAF patients have a $CHADS_2$ ≥1 is reasonable, but notes that the NICE guideline CG180[24] now recommends the use of the CHA_2DS_2-VASc[16] assessment tool rather than the $CHADS_2$ tool to assess the need for anticoagulation treatment. The European-based PREFER[4] registry data suggest that 80.2% of patients in the UK have a CHA_2DS_2-VASc score of ≥2; these patients would be considered for anticoagulation treatment according to the NICE guideline.[24]

Clinical advice to the ERG is that the majority of patients in clinical practice who have a $CHADS_2$=1 are likely to score ≥2 on a CHA_2DS_2-VASc assessment and will, therefore, meet NICE's[24] criteria for requiring anticoagulation treatment.

If an estimate that 90% of all patients with AF have NVAF is applied to the company's figure for the number of patients with AF, and 78.8% are considered at risk of stroke ($CHADS_2$≥1) the ERG calculates that approximately 740,830 patients may be eligible for treatment with edoxaban in England and Wales. If an estimate that 90% of all patients with AF have NVAF is applied to the company's figure for the number of patients with AF, and 80% of these patients are considered for anticoagulation treatment according to the NICE guideline[24] (CHA_2DS_2-VASc), the ERG calculates that approximately 752,112 patients may be eligible

for treatment with edoxaban in England and Wales. Both of the ERG's estimates are higher than the company's estimate of 617,358.

2.6 Managing adverse reactions and NHS resource use

It is reported in the CS (Section 2.8) that there is no specific antidote to bleeding for people taking NOACs; however, a number of treatments are in development for this purpose.

However, it is reported in the CS, that the Summary of Product Characteristics (SPC)[37] for edoxaban recommends the use of 4-factor prothrombin complex concentrate in the event of life-threatening bleeding.

The company states that no additional costs in addition to the drug acquisition cost are anticipated.

2.7 Equality

No equality issues are identified in the CS.

2.8 Innovation

In Section 4.1 of the CS the company discusses the potential disadvantages of treatment with warfarin and the potential advantages of treatment with NOACs (Box 7).

Box 7 Treatment with warfarin vs NOACs

Warfarin has been established as the standard of care to reduce the risk of stroke in patients with AF, but it is associated with several limitations, including the following: unpredictable pharmacokinetics and pharmacodynamics; numerous drug and dietary interactions; genetic variability in metabolism response; and a narrow therapeutic window requiring frequent monitoring and dose adjustments to maintain a therapeutic level of anticoagulation.[38] The NOACs currently recommended by NICE[24] have predictable pharmacokinetics and pharmacodynamics, have minimal interactions with other drugs compared to VKAs, and do not require INR monitoring.

The ERG agrees with the comparisons made by the company between warfarin and NOACs. However, the ERG notes that, as treatment with NOACs does not require regular blood monitoring to ensure that anticoagulation treatment is optimal, there is no measure of treatment compliance. For patients who are treated with NOACs, failure to take the prescribed doses results in sub-therapeutic levels of anticoagulation.[39] Cohen[39] suggest that missing doses of NOACs may be more serious than missing doses of warfarin as NOACs have a shorter half-life than warfarin.

In Section 4.1 of the CS the company lists the potential limitations of treatment with dabigatran and rivaroxaban and the potential advantages of treatment with edoxaban (Box 8).

Box 8 Limitations of treatment with dabigatran and rivaroxaban and potential advantages of edoxaban

Dabigatran is limited by:

- twice daily dosing
- association with dyspepsia
- dabigatran capsules are not stable outside of their blister pack, so they cannot be added to any compliance aid (often done by pharmacists for patients with multiple medications to help patients remember to take them on the right day and at the right time)

Rivaroxaban is associated with several limitations:

- the need to be administered with food
- an initiation dose which differs from its maintenance dose

Edoxaban

- can be taken with or without food
- once-daily dosing
- stable outside its blister pack
- dose can be halved in specific patient groups anticipated to be at increased risk of edoxaban overexposure (i.e. patients with moderate or severe renal impairment, low body weight ≤ 60 kg or concomitant use of P-glycoprotein inhibitors)
- edoxaban is currently the only NOAC to include explicit guidance for treatment in the event of uncontrolled bleeding in its SPC[1] based on clinical data

The ERG agrees with the company's summary of limitations associated with rivaroxaban and dabigatran but notes that apixaban is also recommended as a treatment option by NICE.[31] Apixaban is taken twice daily (with or without food) and the dose, as for edoxaban, can be halved for specific patient groups.

The ERG agrees that edoxaban is the only NOAC for which specific recommendations have been made for the treatment of uncontrolled bleeding associated with treatment. However, clinical advice to the ERG is that the strategy recommended in the SPC[37] for uncontrolled bleeding is also applicable to treatment with apixaban and rivaroxaban.

The ERG notes that the relevant SPCs[40-42] state that treatment with rivaroxaban, dabigatran and apixaban can be continued during cardioversion. However, it is unclear whether treatment with edoxaban can be continued during cardioversion. The protocol for the pivotal trial for edoxaban, the ENGAGE AF-TIMI 48 trial[26] (ENGAGE) (p143) provides guidance on the procedures for patients undergoing cardioversion and states that cardioversion should be performed whilst the patient is on the study drug. The trial protocol also states (p36) that summary data were planned to be evaluated for patients undergoing cardioversion during the trial. However, there are no data presented in the CS that pertain to patients undergoing cardioversion in the ENGAGE trial.

It is reported in the CS (Section 1.6) that the PROBE[43] trial is due to complete in August 2015. The PROBE[43] trial is a randomised controlled trial (RCT) designed to evaluate the efficacy of edoxaban versus warfarin in patients undergoing cardioversion. Until the results of this trial are published, the ERG considers that the efficacy of edoxaban for patients with NVAF undergoing cardioversion is unknown.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The decision problem described in the final scope[44] issued by NICE, and the company rationale for any deviation from the scope, are presented in Section 5 of the CS and this information is reproduced in Table 3. The company reports no deviations from the scope.

Table 3 Decision problem issued by NICE (reproduced from CS)

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism	As per NICE scope	N/A
Intervention	Edoxaban tosylate	As per NICE scope	N/A
Comparator(s)	• Warfarin • Apixaban • Dabigatran etexilate • Rivaroxaban	As per NICE scope	N/A
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	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per NICE scope	N/A
Subgroups to be considered	If evidence allows, consideration will be given to subgroups defined by: • Time in therapeutic range on warfarin • Level of stroke/embolic risk	As per NICE scope	N/A
Special considerations, including issues related to equity or equality	None	N/A	N/A

N/A=not applicable.
Source: CS, Section 5

3.1 Population

The key clinical evidence submitted by the company is derived from a single RCT, the ENGAGE AF-TIMI 48 trial[26] referred to hereafter as the ENGAGE trial.

In the ENGAGE trial, patients with NVAF were randomised to receive either edoxaban (60mg or 30mg daily) or warfarin. The randomised patients all had a $CHADS_2$ ≥2 and were considered to be at moderate to high risk of stroke and SE. This means that patients at lower risk of stroke, i.e. those with a $CHADS_2$=1, were not included in the ENGAGE trial. Hence, there are no data to evaluate the efficacy and safety of edoxaban in the treatment of patients with a $CHADS_2$=1.

In support of the efficacy of edoxaban compared with warfarin in patients with NVAF who have a $CHADS_2$=1 (Section 6.10.2 of the CS), the company states that:

- hazard ratios (HRs) for the outcomes for the primary and safety endpoints were stable across all the $CHADS_2$ categories studied (2 to 6) and there is no reason to expect that the $CHADS_2$ =1 would be inconsistent with this finding
- number of events for the primary and safety outcomes and for the outcome of net clinical outcome decreased with the decrease in $CHADS_2$ category and that events for patients with a $CHADS_2$=1 would be further decreased
- overall trial results can be assumed to be generalisable to patients with a $CHADS_2$=1 as the underlying disease pathophysiology is the same across all NVAF patients regardless of $CHADS_2$ status.

The ERG is uncertain whether the company's assertion that the efficacy of edoxaban can be generalised to a patient group with a $CHADS_2$=1 is valid. However, the ERG notes that:

- the draft SPC[37] for edoxaban indicates that the anticipated marketing authorisation appears to include patients with a $CHADS_2$=1, i.e. the prevention of stroke and systemic embolism in adult patients 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 (TIA).
- during the appraisal of rivaroxaban,[30] the Appraisal Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of the ROCKET-AF[28] trial (rivaroxaban versus warfarin) would not translate to people with a lower $CHADS_2$ score (i.e. less than 2).
- NICE clinical guideline CG180[24] recommends that anticoagulation treatment should be considered for men with a CHA_2DS_2-VASc score of 1 and offered to men and women with a CHA_2DS_2-VASc score of 2 or above, taking their bleeding risk into account. The ERG considers NICE's guideline[24] encompasses patients with a lower risk of stroke (i.e. similar to a $CHADS_2$=1).

3.2 Intervention

The intervention described in the CS is edoxaban and this matches the intervention defined in NICE's scope.[44] Edoxaban is an orally active selective inhibitor of Factor Xa that inhibits thrombin generation. The inhibition of Factor Xa decreases thrombin generation and reduces fibrin formation and coagulation.

Edoxaban does not yet have a marketing authorisation in Europe. It is stated in the CS that the expected licensed indication for edoxaban is: for the prevention of stroke and systemic embolism in adult patients 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 (TIA). The expected date of a positive opinion for edoxaban from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use is February 2015 and EMA marketing authorisation is expected in May 2015. At the time that this ERG report was submitted to NICE, the EMA had not published any decision regarding edoxaban.

Edoxaban was recently (January 2015) approved[45] for use in the US by the Food and Drug Administration (FDA) to reduce the risk of stroke and SE in patients with NVAF. Its use is limited as follows: edoxaban should not be used in patients with creatinine clearance (CrCL) >95mL/min because of increased risk of ischaemic stroke (IS) compared to warfarin at the highest dose studied (60mg). Edoxaban is also approved for use in Japan for the prevention of stroke and SE in patients with NVAF.[1]

Edoxaban is formulated as film-coated tablets of 60mg, 30mg or 15mg. The recommended dose is 60mg once daily, or 30mg in specific patient groups (i.e. patients with moderate or severe renal impairment, body weight ≤60kg, concomitant use of cyclosporine, dronedarone, erythromycin, ketoconazole). Therapy with edoxaban should be continued indefinitely.

3.3 Comparators

The final scope[44] issued by NICE states that the comparators to edoxaban are warfarin, apixaban, dabigatran and rivaroxaban. In the CS, the direct evidence for the clinical effectiveness of edoxaban versus warfarin is derived from the ENGAGE trial. In the absence of any direct trial evidence comparing edoxaban with apixaban, dabigatran or rivaroxaban, the company has conducted a network meta-analysis (NMA).

3.4 Outcomes

The outcomes specified in the NICE scope[44] are stroke, SE, myocardial infarction (MI), TIA, mortality, adverse effects (AEs) of treatment including haemorrhage and health-related quality of life (HRQoL).

All of the specified clinical effectiveness outcomes are addressed in the CS and are included in the direct and indirect evidence. For the outcome of HRQoL, it is reported in the CS (Section 6.5.4) that EQ-5D data were collected during the ENGAGE trial as part of an economic sub-study. The findings of the study were made available to the ERG via the clarification process. However, the results are only utilised in the cost effectiveness section as a sensitivity analysis.

3.5 Economic analysis

As specified in the NICE scope,[44] the cost effectiveness of treatments is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. The analysis is based on a lifetime horizon (assuming a maximum of 30 years base from a starting age of 71 years. Costs are considered from an NHS perspective.

3.6 Subgroups to be considered

Clinical and cost effectiveness evidence is provided in the CS (Section 6.5 and 7.9 respectively) for the efficacy of edoxaban in both of the subgroups identified in the NICE scope,[44] i.e. time in therapeutic range (TTR) on warfarin and level of stroke or thromboembolism risk.

3.7 Other relevant factors

No equality issues were identified in the CS. The ERG is unaware of any Patient Access Scheme application submitted by the company.

4 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical evidence submitted by the company in support of edoxaban for the prevention of stroke and SE in people with NVAF.

4.1 Critique of the methods of review(s)

The company conducted two main systematic reviews of clinical effectiveness evidence. One systematic review was designed to identify RCT evidence relevant to the efficacy and safety of the use of edoxaban and relevant comparators (warfarin, rivaroxaban, dabigatran and apixaban) in the prevention of stroke and SE in people with NVAF. The second systematic review was designed to identify non-RCT evidence relevant to the efficacy and safety of edoxaban in the prevention of stroke and SE in people with NVAF.

The methods used by the company to identify relevant articles for inclusion in the systematic reviews are reported in the CS (Section 6 and Appendix 2 [RCT evidence] and Appendix 6 [non-RCT evidence]).

4.1.1 Searches

Searches for evidence from randomised controlled trials

The searches completed by the company are described in Section 6.1, 7.1 and 10.2 of the CS. They were conducted in the following databases:

- Medline (OvidSP) – 9th May 2014
- Medline in process (OvidSP) – 9th May 2014
- Embase (OvidSP) – 9th May 2014
- The Cochrane Library

The CS does not specify if all the Cochrane Library databases (CDSR, CENTRAL, HTA, DARE) were searched, but as no specific database is mentioned the ERG assumes that they were all included.

The ERG considers the company's search strategies to be comprehensive and relevant MeSH and free text terms were used. The search strategies focus on the condition of AF and do not include any stroke or SE search terms. The ERG is of the opinion that the inclusion of stroke or SE terms would render the searches more inclusive. The search strategy for RCT evidence included an RCT filter and a human filter, an approach that the ERG considers to be correct and relevant. The company also searched the websites of the European Society of Cardiology, the American Heart Association and the American College of Cardiology with a date limit of 2012-2014. No other grey literature sites were searched.

The company used the search as described above for the NMA comparisons and the AE search. The details of these are presented in Section 6.1, 6.2 and 10.2 of the CS.

The company completed a similar search for non-RCT evidence. This search included a good quality observational studies search filter. The same grey literature sites already described were also searched.

The ERG believes the company's searches to be comprehensive and of a good standard. To be more inclusive, the company could have included more grey literature websites and searched all of the databases in the Cochrane Library. The ERG carried out a comprehensive search and no additional relevant papers were found.

4.1.2 Inclusion criteria

The study selection process used by the company is presented in Section 6.2 of the CS. Table 4 lists the inclusion and exclusion criteria applied to studies in the selection of RCTs. Similar inclusion criteria were applied to studies in the selection of non-RCT evidence (but with no restriction in terms of eligible comparators). The ERG is satisfied that the eligibility criteria are relevant to the aims of the company's systematic reviews.

Table 4 Eligibility criteria for systematic review of RCTs

	Inclusion	**Exclusion**
Population	Adults (≥18 years) with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism	<18 years, patients with valvular/rheumatic AF
Interventions	• Warfarin • Apixaban • Rivaroxaban • Dabigatran • Edoxaban	Studies not investigating edoxaban or relevant comparator
Outcomes	• Stroke (all-cause, ischaemic, haemorrhagic, disabling, fatal) • Systemic embolism • Myocardial infarction • Transient ischaemic attack • Mortality (All-cause, cardiovascular) • Major / minor bleeding • Clinically relevant non-major bleeding • Major gastrointestinal bleeding • Fatal bleeding • Intracranial bleeding • Life-threatening bleeding	Studies not reporting the outcomes listed in the scope
Study design	RCTs	Non-RCT (identified by separate search)

Source: CS, Table 3

4.2 Results of the company's searches

The company's search for RCT evidence identified 4712 non-duplicate records from electronic databases and 101 of these were selected for full-text screening. A further 27 articles were identified from conference proceedings. Of the identified articles, four[26,46-48] met the inclusion criteria for the systematic review of the clinical effectiveness of edoxaban. A further three articles[25,27,28] met the inclusion criteria for the NMA. The company's PRISMA diagram outlining the inclusion process is presented in the CS (Figure 61 of Appendix 2).

The company's search for non-RCT evidence identified 45 non-duplicate records from the electronic databases that were interrogated. No records met the company's inclusion criteria. The company's PRISMA diagram outlining the inclusion process is presented in the CS (Figure 62 of Appendix 6).

4.3 Identified studies

Four RCTs[26,46-48] were identified by the company as being relevant to the systematic review for the clinical effectiveness of edoxaban, including the ENGAGE study.

However, three of the RCTs[46-48] were then excluded from the systematic review. The company's rationale for excluding the three trials[46-48] is not explicitly stated in the CS. However, the ERG assumes that the trials were excluded as they were all phase II dose-ranging trials that compared differing doses of edoxaban with warfarin and were of only 3 months duration. The ERG notes that specific exclusion criteria relating to design and duration of RCTs were not listed in trial eligibility criteria described in Table 3 of the CS. The ERG considers it appropriate that the three phase II trials were excluded from the company's systematic review. The ERG is not aware of any other studies relevant to the present appraisal.

The key design features of the three RCTs[46-48] that were excluded from the systematic review are described in the CS and a summary of results of the largest of the trial[47] (n=1146) is reported in the Appendices of the CS (Section 10.14).

The CS focuses on the ENGAGE trial. This trial compares edoxaban (60mg or 30mg daily) with warfarin in a population of patients with NVAF and has a median follow-up of 2.8 years.

4.3.1 Critique of data extraction

It is reported in the Appendices of the CS (Section 10.6.7) that the identified study was independently assessed by two reviewers and any disagreements were resolved by a third party. Relevant data were extracted by one reviewer and checked by a second reviewer. Any inconsistencies were resolved through discussion. The ERG considers this to be good standard practice.

4.3.2 Quality assessment

The company conducted a quality assessment of the included study using the checklist recommended for RCTs published in NICE's Guide to the Methods of Technology Appraisal.[49]

4.3.3 Evidence synthesis

The evidence for the clinical effectiveness of edoxaban versus warfarin was derived from the ENGAGE trial. The results of the ENGAGE trial are presented narratively. To compare the clinical effectiveness of edoxaban with the other comparators stated in the NICE scope[44] (dabigatran, rivaroxaban and apixaban) the company conducted a NMA. The ERG's critique of the company's NMA is presented in Section 4.6 of this ERG report.

4.4 Critique of the direct evidence: ENGAGE

4.4.1 Characteristics of ENGAGE study

The characteristics of the ENGAGE trial are summarised in Table 5. The study was conducted internationally (including UK centres) and randomised 21,105 patients in a 1:1:1 ratio to receive either 30mg edoxaban once daily (or 15mg once daily for subjects requiring dose adjustments), 60mg edoxaban once daily (or 30mg once daily for subjects requiring dose adjustments), or warfarin (titrated to an INR within the range of 2.0 to 3.0). The company focuses on the edoxaban 60mg/30mg dose reduction (DR) arm in their submission, since this arm represents the expected licensed dosing. This ERG report also focuses on the high-dose (60mg/30mg DR) edoxaban group, referred to as 'edoxaban'.

Randomisation was stratified according to $CHADS_2$ risk score and edoxaban dose adjustment requirements. Inclusion and exclusion criteria for the trial are provided in the CS (pp45-47) and are presented in Appendix 1 of this ERG report. Only patients with a $CHADS_2$ ≥2 (moderate to high risk) were eligible for inclusion in the trial, and the ERG notes that the trial therefore excludes patients who are at a lower risk of stroke ($CHADS_2$=1). The ERG is satisfied that the remaining inclusion and exclusion criteria employed by the company are reasonable.

The ERG considers that the ENGAGE study is well-designed and conducted. A large number of patients were recruited to the study and the length of trial follow-up means that the collected data are mature and allow valid conclusions to be drawn.

Table 5 Key characteristics of the ENGAGE trial

Category	ENGAGE trial characteristics
Study objective	To demonstrate non-inferiority of a OD, high-dose of edoxaban (60mg / 30mg DR) and also a OD low-dose of edoxaban (30mg / 15mg DR) compared with warfarin (INR target range 2.0–3.0), for the prevention of stroke and SE in patients with NVAF with a CHADS2 ≥2 or more
Location	1393 sites in 46 countries (31 UK centres)
Design	Phase III, event-driven, randomised, double-blind, double-dummy, parallel-group, multi-centre, multi-national, non-inferiority study
Duration of study	This was an event-driven study. All subjects were to be 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
Method of randomisation	Subjects were randomly assigned to 1 of 3 treatments in a 1:1:1 ratio via an Interactive Response Technology System. Randomisation stratified by CHADS2 score (stratum 1: CHADS2 score 2 and 3; stratum 2: CHADS2 score 4, 5, and 6) and edoxaban dose adjustment requirements (for factors such as an estimated creatinine clearance of 30 to 50 ml per minute, a body weight of 60 kg or less or a concomitant use of specific P-gp inhibitors (verapamil, quinidine, or dronedarone)
Method of blinding (care provider, patient and outcome assessor)	Study drugs were packaged using double-dummy blinding with placebo tablets identical in appearance and packaging to that of active drug substance. Investigators received a “sham” INR value for subjects randomised to edoxaban in order to maintain blinding. During double-blind treatment and follow-up, the investigator, study site personnel, patients, sponsor and sponsor’s representatives were blinded to the identity of the randomised drug assignment
Interventions, N randomised	30 mg edoxaban OD (or 15mg OD for subjects requiring dose adjustments) plus placebo-to-match warfarin, N=7034 60 mg edoxaban OD (or 30mg OD for subjects requiring dose adjustments) plus placebo-to-match warfarin, N=7035
Comparators, N randomised	Warfarin (titrated to INR between 2-3) plus placebo-to-match edoxaban, N=7036
Assessments	In the first month of treatment, visits occurred at days 1, 8, 15, and 29. Subsequently visits occurred every month until the end of the study
Primary efficacy endpoint	Time to the first adjudicated stroke (ischaemic or haemorrhagic) or systemic embolic event
Principal safety endpoint	Adjudicated major bleeding during treatment, in line with the modified International Society on Thrombosis and Haemostasis definition
Duration of follow-up	As the study 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]

DR=dose reduction; INR=International Normalised Ratio; NVAF=non-valvular atrial fibrillation; OD=once daily; P-gp=P-glycoprotein; SE=systemic embolism
Source: CS, Table 7

4.4.2 Participant characteristics

The characteristics of patients randomised to edoxaban 60mg per day and the warfarin arms arm of the ENGAGE trial are provided in Table 6.

The company comments that demographic and baseline characteristics are well-balanced across the trial; the ERG agrees with this statement. The ERG also notes that 254 patients (1.8%) from 31 UK treatment centres participated in the ENGAGE trial.

The ERG considers that the age and baseline characteristics of the trial participants match those of patients seen in clinical practice in England and Wales; although, as noted, patients at lower risk of stroke (i.e. $CHADS_2$=1) are not represented in the trial.

Table 6 Baseline characteristics of the ENGAGE patient population

Characteristic	Edoxaban (N=7035)	Warfarin (N=7036)
Median age (years) Interquartile range (years)	72 64-78	72 64-78
Female sex, n (%)	2669 (37.9)	2641 (37.5)
Region, n (%) North America Latin America Western Europe *United Kingdom* Eastern Europe Asia–Pacific and South Africa	 1559 (22.2) 886 (12.6) 1079 (15.3) *121 (1.7)* 2383 (33.9) 1128 (16.0)	 1562 (22.2) 888 (12.6) 1078 (15.3) *133 (1.9)* 2381 (33.8) 1127(16.0)
Paroxysmal atrial fibrillation, n (%)	1753 (24.9)	1778 (25.3)
Qualifying risk factor, n (%) Aged ≥75 years Prior stroke or TIA Congestive heart failure Diabetes mellitus Hypertension requiring treatment	 2848 (40.5) 1976 (28.1) 4097 (58.2) 2559 (36.4) 6591 (93.7)	 2820 (40.1) 1991 (28.3) 4048 (57.5) 2521 (35.8) 6588 (93.6)
$CHADS_2$ score, n (%) 0 1 2 3 4 5 6 2-3 4-6 Mean (SD)	 0 (0.0) 5 (<0.1) 3235 (47.4) 2182 (31.0) 1125 (16.0) 402 (5.7) 86 (1.2) 5417 (77.0) 1613 (22.9) 2.8±1.0	 1 (<0.1) 4 (<0.1) 3335 (47.4) 2105 (29.9) 1075 (15.3) 426 (6.1) 90 (1.3) 5440 (77.3) 1591 (22.6) 2.8±1.0
Renal function, creatinine clearance CrCL (mL/min), n (%) <30 30 - ≤50 >50 - <80 ≥80	 70 (1.0) 1287 (18.3) 2985 (42.4) 2612 (37.1)	 51 (0.7) 1297 (18.4) 3030 (43.1) 2595 (36.9)
Patients dose-adjusted (or placebo) at randomisation, n (%) CrCl ≤50 mL/min Weight ≤60 kg Use of verapamil or quinidine	1784 (25.4) 1379 (19.6) 684 (9.7) 258 (3.7)	1787 (25.4) 1361 (19.3) 701 (10.0) 243 (3.5)
Previous use of VKA for ≥60 days, n (%)	4140 (58.8)	4138 (58.8)
Medication at time of randomisation, n (%) Aspirin Thienopyridine Amiodarone Digoxin or digitalis preparation	 2070 (29.4) 174 (2.5) 866 (12.3) 2078 (29.5)	 2092 (29.7) 164 (2.3) 827 (11.8) 2176 (30.9)

CrCl=creatinine clearance; ITT=intent-to-treat; SD=standard deviation; TIA=transient ischaemic attack; VKA=vitamin K antagonist
Source: CS, Table 8

4.4.3 Statistical approach

Information relevant to the statistical approach taken by the company to analyse data from the ENGAGE trial has been extracted from the CS, the clinical study report (CSR)[50] and the statistical analysis plan (SAP).[51] The SAP was provided as part of the trial protocol.[51]

ENGAGE trial data analysis sets

The company performed analyses for various populations, for two observational periods. Definitions of these analysis sets are provided in Table 7.

Table 7 Definitions and summary of ENGAGE trial analysis sets

Population	Definition
Intent-to-treat (ITT) analysis set	All randomised subjects whether or not they received a single dose of randomised study drug. Analyses were based on the randomised treatment even if a subject inadvertently received the incorrect drug or dosage or had his/her edoxaban dose adjusted (decreased/increased) 1 or more times during the study. The reference date for consideration of endpoints was the date of randomisation
Modified intent-to-treat (mITT) analysis set	All randomised subjects who received at least 1 dose of randomised study drug. Analyses were based on the randomised treatment even if a subject inadvertently received the incorrect drug or dosage or had his/her edoxaban dose adjusted (decreased/increased) 1 or more times during the study. The reference date for consideration of endpoints was date of the initial dose of study drug
Per protocol (PP) analysis set	All randomised subjects who received at least 1 dose of randomised study drug and did not have any major protocol violations. Subjects excluded from the per protocol analysis set because of major protocol violations were identified by a documented process prior to unblinding. Analyses were based on the randomised treatment even if a subject inadvertently received the incorrect drug or dosage or had his/her edoxaban dose adjusted (decreased/increased) 1 or more times during the study. The reference date for consideration of endpoints was the date of the initial dose of study drug
Safety analysis set	All randomised subjects who received at least 1 dose of randomised study drug. Analyses were based on the randomised treatment, even if the subject's edoxaban dosage was adjusted after randomisation, unless a subject inadvertently received the incorrect drug or dosage during the entire study, in which case, the subject was grouped according the treatment actually received. The reference date for consideration of endpoints was date of the initial dose of study drug
Observation period	**Definition**
On-treatment period	The time period the subject was taking study drug and up to 3 days after their last dose. The rationale for the 3 days following the last dose was based on 3 days being approximately 5 times the $t_{1/2}$ of edoxaban. However, for subjects who were receiving study drug up until the day of the Common Study End Date (CSED*) visit, the subject was not considered at risk after the CSED Visit for primary statistical analyses
Overall study period	The time from the reference date (randomisation date or initial dose of study drug date) to the CSED visit

CSED=Common Study End Date - this is the actual calendar date for the projected point in time when the study will have accrued the required number of primary endpoint events
Source: CS, Table 10

Primary efficacy endpoint: time to the first adjudicated stroke or systemic embolism

A hierarchical testing order was implemented for the primary efficacy analysis to prevent spurious results from multiple testing. A non-inferiority test using the modified intent-to-treat (mITT) population for the on-treatment period was pre-specified in the SAP. 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. Analyses were performed using the Cox proportional hazards model including treatment groups and the randomisation stratification factors (dichotomised $CHADS_2$ score and dichotomised dose-adjustment factor) as covariates.

The ERG is satisfied that adherence to the hierarchical testing order would reduce the likelihood of false positive results occurring as a result of multiple testing. As part of the clarification process, the ERG asked for justification for the choice of mITT population and on-treatment period for the primary efficacy analysis. The company responded that it is a regulatory requirement to conduct a non-inferiority analysis in an on-treatment population. Analysis of studies with long follow-up periods have shown that as patients discontinue treatment over time, the treatment effect is reduced, and the on-treatment analysis set provides a clearer indication of whether an intervention is truly non-inferior to the relevant comparator. . As the on-treatment period is the period of time for which patients were taking the study drug, the mITT population and the ITT population on-treatment results are identical; any patients who may have been included in the ITT population but not the mITT as they never received the study drug would not have results for the on-treatment period. The ERG agrees that the company had valid reasons for performing a mITT on-treatment analysis.

Secondary efficacy endpoints

The following secondary efficacy endpoints were pre-specified in the trial SAP:

- Time to first occurrence of composite of stroke, SE and cardiovascular (CV) mortality
- Time to first occurrence of MACE (non-fatal MI, non-fatal stroke, non-fatal SE, and death due to CV cause or bleeding)
- Time to first occurrence of composite of stroke, SE, and all-cause mortality
- Adjudicated composite endpoint of stroke, SE, major bleeding, and all-cause mortality
- Adjudicated composite endpoint of disabling stroke, SE, life-threatening bleeds/ischaemic cranial haemorrhage (ICH), and all-cause mortality
- Investigator reported venous thromboembolism (VTE), including both pulmonary embolism (PE) and deep vein thrombosis (DVT), as well as each individual component

- Composite of adjudicated stroke, adjudicated SE, and investigator reported TIA, as well as each individual component
- Incidence of hospitalisation
- Severity of strokes

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 of type I errors (i.e. falsely rejecting the null hypothesis of no difference between treatment groups) occurring is likely to be high. The ERG considers that it would be more appropriate to pre-specify a single method of analysis to apply to all secondary outcomes.

Analyses of the secondary outcomes used the randomisation stratification factors (dichotomised $CHADS_2$ score and dichotomised dose-adjustment factor) as covariates if a proportional hazards model was applied.

The company provides a full list of outcome measures and relevant definitions employed in the ENGAGE trial (CS, Table 9). As part of the clarification process, the ERG asked the company to confirm whether specific analyses of secondary outcomes (i.e. using various analysis sets and observation periods) were pre-specified, and to provide the results of several pre-specified analyses for the secondary endpoints. The ERG is satisfied that all outcomes were pre-specified in the trial SAP by the company and notes that all outcomes were fully reported in the CSR and CSR appendices.

ERG assessment of statistical approach

A summary of the checks made by the ERG in relation to the statistical approach adopted in the ENGAGE trial is provided in Table 8.

Table 8 ERG assessment of statistical approach used to analyse ENGAGE trial data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CS (pp54-55)	The ERG is satisfied that the company's pre-specified sample size calculation is correct
Protocol amendments	Provided in the appendices to the CSR (Appendix 16.1.1)	The ERG notes that the changes detailed in the protocol amendments were unlikely to have been driven by the results of the trial and are therefore not a cause for concern
Subgroup analyses for the primary outcome	The CS lists the following pre-specified subgroup analyses: • Age (≥75 vs <75) • Gender (M vs F) • $CHADS_2$ scores (≤ 3 vs >3) • Dose adjustment factor, (dose adjusted: yes/no) and also by: • Body weight ≤60 vs >60kg, • Calculated CrCL 30-50 vs >50 mL/min • Concomitant use of Verapamil/Quinidine at randomization (yes/no) • VKA-Naïve vs VKA-experienced • Geographic region/country • Race • Ethnicity (Hispanic/Latino vs Not) (USA subjects only) • Concomitant diseases (prior stroke/TIA: yes/no; prior CHF: yes/no; prior hypertension: yes/no; prior diabetes: yes/no) • Concomitant aspirin use (yes/no) • Concomitant use of lipid lowering therapy (yes/no) • Concomitant ACE or ARB inhibitors (yes/no) • Concomitant amiodarone or dronedarone (yes/no) • Concomitant diuretics (yes/no) • Centre-level INR Percent Time in Therapeutic Range (INR-TTR) for warfarin subjects (e.g. <60% vs ≥60%, <median vs ≥median)	The SAP clearly states that subgroup analyses would not be limited to the pre-specified list. However, the majority of the subgroup analyses presented in the CS (CS, Figure 7) were pre-specified The ERG's only concern relating to the subgroup analyses is the post-hoc analysis for the Western Europe region (see section 4.5)
Sensitivity analyses for the primary outcome	The following sensitivity analyses were pre-specified in the protocol: • PP analysis set and on-treatment period • PP analysis set and overall study period • mITT analysis set and overall study period	The ERG is satisfied that the results of all sensitivity analyses are provided in the CSR

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blockers; CHF=congestive heart failure; CrCl=creatine clearance; CS=company submission; CSR=clinical study report; ERG=Evidence Review Group; INR=international normalised ratio; ITT=intent-to-treat; mITT=modified intent-to-treat; PP=per protocol; SAP=statistical analysis plan TIA=transient ischaemic attack; TTR=time in therapeutic range; VKA=vitamin K antagonist; ERG=Evidence Review Group; SAP=statistical analysis plan
Source: CS and ERG comment

4.4.4 Quality assessment

The company conducted a quality assessment of the ENGAGE trial using the criteria recommended by NICE in the Guide to the Methods of Technology Appraisal.[49] The results of the assessment are presented in Table 9. The ERG agrees with the company that the study is of good quality.

Table 9 Quality assessment results for the ENGAGE trial

Assessment criteria	ENGAGE trial
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

*Outcomes for patients undergoing cardioversion are described in the trial protocol; these data are not presented in the CS
Source: CS, Table 12

4.5 Results from the ENGAGE trial

4.5.1 Treatment overview

The company provides a summary of exposure to study drug and overall study period follow-up for patients in the ENGAGE trial according to treatment group (Table 13 of the CS). The median follow-up across both groups was 904 days (2.8 years), with patients receiving the study drug more than 80% of the time during the study period in all treatment groups. The company comments that patient-year exposure on study drug and patient-year follow-up were similar in the edoxaban and warfarin groups; the ERG agrees with the company's observation and further notes that only one patient was lost to follow-up.

A summary of study drug discontinuations throughout the ENGAGE trial is provided in the CS (Table 14). The percentages of patients who discontinued treatment were comparable between the edoxaban and warfarin arms (34.4%, and 34.5%, respectively). Furthermore, the percentages of discontinuations due to AEs were also similar across treatment arms (17.2% in the edoxaban arm, and 16.7% in the warfarin arm).

Compliance was assessed in the edoxaban arm of the trial by calculating the percentage of doses taken (≥80% versus <80%) at each compliance visit (every 3 months). At least 98% of subjects in the edoxaban arm were more than 80% compliant at all compliance visits. Compliance in the warfarin group was assessed by the percentage of time subjects' INR was within the range of 2.0 to 3.0; the median (TTR 2-3) was 68.4% (mean 64.9%). The times spent in various INR ranges for subjects in the warfarin group are provided in Table 15 of the CS (p63).

4.5.2 Datasets analysed

The numbers of patients in each of the analysed datasets from the ENGAGE trial are provided in Table 10.

Table 10 Overview of the ENGAGE trial analysis sets

Analysis set	**Warfarin n (%)**	**Edoxaban n (%)**
ITT (randomised)	7036 (100.0)	7035 (100.0)
Never received study drug	24 (0.3)	23 (0.3)
mITT (received at least one dose of study drug)	7012 (99.7)	7012 (99.7)
Dosed but excluded from PP analysis	19 (0.3)	17 (0.2)
PP analyis	6993 (99.4)	6995 (99.4)
Safety	7012 (99.7)	7012 (99.7)

ITT=intent-to-treat (randomised subjects); mITT=modified intent-to-treat (treated subjects); PP=per protocol

4.5.3 Primary efficacy analysis

The results of the primary efficacy analysis are presented in Table 11. The HR provided for the mITT population for the on-treatment period suggests that edoxaban is non-inferior to warfarin in terms of preventing stroke or SE (HR=0.79; 95% CI 0.63 to 0.99, p<0.001).

The company also provides results for the mITT population for the overall study period as these are the data inputs for the NMA. The results of the non-inferiority test for this population and observation period also demonstrate that edoxaban is non-inferior to warfarin, suggesting that the results of the primary efficacy analysis are robust.

As the non-inferiority test provided a significant result, the next step of the hierarchical statistical testing plan was implemented. A superiority test was performed for the ITT population and the overall study period, resulting in a non-significant outcome (HR=0.87; 95% CI 0.73 to 1.04, p=0.08). Therefore, there is no

evidence to suggest that edoxaban is superior to warfarin in terms of preventing stroke or SE.

The company presents a p-value for superiority for the mITT on-treatment population and the observation period (p=0.02). However, the ERG considers that the results of this test for superiority should be treated with caution as the test for superiority was not pre-specified as part of the hierarchical statistical testing order.

Table 11 Primary efficacy results from the ENGAGE trial: adjudicated primary endpoint (stroke or SE)

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

[a]Not pre-specified
CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; mITT=modified intent-to-treat; SE=systemic embolism
Source: CS, Table 17

The company provides a Kaplan-Meier (K-M) plot for the primary efficacy outcome (CS, Figure 6). As the company used a Cox proportional hazards model for this analysis, the ERG considered it important to investigate whether the assumption of proportional hazards holds across treatment groups. The ERG requested additional data as part of the clarification process in order to conduct exploratory analyses of the proportional hazards assumption. These exploratory analyses focused on considering the assumption of proportional hazards for subcomponents of the primary outcome, haemorrhagic stroke (HS), IS and SE. The results of the ERG exploratory analyses indicate that for HS (

Figure 2), there is clear evidence that the assumption of proportional hazards is violated; the hazard trend in the warfarin arm changes sharply at about 6 months, but the edoxaban trend is smooth throughout. This violation is confirmed by the Lee & Pirie rank sum test ($p<0.0002$).

For IS, there is minimal difference in treatment effect across the two arms of the trial, (Appendix 2). Therefore, the treatment effect in favour of edoxaban demonstrated for the primary outcome is wholly the result of treatment benefit for HS+SE. The cumulative hazard plot indicates approximately constant hazards in both trial arms for SE (Appendix 2). However, as the HS difference between treatment groups is much larger than for SE (in terms of the number of patients), it is likely that the proportional hazards assumption will not be valid for the primary outcome either. Therefore, the ERG considers that the HR for the primary outcome is not robust.

[redacted]

Figure 2 Cumulative hazard plot for haemorrhagic stroke; ENGAGE trial

The assessment of the proportional hazards assumption is discussed further in Section 4.8.4 in relation to the NMA.

4.5.4 Components of the primary endpoint and subcomponents of stroke

The company presents results for the analyses of the components of the primary endpoint (stroke and SE) and subcomponents of stroke (IS and HS) for the mITT analysis set and the on-treatment period (CS, Table 18), for the ITT analysis set and the overall study set (CS, Table 19), and for the mITT analysis set and the overall study period (CS, Table 20). The ERG is concerned about the large number of analyses performed for these endpoints as there is no adjustment for multiplicity. Performing a large number of statistical tests increases the likelihood of significant results occurring by chance. For this reason, the ERG has chosen to focus only on one analysis for the components of the primary endpoint and subcomponents of stroke. The ERG's choice is the analysis conducted using the mITT population and the overall study period, as these results are utilised in the NMA. Results from this analysis are summarised in

Table 12. Regarding the components of the primary outcome: edoxaban was shown to be superior to warfarin for HS (p=0.001). There was no statistically significant difference between edoxaban and warfarin for any other listed component or subcomponent. The results were similar for the mITT population, on-treatment period analysis and the ITT population analysis

Table 12 Stroke and SE results from the ENGAGE trial (mITT analysis set, 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**
Any stroke	316 (1.69)	278 (1.48)	0.87 (0.74 to 1.02) p=0.09
Haemorrhagic stroke	90 (0.48)	49 (0.26)	0.54 (0.38 to 0.77) p=0.001
Ischaemic stroke	234 (1.25)	233 (1.24)	0.99 (0.82 to 1.18) p=0.90
Disabling stroke	57 (0.30)	53 (0.28)	0.92 (0.64 to 1.34) p=0.67
Fatal stroke	86 (0.45)	79 (0.41)	0.91 (0.67 to 1.24) p=0.56
SEE	23 (0.12)	14 (0.07)	0.60 (0.31 to 1.17) p=0.14
First TIA	95 (0.50)	106 (0.56)	1.11 (0.84 to 1.47)

			p=0.45

CI=confidence interval; HR=hazard ratio; mITT=modified intent-to-treat; SE=systemic embolic; TIA=transient ischaemic attack. Source: CS, Table 20

4.5.5 Subgroup analyses: primary efficacy endpoint

The company provides the results of tests for interaction for several subgroup analyses of the primary efficacy endpoint (CS, Figure 7). These analyses were performed using the mITT population and the overall study period. The tests for interaction indicate whether patients in different subgroups experience significant differences in treatment effect.

The company states that the subgroup analyses demonstrate consistency of treatment effect across major subgroups. The ERG agrees that, for the majority of subgroups, the treatment effect appears to be consistent. Characteristics shown to have a significant effect on the efficacy of edoxaban in comparison to warfarin include VKA use at randomisation (efficacy of edoxaban was reduced in patients who had used a VKA at randomisation, p=0.0253), type of AF (efficacy of edoxaban was reduced in patients with paroxysmal AF, p=0.0416) and centre level TTR (cTTR) (efficacy of edoxaban was reduced in patients with cTTR ≥60%, p=0.0361). However, these results were shown to be non-robust as the significance did not hold for the mITT population and on-treatment period analysis. Using the ITT population and overall study period dataset, VKA use was shown to have a significant interaction effect. However, no significant interaction effect was found for type of AF or cTTR.

4.5.6 Subgroup analysis: renal function

The results of the subgroup analyses carried out by the company suggest that renal function, as measured by level of creatine clearance (CrCl), has a significant impact on the efficacy of edoxaban in comparison to warfarin (p=0.0042). This result was shown to be consistent across analysis sets; a significant effect was also observed for the mITT population and on-treatment period (p=0.0002) and for the ITT population and overall study period (p=0.0039).

The HRs for stroke or SE were 0.86 (95% CI 0.63 to 1.17) and 0.68 (95% CI 0.54 to 0.85) for edoxaban versus warfarin for patients with CrCl of ≥30 to ≤50 mL/min and >50 to <80 mL/min, respectively, indicating that the observed likelihood of a primary outcome event occurring was higher in the warfarin group than in the edoxaban group. However, the HR for patients with normal renal function (CrCL ≥80 mL/min) was 1.31 (95% CI 0.96 to 1.79), demonstrating that the observed likelihood of a

primary outcome event occurring was higher in the edoxaban group than in the warfarin group.

The company states that annualised event rates for the primary outcome in the edoxaban arm were similar across normal renal function and mild renal impairment subgroups (1.06%/year and 1.07%/year, respectively), but differed across the same groups of patients treated with warfarin (0.76%/year and 2.0%/year, respectively). The company states that this magnitude of difference in the warfarin group has not been observed in recent NOAC studies.[25,27,28] For the edoxaban treatment group, the company suggests that the event rate in the mild renal impairment subgroup should have been higher than in the normal renal function subgroup, due to the difference in median $CHADS_2$ score at baseline (2.9 and 2.6, respectively). The company proposes that the combination of the inexplicably low event rate in the warfarin arm amongst normal renal function patients and the unexpectedly low event rate in the edoxaban arm amongst the mild renal impairment patients may have been the reason for the statistically significant subgroup difference.

The company also highlights the fact that lack of stratification using the three categories of CrCl may be an explanation for the subgroup differences. When testing for subgroup differences between the dichotomous categories of CrCl (which were used for stratification of randomisation), the test for interaction was no longer statistically significant.

The ERG sought clinical advice as to whether renal function across the three categories of CrCl may cause subgroup differences in the efficacy of edoxaban in comparison to warfarin. The clinical advice received by the ERG suggested that levels of CrCl may have an impact on treatment efficacy as impaired renal function is an independent predictor of stroke. The ERG considers it important to highlight 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 is 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 acknowledges that the company presents reasonable arguments that suggest that the detected subgroup differences may be spurious results. Therefore, the ERG concludes that the results of this subgroup analysis should be interpreted with caution.

4.5.7 Subgroup analysis: centre-level time in therapeutic range

The results of the subgroup analyses by cTTR are provided in Table 13 of this ERG report. The company presents results for the mITT population and the overall study period; the ERG believes it is appropriate to focus on the results from this analysis set as it is used in the NMA performed for patients in the cTTR ≥60% subgroup.

The results of the subgroup analysis suggest 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). However, as previously mentioned, 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.

Table 13 Primary efficacy (stroke or SE) results from the ENGAGE trial by cTTR (mITT analysis set and overall study period)

Stroke or SE	Warfarin (N=7012) n(%/year)	Edoxaban (N=7012) n (%/year)	Edoxaban vs warfarin HR (95% CI)	p-value for interaction
cTTR >66.4%	142 (1.54)	125 (1.40)	0.91 (0.72 to 1.16)	0.5159
cTTR ≤66.4%	195 (2.07)	159 (1.70)	0.82 (0.67 to 1.02)	
cTTR ≥60%	227 (1.62)	208 (1.55)	0.96 (0.80 to 1.16)	0.0361
cTTR <60%	110 (2.36)	76 (1.57)	0.66 (0.50 to 0.89)	
First cTTR quartile (≤57.7%)	84 (2.32)	65 (1.74)	0.74 (0.54 to 1.03)	0.5028
Second cTTR quartile (>57.7% to ≤66.4%)	111 (1.91)	94 (1.67)	0.88 (0.67 to 1.16)	
Third cTTR quartile (>66.4% to ≤73.9%)	92 (1.68)	70 (1.36)	0.82 (0.60 to 1.12)	
Fourth cTTR quartile (>73.9%)	50 (1.34)	55 (1.47)	1.08 (0.74 to 1.59)	

CI=confidence interval; cTTR=centre-level time in therapeutic range; HR=hazard ratio; mITT=modified intent-to-treat; SE=systemic embolism
Source: CS, Table 24

4.5.8 Subgroup analysis-risk of stroke (as defined by the $CHADS_2$ score)

The HRs by each $CHADS_2$ score are provided in the CS (Table 25). The company states that the HRs are stable and non-inferior across $CHADS_2$ scores of 2 to 6. Considering the presented HRs and the non-significant p-value for interaction for dichotomised $CHADS_2$ scores (CS, Figure 7, p77), the ERG agrees that treatment effect is stable across $CHADS_2$ scores of 2 to 6.

4.5.9 Post-hoc analysis for Western Europe region

[redacted]

[redacted]

[redacted] The company conducted an alternative post-hoc analysis to estimate the treatment effect of edoxaban in comparison to warfarin in patients from the European Economic Area and Switzerland. The estimate of treatment effect for the primary outcome from this post-hoc analysis favoured edoxaban over warfarin (HR=0.92; 95% CI 0.69 to 1.22).

The ERG is of the opinion 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.

4.5.10 Secondary efficacy analysis

The company presents results for the analyses of the secondary outcomes. The relevant tables in the CS are:

- Table 21 for the mITT analysis set and on-treatment period
- Table 22 for the ITT analysis set and overall study set
- Table 23 for the mITT analysis set and overall study period

To reduce the chance of emphasising false positive results the ERG has chosen to present only one analysis for secondary outcomes, namely the analysis conducted using the mITT population and the overall study period, as estimates from this analysis are used in the NMA. The results from this analysis are provided in Table 14 and show that edoxaban was found to be superior to warfarin in terms of: the composite outcome of stroke, SE or death from CV cause; MACE; the composite outcome of stroke, SE or death; all-cause death and death from CV cause.

Table 14 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

4.6 Adverse events

The company has provided comprehensive analyses of AEs from the ENGAGE trial (CS, Section 6.9). The analyses include bleeding events experienced in the safety analysis set (SAS), other AEs in the SAS, and net clinical outcome in the SAS. The SAS is defined as all patients in the trial who received at least one dose of a study drug and, the company states, is equivalent to the mITT analysis set for the on-treatment period.

An analysis of major bleeding outcomes in a range of subgroups is presented in the CS, as are the safety results for the two subgroups specified in the NICE scope:[44] TTR and safety by risk of stroke (defined by $CHADS_2$ scores).

In addition to the results from the ENGAGE trial, the CS includes a summaries of safety data derived from: i) a 6 month post-marketing study of the safety of edoxaban in Japan in patients with VTE[52] and ii) safety data from an RCT that compares edoxaban with warfarin in patients with acute symptomatic DVT or PE.[53] These are presented in Appendix 3 of this ERG report. These company reports that the safety data were consistent with the known safety profile of edoxaban and did not identify any unforeseen safety concerns.

4.6.1 ENGAGE trial adverse events

Adjudicated bleeding events reported in the ENGAGE trial are presented in Table 15. Patients in the edoxaban arm experienced statistically significantly fewer major bleeding events than patients treated with warfarin (HR=0.80; 95% CI 0.71 to 0.91, p<0.001). Across the majority of secondary bleeding outcomes, patients in the edoxaban arm of the trial experienced statistically significantly fewer events compared with patients in the warfarin arm. However, the company reports that a statistically significantly greater number of gastrointestinal (GI) bleeding events was recorded for patients treated with edoxaban compared with patients treated with warfarin (1.51% versus 1.23%, p=0.03).

Table 15 ENGAGE trial bleeding events

Bleeding outcome	Warfarin (N=7012) n (%/year)	Edoxaban 60mg/30mg DR (N=7012) n (%/year)	Edoxaban 60mg/30mg DR vs warfarin HR (95% CI) p-value
Major bleeding	524 (3.43)	418 (2.75)	0.80 (0.71 to 0.91) p<0.001
Fatal bleeding	59 (0.38)	32 (0.21)	0.55 (0.36 to 0.84) p=0.006
Any intracranial bleeding	132 (0.85)	61 (0.39)	0.47 (0.34 to 0.63) p<0.001
Fatal intracranial bleeding	42 (0.27)	24 (0.15)	0.58 (0.35 to 0.95) p=0.03
Gastrointestinal bleeding	190 (1.23)	232 (1.51)	1.23 (1.02 to1.50) p=0.03
Bleeding at a critical organ	211 (1.36)	108 (0.70)	0.51 (0.41 to 0.65) p<0.001
Overt bleeding with blood loss of ≥2 g/dLdL	327 (2.13)	317 (2.08)	0.98 (0.84 to 1.14) p=0.7878
Minor bleeding	714 (4.89)	604 (4.12)	0.84 (0.76 to 0.94) p=0.002
Any overt bleeding	2114 (16.40)	1865 (14.15)	0.87 (0.82 to 0.92) p<0.001
Major or clinically relevant non-major bleeding	1761 (13.02)	1528 (11.10)	0.86 (0.80 to 0.92) p<0.001
Clinically relevant non-major bleeding	1396 (10.15)	1214 (8.67)	0.86 (0.79 to 0.93) p<0.001

DR=dose reduction
Source: CS, Table 32

Other adverse events

Table 33 in the CS provides a summary of the AEs reported during the ENGAGE trial (Table 16). Both the overall frequency of AEs and the frequency of AEs leading to discontinuation of treatment are similar for patients treated with edoxaban and patients treated with warfarin. It is stated in the CS that the five most frequently reported treatment-emergent AEs in both the edoxaban and the warfarin arms of the trial were urinary tract infections, nasopharyngitis, peripheral oedema, bronchitis and dizziness. All of these five AEs were experienced by similar numbers of patients in each arm of the trial.

Table 16 ENGAGE trial adverse events

Outcome	Warfarin (N=7012) n (%)	Edoxaban 60mg/30mg DR (N=7012) n (%)
Overall AEs (excluding bleeding)		
Any	5910 (84.3)	5911 (84.3)
Any drug-related	861 (12.3)	778 (11.1)
Serious	2698 (38.5)	2530 (36.1)
Serious and drug-related	119 (1.7)	77 (1.1)
Severe	1290 (18.4)	1212 (17.3)
Leading to a fatal outcome	310 (4.4)	283 (4.0)
On-treatment AEs (excluding bleeding) leading to discontinuation	2480 (35.4)	2235 (31.9)
Drug-related	374 (5.3)	281 (4.0)
Serious	1413 (20.2)	1268 (18.1)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Neoplasms	461 (6.6)	457 (6.5)
Bone Fractures	371 (5.3)	328 (4.7)

DR=dose reduction
Source: CS, Table 33

Changes in haemoglobin levels, renal function, vital signs and hepatic events

The company reports that the mean change in haemoglobin levels from baseline was [redacted] in the edoxaban arm and [redacted] in the warfarin arm. The company describes these reductions as 'minor'. The ERG agrees with the company's assessment of severity.

The company reports that the proportion of patients with a reduction in renal function from CrCl >50mL/min and CrCl 30 to 50mL/min at baseline to CrCl <30mL/min at any point in the study, or at the end of treatment was similar across treatment arms. The company further reports that the change from baseline in mean CrCl was lower for patients in the edoxaban arm [redacted] than it was for patients in the warfarin arm [redacted]

The company reports that changes in blood pressure recordings and electrocardiogram recordings were similar for patients treated with edoxaban and those treated with warfarin.

The numbers of patients who experienced elevated levels of liver enzymes or hepatocellular injury were similar in both treatment arms of the ENGAGE trial (see CS, Table 34).

4.6.2 Net clinical outcome

The company conducted an assessment of the risks and benefits of treatment with edoxaban compared with warfarin (net clinical outcome) using results from the ENGAGE trial. The net clinical outcome results are presented in Table 17. The company states that for the three composite outcomes included in the assessment, edoxaban was statistically significantly superior to warfarin. The company considers the net clinical outcome results to be particularly robust given the low rate of missing data from the trial.

The ERG notes that a recent paper by Chan[54] suggests that the net clinical outcome calculated for trials of NOACs may overestimate the benefit of NOACs versus warfarin as the outcome of HS is included as a component of both the primary efficacy outcome and as a safety outcome (as a bleeding event). This means that HSs are double-counted.

Table 17 Net clinical outcome results from the ENGAGE trial

Outcome	**Warfarin (N=7012) N (%/year)**	**Edoxaban 60mg/30mg DR (N=7012) n (%/year)**	**Edoxaban 60mg/30mg DR vs warfarin HR (95% CI) p-value**
Primary (stroke, SE, major bleeding or death)	1462 (8.11)	1323 (7.26)	0.89 (0.83 to 0.96) p=0.003
Secondary (disabling stroke, life-threatening bleeding or death)	987 (5.23)	883 (4.64)	0.88 (0.81 to 0.97) p=0.008
Tertiary (stroke, SE, life-threatening bleeding or death)	1123 (6.02)	999 (5.30)	0.88 (0.81 to 0.96) p=0.003

SE=systemic embolism; DR=dose reduction
Source: CS, Table 35

4.6.3 Major bleeding in different patient subgroups

The company has conducted an analysis of major bleeding events across a range of 16 different patient subgroups (CS, Figure 19) and concludes that, for the majority of the subgroups considered, patients treated with edoxaban experienced fewer major bleeding events than patients treated with warfarin. The ERG agrees with the company's assessment.

The company provides a more detailed analysis of the major bleeding outcomes for the two subgroup analyses identified in the NICE scope:[44] outcomes by TTR (measured by centre level TTR) and outcomes by risk of stroke.

Centre level TTR

The company presents the comparison of treatment with edoxaban versus warfarin for the outcome of major bleeding disaggregated by cTTR (Table 18). It is stated in the CS that, compared with patients in the warfarin arm, fewer patients treated with edoxaban experienced major bleeding events. The ERG notes that, in terms of TTR, there are no statistically significant differences between centres.

Table 18 ENGAGE trial major bleeding events by centre level time in therapeutic range

Subgroup	Warfarin N=7012	Edoxaban 60mg/30mg DR N=7012	Edoxaban 60mg/30mg DR vs warfarin HR (95% CI)	p-value for interaction
Centres with TTR >66.4%, n(%/year)	273 (3.51)	225 (3.15)	0.90 (0.75 to 1.07)	0.060
Centres with TTR ≤66.4%, n(%/year)	251 (3.35)	177 (2.33)	0.70 (0.58 to 0.85)	
Centres with TTR ≥60%, n(%/year)	[redacted]	[redacted]	[redacted]	[redacted]
Centres with TTR <60%, n(%/year)	[redacted]	[redacted]	[redacted]	
First quartile (≤57.7%) n(%/year)	[redacted]	[redacted]	[redacted]	[redacted]
Second quartile (>57.7% to ≤66.4%) n(%/year)	[redacted]	[redacted]	[redacted]	
Third quartile (>66.4% to ≤73.9%) n(%/year)	[redacted]	[redacted]	[redacted]	
Fourth quartile (>73.9%) n(%/year)	[redacted]	[redacted]	[redacted]	

DR=dose reduction; TTR=time in therapeutic range
Source: CS, Table 36

Analysis by stroke risk

The company states that for the outcome of major bleeding, the HRs (see Table 19) for edoxaban versus warfarin are comparable across the range of $CHADS_2$ scores. Considering the HRs in Table 19, and the non-significant p-value for interaction for dichotomised $CHADS_2$ scores (CS, Figure 19), the ERG agrees that major bleeding events in the trial are comparable across $CHADS_2$ scores 2 to 6.

Table 19 Major bleeding by $CHADS_2$ score

$CHADS_2$ Score	Warfarin (N=7012) N (%/year)	Edoxaban 60mg/30mg DR (N=7012) n(%/year)	Edoxaban 60mg/30mg DR vs warfarin HR (95% CI)
All scores	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]

DR=dose reduction
Source: CS, Table 37

ERG Summary of adverse events and safety data

The ERG considers 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 GI 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 AEs.

4.6.4 Quality of life

The CS states that HRQoL data were collected during the ENGAGE trial using the EQ-5D questionnaire. Patients were scheduled to complete questionnaires at baseline and every 3 months until study end. It is reported in the CS that, of the 60% of patients who participated in the HRQoL sub-study, 'a sizeable proportion' were enrolled after the initiation of trial treatment. Data were collected internationally and there were 164 respondents from the 254 UK-based patients.

As part of the clarification process, the company provided the EQ-5D data relevant to the UK patients who participated in the trial. [redacted]

[redacted]

The ERG considers that the EQ-5D response rates were low and the data are not fully analysed. It is therefore difficult to draw any firm conclusions as to any difference in patients' experiences attributable to the choice of treatment.

4.7 Critique of the indirect evidence

4.7.1 Summary and critique of the indirect evidence

[redacted]

4.7.2 Network meta-analysis: overview of trials and statistical approach

Four RCTs were identified for inclusion in the company's NMA. Evidence for efficacy was provided for edoxaban (ENGAGE trial),[26] apixaban (ARISTOTLE trial),[27] dabigatran (RE-LY trial)[25] and rivaroxaban (ROCKET-AF trial).[28] All four RCTs compared treatment with warfarin, creating a network of evidence as shown in Figure 3.

The ERG did not identify any additional trials that met the company's eligibility criteria.

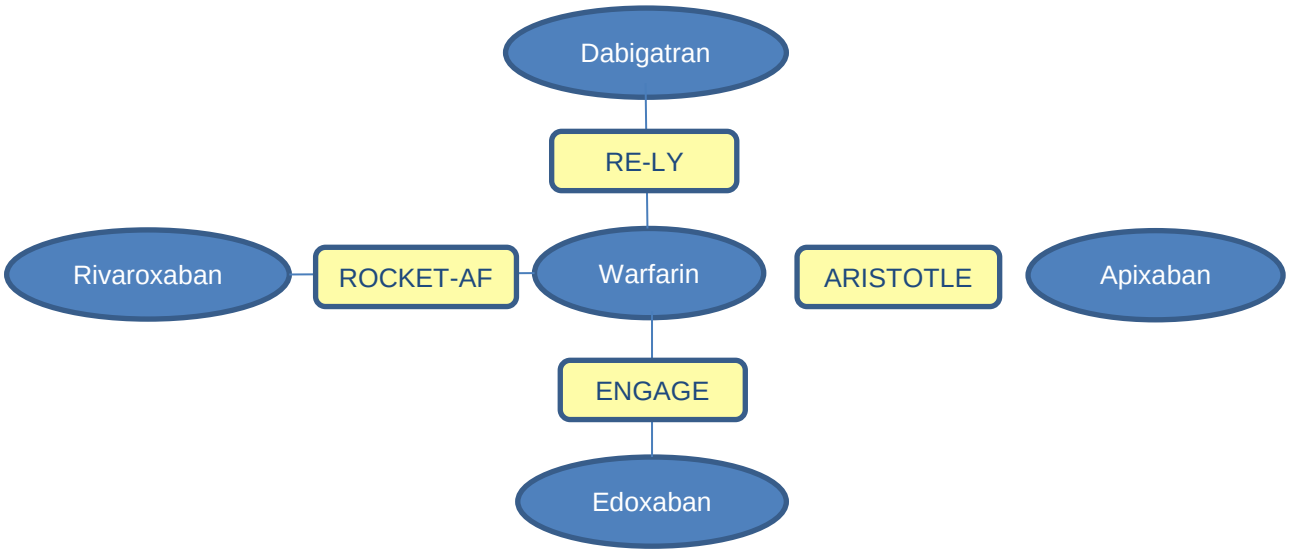

Figure 3 Network diagram of included studies

Source: CS, Figure 8

[redacted]

The company's base case NMA comprised only patients with $CHADS_2 \geq 2$.

[redacted]

[redacted]

[redacted]

Secondary analyses

[redacted]

Statistical approach

[redacted]

Characteristics of the included trials

A summary of the characteristics of the trials included in the NMA is presented in Table 20.To allow a more complete comparison between the baseline characteristics of the included trials, the ERG also included details additional to those provided in the CS.

Table 20 Summary of the characteristics of the trials used to conduct the NMA

	Treatment	[redacted]	Trial design	Patient population	[redacted]	[redacted]	[redacted]	[redacted]	No randomised patients	Trial length (years)*
ENGAGE	Edoxaban 60mg	[redacted]	Randomised double-blind, double-dummy	Adult patients ≥20 years old with NVAF and a $CHADS_2$ ≤2	[redacted]	[redacted]	[redacted]	[redacted]	21,105	2.8
	Edoxaban 30 mg	[redacted]			[redacted]	[redacted]		[redacted]		
	Dose-adjusted warfarin	[redacted]			[redacted]	[redacted]		[redacted]		
ARISTOTLE[27]	Apixaban	[redacted]	Randomised, double-blind, double-dummy	Patients with AF and a $CHADS_2$ score ≥1	[redacted]	[redacted]	[redacted]	[redacted]	18,201	1.8
	Dose-adjusted warfarin	[redacted]			[redacted]	[redacted]		[redacted]		
RE-LY[25]	Dabigatran 110 mg	[redacted]	Randomised, two doses of dabigatran administered in a blinded fashion, open-label use of warfarin	Patients with AF and a $CHADS_2$ ≥1	[redacted]	[redacted]	[redacted]	[redacted]	18,113	2
	Dabigatran 150 mg	[redacted]			[redacted]	[redacted]		[redacted]		
	Dose-adjusted warfarin	[redacted]			[redacted]	[redacted]		[redacted]		
ROCKET-AF[28]	Rivaroxaban	[redacted]	Randomised, double-blind, double-dummy	Patients with NVAF and a $CHADS_2$ ≥2	[redacted]	[redacted]	[redacted]	[redacted]	14,262	1.9
	Dose-adjusted warfarin	[redacted]			[redacted]	[redacted]		[redacted]		

*: Median follow-up
AF=atrial fibrillation; BD=twice daily; DR=dose reduction; INR=international normalised ratio; NVAF=non-valvular atrial fibrillation; OD=once daily; TTR=time in therapeutic range;
Source: CS, Table 26

The ERG is of the opinion 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 NMA are sufficiently similar to justify combining the results. There were differences in study durations between the included trials (ranging from 1.8 years in ARISTOTLE[27] to 2.8 years in ENGAGE). However, the company's approach used annualised event rates and this approach minimises any potential biases resulting from differences in trial duration.

[redacted]

[redacted]

4.7.3 Quality assessment

The company conducted a quality assessment of each of the trials included in the NMA. The company used the risk of bias tool recommended by the Cochrane Collaboration.[55] The ERG considers that the results of the quality assessment carried out by the company are valid and that the included trials are of good quality. The quality assessment results are presented in Appendix 4 of this ERG report.

4.7.4 Individual trial findings

The company provided results from the individual trials included in the NMA as part of their clarification response. The ERG provides summary tables of these results in Appendix 5 of this ERG report.

4.8 Results of the network meta-analyses

In the following results section, the main analysis for each outcome is referred to as the "base case analysis". Exploratory analyses with varying patient populations are the "secondary analyses".

4.8.1 Base case analysis ($CHADS_2 \geq 2$)

<u>Primary efficacy outcome (composite of stroke and systemic embolism)</u>

The results from the NMA [redacted]

.

Table 21 NMA risk ratios for the composite of stroke and systolic embolism, $CHADS_2$ ≥2 patients; RR (95% CrI)

	[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]

CrI=credible interval; RR=risk ratio; SE=systemic embolism
Source: CS, Table 28

Other efficacy outcomes

The results from the NMA for the other efficacy endpoints are provided in Table 22. [redacted]

Table 22 NMA risk ratios for other efficacy outcomes, $CHADS_2$ ≥2 patients; RR (95% CrI)

	[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]

CrI=credible interval; CV=cardiovascular; N/A=Not available (No more than one trial had data, so analysis was not conducted); MI=myocardial infarction; RR=risk ratio; SE=systemic embolism
Source: CS, Table 29

Principal safety endpoints: major bleeding; composite of major bleeding and clinically relevant non-major bleeding

[redacted]

The results from the NMA for major bleeding are provided in Table 23. [redacted]

[redacted]

Table 23 NMA risk ratios for major bleeding, $CHADS_2$ ≥2 patients; RR (95% CrI)

	[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]

CrI=credible interval; N/A=not available; RR=risk ratio
Source: CS, Table 30

Other safety outcomes

The results from the NMA for the other safety endpoints are provided in Table 24 and have been generated subject to data availability. The results demonstrate that [redacted]

Table 24 NMA risk ratios for other safety outcomes, $CHADS_2$ ≥2 patients; RR (95% CrI)

	[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]

CrI=credible interval; N/A=not available; RR=risk ratio
Source: CS, Table 31

4.8.2 Secondary analyses

The company provided forest plots which present findings from the secondary analyses, for three alternative populations of patients, for the composite outcome of stroke or SE and major bleeding (CS, pp93-95). The ERG has summarised these results in Table 25 (patients with $CHADS_2$ ≥3), Table 26 (patients with cTTR ≥60%), and Table 27 (all patients unrestricted by $CHADS_2$ score).

[redacted]

[redacted]

[redacted]

Patients with $CHADS_2$ score ≥3 at baseline

Table 25 NMA risk ratios, patients with $CHADS_2$ ≥3; RR (95% CrI)

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

CrI=credible interval; RR=risk ratio; SE=systemic embolism
Source: Fig 12 of the CS

Patients with centre-level time in therapeutic range ≥60%

Table 26 NMA risk ratios, patients with cTTR ≥60%; RR (95% CrI)

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

CrI=credible interval; cTTR= centre-level time in therapeutic range; N/A=not available; RR=risk ratio; SE=systemic embolism; TTR=time in therapeutic range
Source: Fig 14 of the CS

Patients unrestricted by $CHADS_2$ score

Table 27 NMA risk ratios, all patients; RR (95% CrI)

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

CrI=credible interval; RR=risk ratio; SE=systemic embolism
Source: Fig 16 of the CS

4.8.3 Other values used in the company's economic model

The ERG notes that, in the company's economic model, values other than those resulting from the NMA ($CHADS_2$≥2) presented in this section of the ERG report were used. The company states (CS, Section 7.3.1) that in instances where HRs were not available from the NMA for patients with $CHADS_2$≥2, the HRs used in the model were derived from an analysis using data from all patients. In cases where data were not available from the all patients source, the company states that the HR was assumed to be 1. The data inputs used in the company's economic model are shown in Table 51 of the CS.

In the all patients analysis set, edoxaban was found to significantly increase the risk of HS in comparison to dabigatran 150mg and dabigatran 110mg, and to significantly increase the risk of non-ICH major bleeding in comparison to apixaban.

4.8.4 ERG critique of the network meta-analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

In conclusion, the ERG believes that the company has used appropriate methodology to overcome the problems of differences in the characteristics of the included trials. However, the violation of the proportional hazards assumption both within trials and across trials is an important limitation of the NMA. The ERG believes that these violations mean that the mathematics used to generate the output HRs has been fundamentally compromised and, therefore, reliable HR estimates have not been generated. The ERG considers that these HR estimates should not be used to inform the company's economic model.

4.9 Conclusions of the clinical effectiveness section

The company provided a detailed submission that fully addressed the NICE scope.

4.9.1 Direct evidence

The key clinical evidence for the efficacy and safety of edoxaban was derived from the ENGAGE trial, which was considered to be of good quality. Trial evidence suggests that treatment with edoxaban is non-inferior to treatment with warfarin for the prevention of stroke or SE in patients with NVAF who have a $CHADS_2$ ≥2. The results of the trial were driven largely by a reduction in HS events in patients treated with edoxaban. The findings held across a range of subgroup analyses. Treatment with edoxaban was demonstrated to be superior to treatment with warfarin for a number of secondary outcomes, with the exception of death and MI. The safety data demonstrate that statistically significantly fewer major bleeding events were experienced by patients treated with edoxaban than patients treated with warfarin. However, there were statistically significantly greater numbers of GI bleeds in patients treated with edoxaban compared with patients treated with warfarin.

The ERG considers 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 HS (one of the components of the primary outcome) appears to be violated.

The HRQoL data provided as part of the clarification process are difficult to interpret due to the low response rate and incomplete analysis.

Patient subgroups

The ENGAGE trial only included patients with a $CHADS_2$ ≥2. It is currently unclear whether results from the ENGAGE trial can be generalised to those with a $CHADS_2$=1, i.e. lower risk patients. NICE's guideline[24] recommends that anticoagulation is considered for men with a CHA2DS2-VASc score of 1 and offered to men and women with a CHA2DS2-VASc score of 2 or above, taking their bleeding risk into account. The ERG considers that that the recommendations encompass patients with a lower risk of stroke (i.e. similar to a $CHADS_2$=1).

The company presented an analysis of patients by renal function as measured by creatinine clearance. The results of the company's subgroup analysis suggest that, for patients with normal renal function (CrCL≥80 mL/min), the risk of experiencing a primary outcome event was higher in the edoxaban arm than in the warfarin arm. However, the ERG acknowledges

that the company presents reasonable arguments which suggest that the detected subgroup difference may be a spurious result.

The company also presents an analysis of outcomes for countries in Western Europe [redacted] The ERG considers that the latter finding should be treated with caution as the analysis was not pre-specified and may be the result of a data-mining exercise.

The company has not provided any outcome results for patients with NVAF who underwent cardioversion during the ENGAGE trial. The PROBE[43] trial comparing edoxaban with warfarin in patients with NVAF treated with cardioversion is underway.

Indirect evidence

In the absence of direct evidence comparing the clinical efficacy and safety of edoxaban with apixaban, dabigatran or rivaroxaban, the company conducted a NMA. [redacted]

The ERG is concerned that the trials included in the NMA may not be comparable. Analyses carried out by the ERG show that the key assumption of proportional hazards is violated on a number of occasions and that these violations occur both within and across the included trials. This means that the mathematics used to generate the HRs in the NMA are fundamentally compromised, rendering the HRs unreliable.

5 COST EFFECTIVENESS

5.1 Introduction

The company, Daiichi Sankyo, submitted cost effectiveness analyses in support of the use of edoxaban for the prevention of stroke and SE in patients with NVAF. This section includes a summary of the economic evidence reported by the company and the ERG's structured critique of that evidence. The two key components of the economic evidence presented in the CS are 1) a systematic review of the relevant literature and 2) a report of the company's de novo economic evaluation. In addition to the report, the company provided an electronic copy of their economic model (developed in Microsoft Excel).

5.2 ERG comment on company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company conducted a systematic review to identify cost effectiveness and costing studies from the published literature of NOACs and warfarin for the prevention of stroke and/or SE in adult patients with NVAF. The search was carried out in standard databases (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), OvidSP Embase, NHS EED, Econlit). There was no lower limit on the date of publication and the search end dates ranged from 28th April to 9th May 2014, depending on the database searched. Additional studies were identified by hand searching reference lists of previous trials and systematic reviews, and those of conference proceedings (2012 – 2014).

5.2.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used in the study selection process are presented in Table 28. The inclusion criteria are consistent with the NICE scope.[44]

Table 28 Inclusion and exclusion criteria for cost effectiveness studies

Category	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) with NVAF who are at risk of stroke or SE	Subjects <18 years, patients with valvular/rheumatic AF
Interventions	Edoxaban, apixaban, rivaroxaban, dabigatran, warfarin	Studies not investigating edoxaban or relevant comparator
Comparators	No restriction on comparator	No restriction on comparator
Outcomes	No restriction on outcomes	No restriction on outcomes
Study design	• All cost-effectiveness and cost-utility studies, budget impact analyses and other forms of economic evaluations were included, whether based on models, observational studies or RCTs • All costing studies that reported cost or resource use by treatment	Case report studies

AF=atrial fibrillation; NFAF=non-vulvular atrial fibrillation; RCT=randomised controlled trial
Source: CS, Table 10.10.6

5.2.1 Included and excluded studies

A total of 1393 records were identified and, after screening, 183 full texts were reviewed. In addition, one full text was identified via hand-searching and 17 abstracts were located via conference proceedings. After applying pre-specified inclusion criteria, a total of 52 papers and nine abstracts assessing cost effectiveness were included in the company's review.

Although 52 full text economic studies met the inclusion and exclusion criteria, none were relevant to the decision problem, as they did not include edoxaban. Two conference abstracts (Magnuson[57] and Mearns[58]) met the inclusion criteria and assessed edoxaban treatment in people with NVAF. Both studies[57,58] assessed the cost effectiveness of edoxaban compared to warfarin and adopted a US payer perspective.

5.3 ERG critique of the company's literature review

The systematic review presented in the CS was comprehensive; however, no conclusions on the findings of the review were reported. This may be due to the lack of evidence on edoxaban from published cost effectiveness evaluations, which is unsurprising as the EMA has not approved edoxaban for use in Europe at the time of writing.

The abstract by Magnuson[57] reported an ICER for edoxaban compared to warfarin of $46,393 and $67,320 per QALY gained for 60mg and 30mg doses respectively. The abstract by Mearns[58] reported that high dose edoxaban dominated warfarin as it was more effective (10.32 QALYs for edoxaban; 10.12 QALYs warfarin) and had lower costs ($100,223 edoxaban; $111,719 warfarin; 2013 values). As both studies[57,58] were conducted from a US payer perspective they are unlikely to be generalisable to patients in the NHS in England

and Wales. In addition, insufficient details were provided in the abstracts[57,58] to allow a full critique of the studies' designs and quality.

The ERG updated the CS searches. One new full text article and three new abstracts reporting the cost effectiveness of edoxaban were identified and are summarised here.[59-62] Two of the identified studies were conducted by the same team. The abstract reported by Marchetti[61] reported an extended analysis of that reported in the full paper by Rognoni.[62]

Rognoni[62] conducted a cost effectiveness analysis comparing edoxaban with warfarin for the prevention of stroke and SE from the perspective of the Italian health-care system. A Markov decision model was used to compare lifetime costs and QALYs associated with adjusted-dose warfarin and high dose (60mg) edoxaban strategies in patients with moderate to high risk NVAF ($CHADS_2 \geq 2$). A Markov model with a lifetime horizon was used in the study with 3 month cycles and transition probabilities derived from the ENGAGE trial. Health states included in the model were: NVAF with no other morbidities (NVAF-only); temporary, mild, moderate to severe or fatal IS; temporary, mild, moderate severe or fatal ICH; minor and major extracranial bleedings and death. Utility data were obtained from a sub-analysis of the RE-LY[25] study. In the absence of an Italian list price for edoxaban at the time of the study, the analysis used the daily cost of dabigatran (€2.18) as a proxy. The cost of edoxaban therapy included, besides the drug cost, one visit with renal function determination (further details not reported) every year. Monitoring of patients with NVAF without complications was assumed to include one visit to the cardiologist and one electrocardiogram every year. Costs and life years were discounted at 3.5% per year. The study estimated an ICER of €7,713 per QALY gained for edoxaban versus warfarin. A probabilistic sensitivity (PSA) analysis found a 92% (96%) probability of edoxaban being cost effective compared to warfarin at a cost effectiveness threshold of €25,000 (€50,000) per QALY gained. The ERG notes that the analysis did not include all comparators relevant to the NICE scope[44] for edoxaban, all relevant events were not included as health states (for example TIA or SE). The study was self-funded by the authors.

The remaining three new studies identified were available as abstracts only and provided limited information[59-61]

- Marchetti[61] reported an analysis of the cost effectiveness of dabigatran, apixaban, rivaroxaban, edoxaban and warfarin, for stroke prevention in NVAF patients with $CHADS_2 \geq 2$. The authors reported a series of pairwise comparisons with warfarin and an ICER of €7,713 per QALY gained (80%CI: €3,909 to €17,963) for edoxaban. The ICERs relative to warfarin were lower for apixaban (€4,567 per QALY gained; 80%CI:

€2,129 to €8,993) and dabigatran (€6,307 per QALY gained; 80%CI: €3,034 to €13,421) but higher for rivaroxaban (€12,156 per QALY gained; 80%CI: €5,147 to €33,200).

- Lip[60] assessed the cost effectiveness of apixaban compared to edoxaban (60mg or 30mg) as intended starting dose strategies for stroke prevention in NVAF patients, from a UK NHS perspective. The results showed an ICER of €6,763 per QALY gained for apixaban compared to high dose edoxaban, and apixaban dominated (more effective and less costly) low dose edoxaban. The results of one-way sensitivity analysis (SA) and PSA indicated that cost effectiveness implications were robust over a wide range of inputs.

- Harenberg[59] reported a cost effectiveness analysis of 60mg and 30mg edoxaban compared to approved NOACs from a German payers' perspective. They reported an ICER of €50,000 per QALY gained and €68,000 per QALY gained respectively for the higher and lower dose of edoxaban based on the results of the Monte Carlo Simulation (MCS). The authors report ICERs of €52,000 per QALY gained (high dose edoxaban) and €67,000 (low dose edoxaban) per QALY gained compared to warfarin. It is unclear from the abstract if a fully incremental analysis was performed.

5.4 Summary of company's submitted economic evaluation by the ERG

5.4.1 NICE reference case

Table 29 NICE Reference case completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients, or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes, fully incremental analyses are reported in the CS although not directly calculated in the economic model
Time horizon	Long enough to reflect all important differences in costs and outcomes between the technologies being compared	Yes, the model uses one month cycles, with a 30 year (remaining lifetime) time horizon
Synthesis of evidence on health effects	Based on systematic review	Yes

Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Partially. Health effects are expressed in terms of QALYs. Utility values for stroke are based on hypothetical descriptions of health states. Other utility values are based on measurements using EQ-5D
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Partially. Utility values for stroke are based on hypothetical descriptions of health states. Other utility values are based on patients' reports of their own health
Source of preference data for valuation of changes in health related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the same benefit	Yes
Evidence on resource use and costs	Costs should relate to the NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs relating to NHS resource use are included in the model
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes, however, discounting was applied monthly rather than annually

PSS=personal social services; QALYs=quality adjusted life years; EQ-5=standardised instrument for use as a measure of health outcome

5.4.2 Drummond checklist

Table 30 Critical appraisal checklist for the economic analysis completed by ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	Yes - the company aimed to estimate the cost effectiveness of edoxaban compared to other NOACs in a population with NVAF
Was a comprehensive description of the competing alternatives given?	Yes	Yes
Was the effectiveness of the programme or services established?	Yes	The ENGAGE trial was a phase III, randomised, double blind, double dummy, non-inferiority study comparing edoxaban to warfarin. Edoxaban was non-inferior to well-controlled warfarin for the prevention of stroke or SE and was associated with a significantly lower rate of major bleeding than well-controlled warfarin. The relative effectiveness of edoxaban compared to other NOACs is estimated via the company's NMA
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Partially	See specific comments in Section 5.5.7
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	The incremental analysis was not implemented correctly in the model but is reported correctly in the CS. Deterministic sensitivity analyses were limited to pairwise comparisons
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic and probabilistic sensitivity analyses were undertaken. The company reports the deterministic incremental analysis as the base case results
Did the presentation and discussion of study results include all issues of concern to users?		-

QALY=quality adjusted life year; HRQoL=health related quality of life; ERG=Evidence Review Group; ICERs=incremental cost effectiveness analysis; NMA=network meta-analysis; NVAF=non-valvular atrial fibrillation; CS=company submission; NOACs=novel oral anticoagulants

5.4.3 Model structure

A Markov cohort model is used to evaluate the cost effectiveness of edoxaban compared to warfarin, dabigatran 110mg, dabigatran 150mg, apixaban and rivaroxaban. The model comprises 18 health states, has a one month cycle, and spans a 30-year time horizon. The main health states included in the model are: stable AF, HS, IS, SE, MI and dead. Stroke events (HS and IS) are divided into mild, moderate and severe categories. Health states (IS, HS, SE and MI) are further divided into acute events and long-term impacts. See Table 31 for further details. Anticoagulation treatment is associated with a reduction in the risk of thrombotic events and increased risk of bleeding. All patients in the model start in the 'Stable AF' health state, where they remain until they experience an event. Following the acute stage of a thrombotic event, patients remain in the 'post-event' health state until they experience another event. The model reflects that patients are able to experience recurrent events.

Other transitional clinical outcomes that are considered to have no long-term impact are also included in the model: ICH, non-ICH major bleeds, clinically relevant non-major bleeds (CRNMBs), and TIA. Patients can experience one of these temporary events whilst in each (initial and post-event) health state of the model.

A schematic of the company's model is provided in Figure 4.

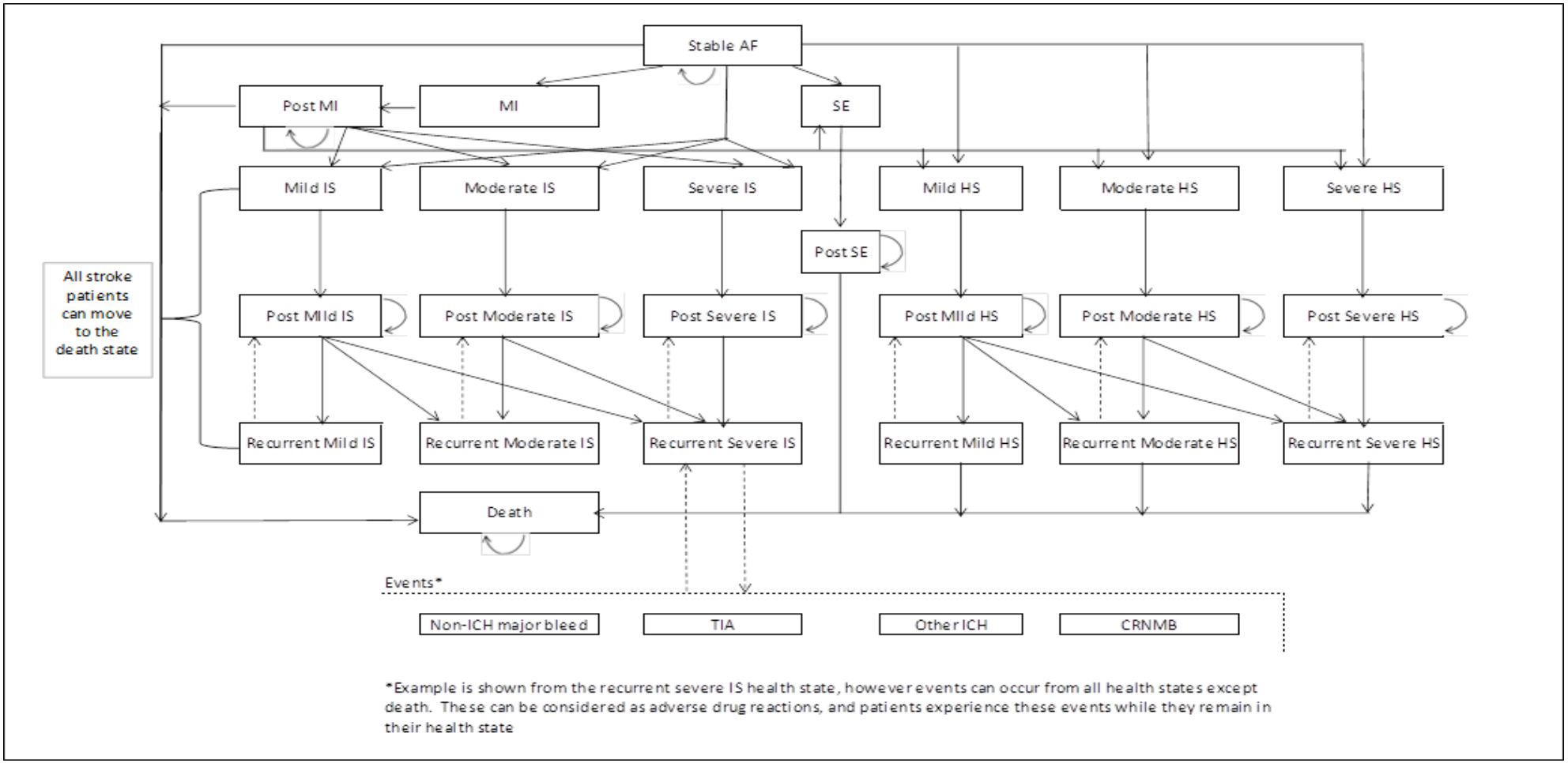

Figure 4 Schematic of the company's model

Source: CS, Figure 22

Table 31 Model health states and events

Health state/event	Description
Health states	
Stable AF	Patients with stable AF who have not yet experienced a clinical event
IS	Patients who are experiencing an ischaemic stroke. Separated into mild (Rankin score of 0-2), moderate (Rankin score of 3-4) and severe (Rankin score of 5-6). Patients stay in this health state for one cycle only before transitioning to the post-IS health state
Post-IS	Patients who have experienced an ischaemic stroke. Separated in mild, moderate and severe strokes (as described for IS state)
HS	Patients who are experiencing a haemorrhagic stroke. Separated in mild, moderate and severe strokes (as described for IS state). Patients stay in this health state for one cycle only before transitioning to the post-HS health state
Post-HS	Patients who have experienced a haemorrhagic stroke. Separated in mild, moderate and severe strokes (as described for IS state)
SE	Patients who are experiencing a systemic embolism. Patients stay in this health state for one cycle only before transitioning to the post-SE health state
Post-SE	Patients who have experienced and survived a systemic embolism
MI	Patients who are experiencing a myocardial infarction. Patients stay in this health state for one cycle only before transitioning to the post-MI health state
Post-MI	Patients who have experienced and survived a myocardial infarction
Death	Terminal state; patients can die due to the events captured in the model and due to all-cause mortality
Temporary events	
Other ICH	Patients who experience an intracranial haemorrhage. Haemorrhagic strokes are excluded from this health state
TIA	Patients who experience a transient ischaemic attack
Non-ICH major bleed	Patients who experience a non-ICH major bleed. Intracranial bleeds are excluded from this health state
CRNMB	Patients who experience a clinically-relevant non-major bleed

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: CS, Table 43

5.4.4 Population

The characteristics of the cohort are based on anticipated licenced population, namely adult patients with NVAF with one or more risk factors, such as congestive heart failure, hypertension, age ≥75years, diabetes mellitus, prior stroke or TIA. The starting age of all patients in the model is, however, 71 years, which is the median age of ENGAGE trial participants. The numbers of patients in each $CHADS_2$ category are based on the proportions recruited to the pooled warfarin and edoxaban 60mg arms of the ENGAGE trial.

5.4.5 Interventions and comparators

The company's base case economic evaluation compares treatment with edoxaban versus warfarin, apixaban, dabigatran and rivaroxaban. The interventions are implemented in the

model in accordance with their UK marketing authorisations and doses (see Table 32). Edoxaban is modelled based on the 60mg dose reported in the ENGAGE trial. Two separate dabigatran regimens are included in the model: 110mg twice daily and 150mg twice daily (reducing to 110mg twice daily at age 80 years).

Table 32 Intervention and comparators

Intervention	Units
Edoxaban	60mg/30mg DR OD
Apixaban	5mg BD
Warfarin	Average daily dose 4.5mg OD
Dabigatran 110mg regimen	110mg BD
Dabigatran 150mg regimen	150mg BD until patient is 80 years of age, then 110mg BD
Rivaroxaban	20mg OD

BD=twice daily; DR=dose reduction; OD=once daily
Source: CS, Table 45

5.4.6 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. The model considers a period of up to a maximum of 30 years from a starting age of 71 years. Both costs and outcomes are discounted at 3.5% in line with the NICE Guide to the methods of technology appraisal.[49] A half-cycle correction is applied to both costs and QALYs (with the exception of drug costs).

5.4.7 Treatment effectiveness and extrapolation

Annual event rates of first clinical events for patients treated with edoxaban were derived from the high dose (60mg) edoxaban arm of the ENGAGE trial (ITT analysis, CS, Table 49) and converted into monthly probabilities (see Appendix 6 of this ERG report).

Event rates for dabigatran, rivaroxaban and apixaban were obtained by applying the HRs from the company's NMA to the baseline edoxaban data (

Table 33). However, in the company's base case analysis, the event rate for warfarin was obtained by applying the HR from the ENGAGE trial to the baseline edoxaban data. The company's model is programmed to allow a sensitivity analysis to be conducted using the HR for warfarin generated by the company's NMA.

Table 33 Hazard ratios used in the model – all relative to edoxaban

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 CS, 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]

*The CS 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: CS, Table 51 and the company's Excel model

The distributions of mild, moderate and severe strokes included in the model were obtained by pooling IS and HS events for the high dose edoxaban and warfarin arms from the mITT analysis for the overall study period in the ENGAGE trial (see Table 34). Patients in the post-HS and post-IS health states were assumed to be at increased risk of recurrent stroke based on estimates obtained from a South London Stroke Registry.[63]

Table 34 Proportion of patients experiencing strokes of each severity category

Stroke severity	Proportion	Distribution
Mild	42.89%	Dirichlet a: 190, b: 253
Moderate	16.48%	Dirichlet a: 73, b: 370
Severe	40.63%	Dirichlet a: 180, b: 263

Source: CS, Table 52

Mortality

The model included death due to clinical events and all-cause mortality. Acute event related mortality and long-term mortality for event survivors were estimated using various sources and are presented in Table 35 and Table 36. It is assumed that there is no risk of mortality from bleeding and TIA.

Table 35 Acute event mortality

Health state	Probability of death	95% CI (distribution)	Source
Health states			
Mild IS	0%	-	Clinical assumption
Moderate IS	16.8%	13.9% to 20.1% (beta)	Janes[64]
Severe IS	16.8%	13.9% to 20.1% (beta)	Janes[64]
Mild HS	0%	-	Clinical assumption
Moderate HS	31.6%	22.7% to 42.8% (beta)	Janes[64]
Severe HS	31.6%	22.7% to 42.8% (beta)	Janes[64]
SE	0%	-	ENGAGE trial
MI	13.2% (10.8 for males and 15.6% for females)	NR in source	Scarborough[65]
Events			
Other ICH	31.6%	22.7% to 42.8% (beta)	Janes[64] (assumed same as for HS)
TIA	0%	-	Clinical assumption
Non-ICH major bleed	0%	-	Clinical assumption
CRNMB	0%	-	Clinical assumption

CRNMB=clinically relevant non-major bleeding; HS=haemorrhagic stroke; ICH=intracranial haemorrhage; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism
Source: CS, Table 55

Table 36 Long-term mortality for event survivors

Health states	HR (distribution)	Source
IS		
Mild	3.18 (lognormal)	Bronnum-Hansen (2001)[66]
Moderate	5.84 (lognormal)	Henriksson (2010)[67]
Severe	15.75 (lognormal)	Huybrechts (2008)[68]
HS		
Mild	3.18 (lognormal)	Bronnum-Hansen (2001)[66]
Moderate	5.84 (lognormal)	Henriksson (2010)[67]
Severe	15.75 (lognormal)	Huybrechts (2008)[68]
SE	[redacted] (lognormal)	Estimated from UK Life Tables[69] and ENGAGE trial data
MI	3.36 (lognormal)	Bronnum-Hansen (2001)[66]

HR=hazard ratio; HS=haemorrhagic stroke; IS=ischaemic stroke; SE=systemic embolism
Source: CS, Table 56

All-cause mortality rates by age and gender were derived from UK life tables.[69] Annual event rates were converted to monthly probabilities and weighted to reflect the proportion of males in the ENGAGE trial. These rates were further adjusted by a HR of 1.34[70] to reflect an increased risk of mortality associated with AF.

Treatment discontinuation

Assumptions regarding the treatment discontinuation rates used in the company's model were based on advice from three health economics experts and two clinical experts. A proportion of patients are assumed to discontinue treatment permanently or temporarily and switch to another treatment following a stroke (IS and HS). Details of discontinuation after suffering a stroke are provided in Table 37. Following discontinuation and switching to a new therapy, the transition probability (of health state and event) does not change to reflect the new therapy. Patients do not discontinue or switch treatment for any other reason.

Table 37 Event-related discontinuation

	Initial treatment	
Event	**Warfarin**	**NOAC**
IS	All patients temporarily discontinue treatment and resume treatment with edoxaban	50% of patients permanently discontinue, and 50% continue on the same therapy
HS	All patients temporarily discontinue treatment and: 20% restart on anti-platelet (aspirin) 20% restart on NOAC (edoxaban) 60% restart on warfarin.	50% of patients permanently discontinue, and 50% continue on the same therapy

HS=haemorrhagic stroke; IS=ischaemic stroke; NOAC=novel oral anticoagulant
Source: CS, Table 57

5.4.8 Health related quality of life

Baseline HRQoL data for people with AF are based on a UK study by Khan[71] previously used in a NICE appraisal of apixaban.[31] The results of a sensitivity analysis are reported using HRQoL data collected directly within the ENGAGE trial and using preference-weights from a US population.

The company assumes that patients who have a stroke, MI and SE experience a permanent decrement to their HRQoL. Temporary reductions in HRQoL are assumed for patients who experience a TIA, non-ICH major bleed, CRNMBs and other ICH. In addition to disease-related quality of life, patients experience a gradual decline in quality of life as they age. In the base case analysis there is no decrease in HRQoL related to the time a patient experiences AF or related to treatment. The sources used to inform utility estimates in the model are provided in

Table 38.

Table 38 Summary of quality of life values for cost effectiveness analysis

Health state/ event	Utility value/ decrement	CI (distribution)	Reference in CS	Justification
Stable AF	0.780 (Base case) 0.74 (Education group) 0.82 (Education and self-monitoring group)	SE 0.0427	Khan (2004)[71]	The only EQ-5D utility from UK based study
	0.836 (Sensitivity analysis)		ENGAGE	Based on US patients
Age-adjustment disutility per year	-0.00029	-0.00059 to 0.0000129 (beta)	Sullivan (2011)[72]	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 (1996)[73]	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 (1996)[73]	It is the only study reporting stroke severity for mild, moderate and severe
SE[†]	0.680	NA**	Sullivan (2011)[72]	Only source identified
MI	0.683	SD: 0.233 (beta)	Lacey (2003)[74]	It is the only UK-based study using EQ-5D identified via the systematic review
Events				
Other ICH disutility	-0.107	NR	Thomson (2000)[75]	Only source identified
	6 weeks	-	Apixaban STA[31]	
TIA disutility	-0.103**	-0.088 to -0.119 (beta)	Sullivan (2006)[76]	Only source identified
	NA	-	-	
Non-ICH major bleed disutility	-0.107	NR	Thomson (2000)[75]	Only source identified
	2 weeks	-	Apixaban STA[31]	
CRNMB disutility	-0.0582	NR	Sullivan (2011)[72]	Only source identified
	2 days	-	Apixaban STA[31]	

[†] Explanation for the term 'NA**' is not provided in the CS
CRNMB=clinically relevant non-major bleeding; HS=haemorrhagic stroke; ICH=intracranial haemorrhage; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism; NR=not reported
Source: CS, Table 60

5.4.9 Resources and costs

Drug costs were based on published list prices and recommended doses for each comparator, and direct from the company for edoxaban (see Table 39). An annual monitoring cost of £265.03 is applied to all patients on warfarin treatment, based on an assumption that 34% of patients are seen in secondary care and 66% are seen in primary care, as reported in a previous NICE submission for rivaroxaban.[30] The unit cost of annual monitoring in primary care was estimated as £188.92 (2004/05 price) and in secondary care as £298.40 (2008/09 cost), as reported in the CS for the NICE appraisal of apixaban;[31] costs were inflated to 2013 prices using the PSSRU Hospital and Community Services Health Index (HCHS).

Table 39 Drug acquisition cost

Items	Edoxaban	Warfarin	Apixaban	Rivaroxaban	Dabigatran 110mg	Dabigatran 150mg
Drug cost per cycle	£63.92	£3.26	£66.85	£63.92	£66.86	£66.86
Dose	60mg OD (30md OD for patients with renal impairment, low body weight or using specific P-gp inhibitors)	Average daily dose: 4.5mg	5mg BD	20mg OD	110mg BD	150mg BD. Switch to 110mg BD when patient is aged 80
Monitoring cost	£0	£22.09	£0	£0	£0	£0
Total	£63.92	£25.35	£66.85	£63.92	£66.86	£66.86

BD=twice daily; DR=dose reduction; OD=once daily
Source: CS, Table 62 and draft edoxaban SPC[37]

The costs applied to the health states in the economic model are shown in Table 40. All costs for the IS, HS, and SE health states were based on the Oxford Vascular study (OXVASC)[77] a large study of healthcare costs after stroke in patients with AF in the Oxfordshire region. The cost of SE was assumed to be equivalent to a weighted average cost of non-disabling mild strokes from this study (acute and post-event separately).

The cost of acute MI was based on NHS reference costs[78] for an MI event, cardiac rehabilitation and a coronary revascularisation assessment. Costs post-MI were calculated using the weighted average cost of monthly treatment with a beta-blocker (bisoprolol), angiotensin-converting-enzyme (ACE) inhibitor (ramipril) and statin (atorvastatin).

Table 40 Costs of health states and events in the economic model

Health states	Value (Standard error)	Duration	Reference
Mild IS	£3,683 (£1,080)	Acute, one off cost	Luengo-Fernandez[77]
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[78]
Post MI	£3.86 (Not reported)	Monthly	Electronic Drug Tariff, BNF68[79]
Death	£2,902 (Not reported)	One off cost	Luengo-Fernandez[77]
Adverse events	Value	Duration	Reference
Other ICH	£2,589	Acute, one off cost	NHS Reference Costs 2012-13[78]
Transient ischaemic attack	£938	Acute, one off cost	
Non-ICH major bleed	£1,803	Acute, one off cost	
CRNMB	£883	Acute, one off cost	

CRNMB=clinically relevant non-major bleeding; HS=haemorrhagic stroke; ICH=intracranial haemorrhage; IS=ischaemic stroke; MI=myocardial infarction; SE=systemic embolism
Source: CS, Table 64 and Table 68

The costs of the other ICH and TIA events were estimated as the weighted average of relevant HRG codes from the NHS Reference Cost 2012-13[78] (See CS Tables 69 and 70). The costs of an acute non-ICH major bleed and CRNMB were also taken from NHS Reference Costs based on weighted averages (by activity) across several codes (See CS Tables 71 and 72).

5.5 Cost effectiveness results

The base case incremental cost effectiveness results generated by the company's economic model are presented in Table 41. In the deterministic base case analysis (patients with

$CHADS_2$ ≥2), edoxaban, dabigatran 110mg, apixaban and rivaroxaban are 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.

Table 41 Company base case (deterministic results)

Technology	Total costs	Total LYG*	Total QALYs*	Inc costs	Inc LYG*	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER per QALY gained (£)
Warfarin	£13,413	8.55	6.32	-	-	-	-	-
Dabigatran 150mg	£15,563	8.88	6.60	£2,150	0.34	0.28	£7,645	£7645
Apixaban	£15,940	8.87	6.59	£377	-0.01	-0.01	£9,383	Strictly dominated
Edoxaban	£15,957	8.79	6.52	£17	-0.08	-0.07	£12,881	Strictly dominated
Dabigatran 110mg	£16,074	8.80	6.51	£117	0.01	0.00	£13.565	Strictly dominated
Rivaroxaban	£16,744	8.69	6.44	£670	-0.10	-0.08	£28,180	Strictly dominated

*discounted
ICER=incremental cost effectiveness ratio; Inc=incremental; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 79

Results from the base case probabilistic analysis are not explicitly included in the CS. However, they have been calculated by the ERG and are shown in Table 42. Based on the probabilistic analysis, edoxaban, dabigatran 110mg and rivaroxaban are strictly dominated (less effective and more costly) by dabigatran 150mg. Apixiban extendedly dominates dabigatran 150mg as is more effective and has a lower ICER when compared with warfarin. Apixiban has an ICER of £13,036 per QALY gained compared to the remaining comparator, warfarin.

Table 42 CS Base case results (probabilistic analysis)

	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

Source: Calculated by the ERG from the company model

Given the ERG's concerns regarding the NMA on which the incremental analysis is based, the ERG has extracted results of the pairwise comparison from the company's model and these are presented in Table 43.

Table 43 CS base case analyses: pairwise results (edoxaban versus warfarin)

Base case	Edoxaban		Warfarin		Incremental		
	Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
Deterministic	£15,957	6.52	£13,413	6.32	£2,544	0.20	£12,881
Probabilistic	£15,471	6.72	£12,868	6.56	£2,603	0.16	£16,269

Source: Company's model

Further base case results (taken from the company model) are included in Appendix 7.

5.5.1 Sensitivity analyses

Probabilistic sensitivity analyses

In the CS the company presents scatter plots displaying the results of the PSA for a series of pair-wise comparisons with edoxaban included in each comparison (CS, Figures 54-58). The company also presents two cost effectiveness acceptability curves (CEACs); one based on an incremental analysis of all comparators (

Figure 5) and one based on a pairwise comparison of edoxaban versus each comparator (CS Figure 60).

The CEAC for the incremental analysis shows that the probability of edoxaban being cost effective is 2.9% at a threshold of £20,000 per QALY gained and 3.4% at a threshold of £30,000 per QALY gained. It also shows that warfarin has 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%).

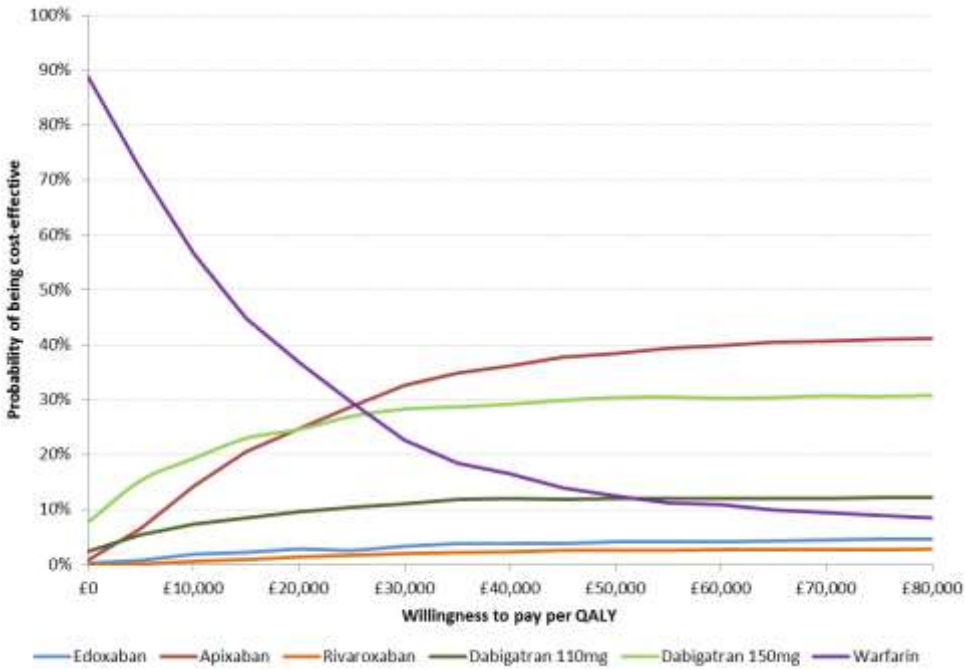

Figure 5 Cost effectiveness acceptability curve (probability of edoxaban being most cost-effective option compared to each comparator arm)
Source: CS, Figure 59

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% (CS, Fig 60).

One-way deterministic sensitivity analyses

The company presents the findings of 14 pair-wise deterministic SAs, each varying 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 HR 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 AF utility, acute disutility and post-outcome utility for each event and other cause discontinuation rates (CS Figures 24-53). Details of the change in parameters used in the SAs are reported in the CS (Appendix 16).

The analyses estimate the effect on net monetary benefit (NMB) and the ICERs per QALY; however, only changes in NMB are reported in the CS. Tornado diagrams reporting the results for variables with the greatest impact on NMB are presented in the CS (Section 7.7.7). The tornado diagrams for edoxaban compared to warfarin and for edoxaban compared to dabigatran 150mg (the most effective option in the incremental deterministic analysis) are reproduced in Figure 6 Figure 7 respectively. Both figures show that the

variables that had the most impact on the deterministic base case results were patients' starting age, cost of treatment and the addition of a monitoring cost for patients treated with edoxaban.

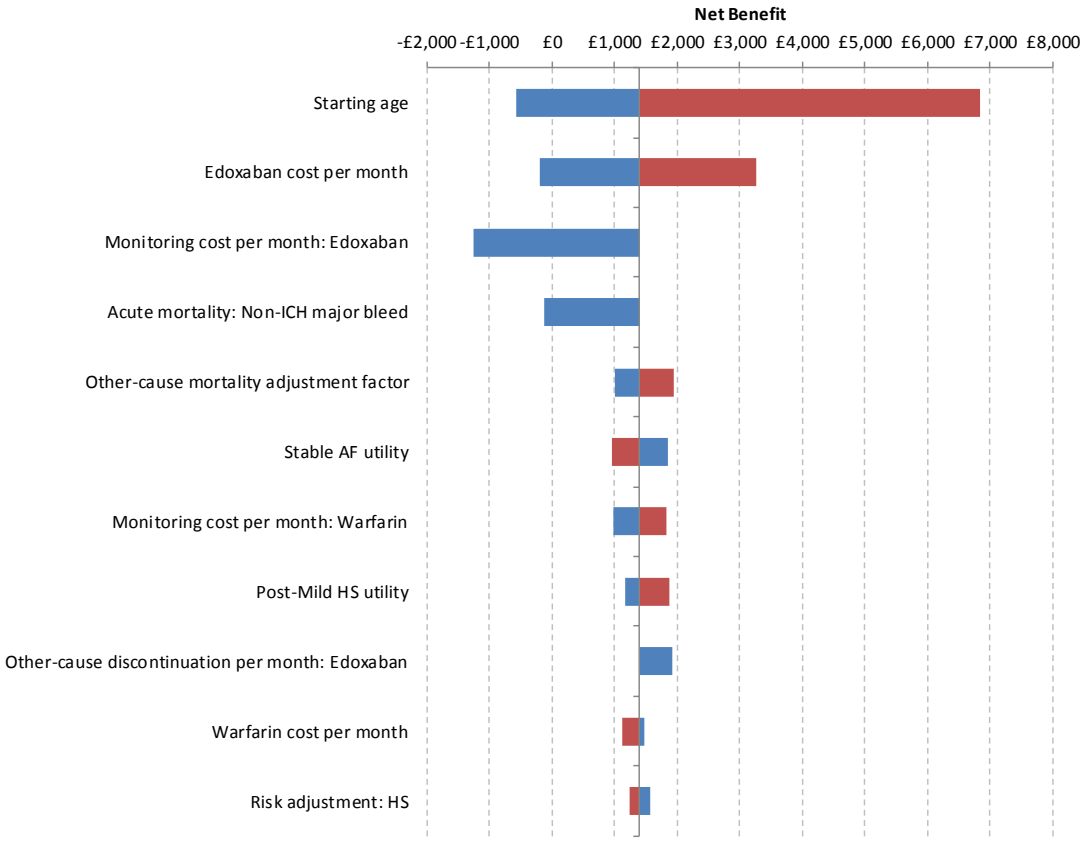

Figure 6 Tornado diagram: edoxaban vs warfarin
Source: CS, Figure 48

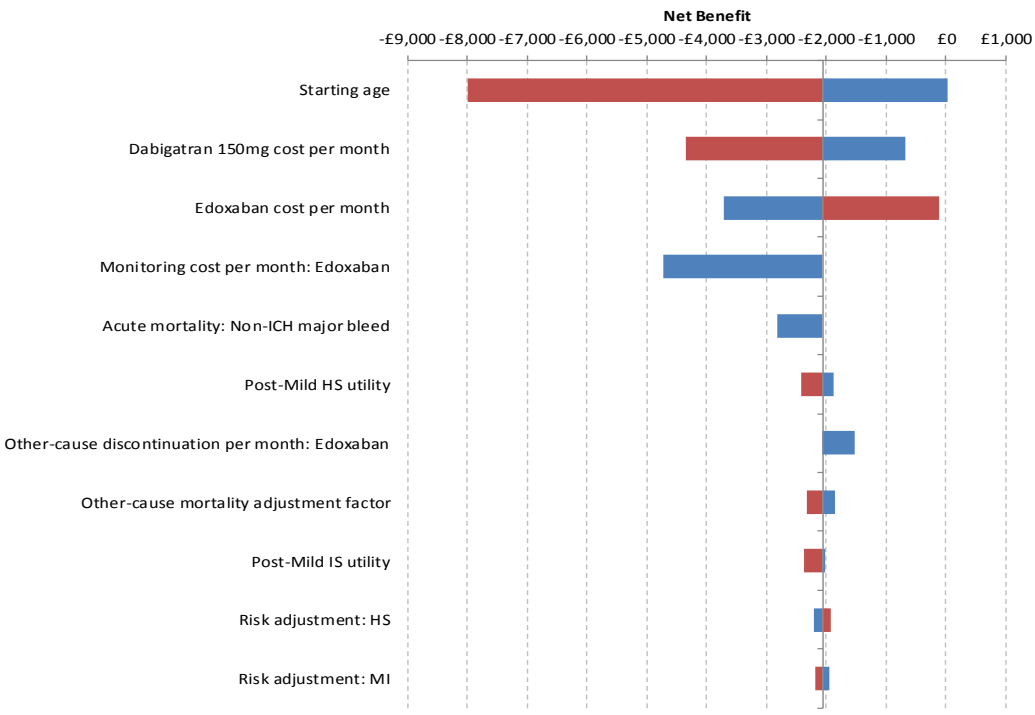

Figure 7 Tornado diagram: edoxaban vs dabigatran 150mg
Source: CS, Figure 42

Scenario analyses

Four scenario analyses were carried out: two varying TIA HRs and two varying CRNMB HRs. The base case analysis assumed values of 1 where data were not available; however, in the scenario analyses, all values of 1 were changed to 0.93 and 0.72 for TIA and 1.19 and 1.25 for CRNMB (source of values not stated). The scenario analysis showed that these changes had little impact on the overall deterministic results and dabigatran 150mg dominated all comparators.

5.5.2 Subgroup analyses

Subgroup analyses were undertaken in accordance with the NICE scope.[44] Analyses were carried out for patients with a higher risk of stroke ($CHADS_2 \geq 3$), and cTTR≥60%. Baseline event rates were based on data from the ENGAGE trial for these subgroups. Limited data were available to the company to inform HRs for these subgroups, so the company used the base case annual event rates from the ENGAGE trial. Where data were unavailable for the subgroup for an event, the HR was assumed to be equivalent to that used in the base case analysis. Hazard ratios for the subgroups have been extracted from the model by the ERG and are shown in Table 44.

Table 44 Hazard ratios used in subgroup analyses

HRs versus edoxaban (network meta-analysis)	IS	HS	SE	MI	Other ICH	TIA	Non-ICH major bleed	CRNMB
$CHADS_2 \geq 3$								
Apixaban	0.84	0.92*	1.23*	0.67	0.733	1*	0.86	1*
Rivaroxaban	1.02	1.15*	1.85	1*	1.28	1*	1.32	1.25*
Dabigatran 150mg	0.75	0.38*	1.09*	1.27*	1.06	0.84*	1.44	1*
Dabigatran 110mg	1.11*	0.46*	1.29*	1.24*	0.53	0.72*	1.13	1*
Warfarin	1.04	1.68	1.63*	1.01	2.31	0.93*	1.23	1.19*
cTTR≥60%								
Apixaban	0.97	0.92*	1.23*	0.82	0.85	1*	0.81	1*
Rivaroxaban	1.02	1.15*	1.85	1*	1.28	1*	1.32	1.25*
Dabigatran 150mg	0.75*	0.38*	1.09*	1.27*	0.82	0.84*	1.18	1*
Dabigatran 110mg	1.11*	0.46*	1.29*	1.24*	0.51	0.72*	0.89	1*
Warfarin	0.99	1.68	1.63*	1*	2.28	0.93*	1.06	1.19*

* indicates same estimate as used in base case analysis
Source: Company's model

Results for the subgroup analyses are not reported in the CS. However, the ERG has extracted details from the company's model. In the analysis for the subgroup of people with $CHADS_2 \geq 3$, apixaban dominated or extendedly dominated the other NOACs and was associated with an ICER of £3730 per QALY gained (Table 45). In the analysis of the cTTR≥60% subgroup, dabigatran 150mg dominated the other NOACs and was associated with an ICER of £11,696 per QALY gained (Table 46) The results presented in Table 45 are taken directly from the economic model and differ slightly from those reported in the CS (Tables 87 and 88).

Table 45 Subgroup analysis - patients with $CHADS_2 \geq 3$

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER Cost per QALY gained
Warfarin	£14,774	6.04	-	-	-
Rivaroxaban	£17,617	6.26	-	-	Dominated
Dabigatran 110mg	£16,922	6.32	-	-	Dominated
Edoxaban	£16,815	6.33	-	-	Dominated
Dabigatran 150mg	£16,401	6.41	-	-	Extendedly dominated
Apixaban	£16,539	6.52	£1765	0.47	£3730

Source: Company's model

Table 46 Subgroup analysis - cTTR≥60%

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER Cost per QALY gained
Warfarin	£12,926	6.37			
Rivaroxaban	£16,725	6.45	-	-	Dominated
Dabigatran 110mg	£15,947	6.51	-	-	Dominated
Edoxaban	£15,958	6.52	-	-	Dominated
Apixaban	£16,003	6.58	-	-	Extendedly Dominated
Dabigatran 150mg	£15,487	6.59	£2,560	0.22	£11,696

Source: Company's model

5.5.3 Model validation and face validity check

The company reports that validity was assessed using two primary criteria: internal (verification) and external consistency (validation).

Internal validity was assessed by:

- extreme value analysis (using minimum and maximum values for parameters)
- using parallel inputs for all interventions for efficacy, costs and utilities
- carrying out logical consistency tests
- validating equations against sources
- checking coding accuracy by verification of separate parts of the model

External consistency was assessed by:

- assessing the face validity of the model (comparing analysis results against published results)
- assessing whether the model structure included all aspects of the patient pathway and were the relationships consistent with underlying medical science
- assessing whether the best available data sources were used (setting, population, interventions, outcomes, assumptions and time horizon)

5.6 Detailed critique of the company's economic model

This section provides a detailed critique of the company's economic analysis. The ERG notes that the results of the incremental analysis rely on figures generated by the company's NMA. As reported in Section 4.7.3, the ERG has serious concerns about the validity of these results given that the assumption of proportionality, for various outcomes, both within and between trials, has been found not to hold. Further information on the incorporation of treatment effects, and the use of HRs generated by the company's NMA, in the model are discussed in Section 5.5.5.

None of the ERG's amendments to the company's model discussed in this section change the result that edoxaban is more expensive and less effective that at least one of the treatment alternatives when full incremental analyses are carried out. Given the ERG's concerns with the company's NMA, where the ERG's amendments to the company's model have an impact on the size of the ICER per QALY gained, the ERG has presented deterministic and probabilistic pairwise results for edoxaban versus warfarin.

5.6.1 Model structure and design

The model structure is largely based on that submitted to NICE by Bristol-Myers Squibb and Pfizer as part of a STA to appraise the clinical and cost effectiveness of apixaban for the prevention of stroke and SE in people with NVAF (TA275[31]). One difference is the inclusion of TIA as an outcome, which is consistent with the NICE scope.[44]

In the company's model, TIA is modelled as an event that has a temporary, short-term impact only. Clinical advice to the ERG is that experiencing a TIA may increase the risk of stroke. The NICE clinical guideline for stroke[80] recommends that people who have had a suspected TIA should be assessed for their risk of subsequent stroke using validated scoring systems. A study by Rothwell[81] reports that up to 23% of strokes are preceded by a TIA. The results of the company's NMA suggest that edoxaban does not lower the risk of TIA relative to warfarin or the other NOACs. Therefore, the ERG considers that including an increased risk of stroke after TIA in the model would not have an impact on the overall cost-effectiveness results (deterministic or probabilistic results). However, the ERG notes that omitting an increased risk of stroke after TIA implies that the model structure is not reflective of the underlying clinical pathway.

The ERG has identified that, in terms of OS, the company's model is not able to accurately reproduce ENGAGE trial data. The company model includes data from other sources in addition to the ENGAGE trial to inform its estimates of survival. The company does not fully justify the selection of some of these sources and does not provide a reason for the

difference between trial and model estimates. This lack of ability to replicate a key trial outcome and the absence of a justification for this has cast doubt on the reliability of all results generated by the company's model. The ERG has employed of a number of adjustments to try to resolve this issue (Section 5.5.4 for further details). However, the Markov model structure used by the company does not directly measure important outcomes in a format that is easily verifiable and it has, therefore, been difficult to trace which parameter is causing which effect.

5.6.2 Population

The company states that the modelled population reflects the characteristics of the company's anticipated licensed population for edoxaban, i.e. adult patients with NFAF with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75 yars, diabetes mellitus, prior stroke or TIA. The ERG notes, however, that the characteristics of the modelled population are based on the baseline characteristics of patients participating in the ENGAGE trial, i.e. adult patients with NVAF who have **two** or more risk factors. The company reports that approximately 27% of people with AF have a $CHADS_2$ =1 (CS, Table 42) and it is unclear whether the results generated by the model are generalisable to this group of patients.

The baseline age of patients, and the gender split values, used in the model reflect the characteristics of the ENGAGE trial population (71 years and 62% male respectively). Figures for all-cause mortality have been extracted from UK life tables[69] to calculate an age-specific mortality rate weighted by gender. This weighted average is based on the initial gender split in the model and remains constant over time. The ERG considers that, as average mortality rates for females are lower than those for males, the relative proportions of each will differ over time, and so this method misrepresents all-cause mortality in the model. In addition, the ERG considers that the use of a distribution of starting ages, rather than a fixed age, would have allowed a more realistic representation of clinical practice.

The ERG carried out an analysis that employed a range of starting ages (in 5 year age bands), each with a specific gender distribution based on data from the ENGAGE trial. The deterministic pairwise results of this analysis show that the ICER for edoxaban versus warfarin reduces to £10,010 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is also reduced (£12,805 per QALY gained).

5.6.3 Interventions and comparators

The ERG considers that all appropriate comparators have been included in the analysis and are consistent with the NICE scope.[44]

The ERG has concerns about the implementation of the dose reduction at age 80 years for patients receiving dabigatran 150mg. All patients are assumed to enter the model at age 71 years and, rather than assuming the 150mg dose is reduced at age 80, the dose reduction is modelled to occur at various ages based on a cumulative normal distribution of the proportion of patients under the age of 80 years in the ENGAGE trial. Event rates and drug costs relating to dabigatran 110mg are then applied following the dose reduction. It is stated in the CS that this is more appropriate than assuming that the starting age is fixed (at 71 years) and all patients receiving the 150mg dose switch to 110mg after 9 years. The ERG considers that it would have been more appropriate to reflect a distribution of different starting ages in the model and to apply the dose reduction at age 80 years for all patients; however, this approach would require substantial structural amendments to the model. The ERG, therefore, conducted an analysis in which it was assumed that all patients switch from dabigatran 150mg to 110mg at age 80. The deterministic pairwise results of this analysis show that the ICER for edoxaban versus warfarin is very slightly reduced to £12,823 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is also reduced (£15,147 per QALY gained).

5.6.4 Perspective, time horizon and discounting

The ERG considers that the perspective and time horizon adopted in the model are appropriate, and consistent with the NICE reference case[49]. Costs and benefits are discounted using a rate of 3.5%. The ERG notes that the rate is applied monthly in the company's model. This is in contrast to the NICE reference case,[49] which recommends that discounting should be carried out annually. The ERG considers that this methodological error is likely to have only a minor impact on model results.

5.6.5 Treatment effectiveness and extrapolation

A wide variety of data sources were used to populate the model, including the company's NMA, ITT and mITT data from the ENGAGE trial, several articles from the literature and clinical assumptions.

Acute stroke-related mortality data

Acute mortality rates following an IS or HS were obtained from a two-year prospective study by Janes[64] using a community-based registry of cerebrovascular events in Udine (Italy) and reporting stroke incidence. The company's model first distinguishes between severity of

stroke (mild, moderate and severe) and then applies the risk of fatality to two of these groups (moderate and severe). Whist it is reasonable to assume that patients experiencing a mild stroke are at a low, or no, risk of stroke-related mortality in the acute stage, the company's approach to implementing this in the model underestimates stroke-related fatalities. For example, 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[64]. In addition, the model does not allow for any stroke-related mortality in the first cycle. Substantial structural amendments to the model would be required to fully correct this error. The ERG has, however, assessed the impact of applying the acute mortality rates reported by Janes[64] to all patients experiencing a stroke (IS and HS separately). The deterministic pairwise results of this analysis show that the ICER for edoxaban versus warfarin is reduced to £12,644 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is very slightly reduced (£16,206 per QALY gained).

The company did not use acute mortality data from the ENGAGE trial. The reason for this is unclear. The ERG extracted acute mortality data relating to IS and HS from the CSR[50] (p132) and pooled it across both the warfarin and edoxaban arms of the trial. The ERG's preferred option is to use the ENGAGE trial data in the model. The deterministic pairwise results from this analysis show that the ICER for edoxaban versus warfarin is slightly reduced to £12,649 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is increased (£17,827 per QALY gained).

Long-term stroke-related mortality data

Three separate references are provided in the CS for long-term mortality following a stroke; a separate source each for mild, moderate and severe stroke. The ERG was unable to identify these estimates from the referenced sources. The ERG hypothesises that the estimates are based on the long-term mortality after stroke reported in a Danish study by Bronnum-Hansen[66] adjusted to reflect an increased risk of death for patients with AF based on a Swedish study by Henrikkson[67] and severity of stroke based on a Greek study by Huybrechts[68]. Whilst the ERG acknowledges that the same long-term mortality data were used in a previous NICE appraisal of apixaban[31], it has been unable to replicate the calculations due to insufficient information in the CS.

Treatment effectiveness

Regarding NMA results, it should be noted that whilst two of the studies included in the NMA recruited patients with $CHADS_2 \geq 2$ (ENGAGE and ROCKET-AF[28]), the remaining two studies recruited patients with $CHADS_2 \geq 1$ (RE-LY[25] and ARISTOTLE[27]). Where data were not available for the company to analyse the data for the other NOACs for patients with $CHADS_2 \geq 2$, they assumed that the HRs were equivalent to those for all patients ($CHADS_2 \geq 1$). Regarding NMA results, it should be noted that whilst two of the studies included in the NMA recruited patients with $CHADS_2 \geq 2$ (ENGAGE and ROCKET-AF[28]), the remaining two studies recruited patients with $CHADS_2 \geq 1$ (RE-LY[25] and ARISTOTLE[27]). Where data were not available for the company to generate outcome HRs for apixaban, dabigatran and rivaroxaban relating to patients with CHADS2 ≥2, the company assumed that the HRs were equivalent to those for all patients (CHADS2 ≥1). Where data for all patients were unavailable the company assumes equivalence with edoxaban (see CS, Table 51). As discussed in Section 4.7, 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 K-M analyses for a variety of outcomes from the ENGAGE trial. On reviewing the data provided by the company, the ERG noted that [redacted] The deterministic pairwise results of this analysis show that the ICER for edoxaban versus warfarin is increased to £17,137 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis could not be estimated.

[redacted]

Figure 8 Cumulative hazard for HS in the ENGAGE trial

Treatment discontinuation

The model has been built on the assumption that the only reason for patients to discontinue treatment is a stroke event. Following a stroke event, all patients taking warfarin are assumed to switch to an alternative treatment (a NOAC or aspirin) or remain on treatment with warfarin. The company assumes that, after an IS or HS, 50% of patients taking a NOAC permanently discontinue treatment and 50% continue on the same therapy. Clinical advice to the ERG is that this may not be reflective 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 IS and 2) all patients discontinuing therapy following an HS. The deterministic pairwise results of this analysis show that the ICER for edoxaban versus warfarin is slightly reduced to £12,813 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is also slightly reduced (£16,150 per QALY gained).

Within the CS there is reference to some patients temporarily discontinuing anticoagulation treatment after they have had a stroke. However, the ERG considers that this possibility is not included in the company's model; rather, patients either switch to an alternative NOAC or permanently discontinue treatment. In a previous NICE appraisal of dabigatran[29], it was suggested that temporary discontinuation would only last for approximately 1 to 2 weeks. The ERG, therefore, considers that introducing temporary discontinuation into the model would have little impact on the overall size of the company's base case results. The ERG

notes that the company has assumed that after patients switch to a new therapy, transition probabilities do not change to reflect the new treatment. Clinical advice to the ERG suggests that this assumption is reasonable.

The ERG notes that the recent FDA approval[45] stipulated that edoxaban (like other anticoagulants) should carry a warning that premature discontinuation increases the risk of stroke. Premature discontinuation would be expected to decrease the QALYs gained by patients treated with all comparators. The ERG considers that modelling premature discontinuation would be unlikely to significantly affect the results of the incremental analysis in that, as the risk of stroke is greater for edoxaban compared to apixaban and dabigatran 150mg, no change to edoxaban being dominated would be expected. Considering the pairwise analysis, including an increased risk of stroke following switching could be expected to have a relatively greater impact (reduction) on the QALY estimates for warfarin compared to edoxaban, and decrease the ICER per QALY gained for edoxaban compared to warfarin.

Validation

Following the ERG's request (via the clarification process) the company provided [redacted]

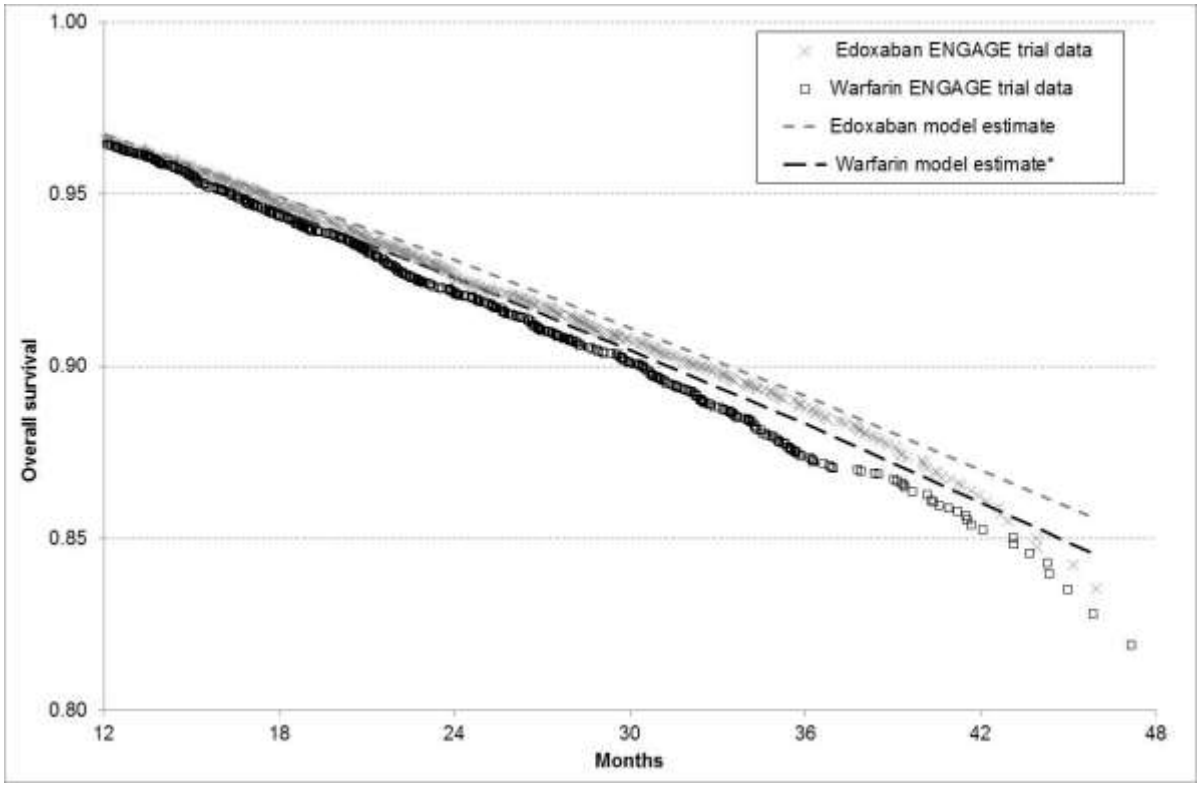

Figure 9 A comparison of OS data from the company's model and the ENGAGE trial

[redacted]

Figure 10 Cumulative hazard plot of OS survival from the company's model and the ENGAGE trial

[redacted]. This raises concern as to the validity of the model. Data relating to OS from the ENGAGE trial are not directly included in the company model. Event rates for key health outcomes, such as stroke and MI, are based on data from the ENGAGE trial, however, these have been adjusted using various other sources to inform key parameters including acute and long-term mortality, risk of recurrence of stroke and other cause mortality. The ERG considers that the plausibility of the model results rest on whether the clinical outcomes reported in the ENGAGE trial could reasonably be expected to be worse than UK clinical practice. The ERG notes that data from clinical trials may sometimes reflect better clinical outcomes than clinical practice, for example, due to the selection of patients or increased monitoring. However, the ERG also notes that the ENGAGE trial was conducted in a range of countries in which there may be variations in outcomes.

Further investigation by the ERG suggests that about half of this difference could be explained by flaws in the method used by the company to incorporate acute stroke mortality into the model; however, this alone does not fully explain the discrepancy between the estimates from the ENGAGE trial and model. Analyses carried out by the ERG show that, after applying an adjustment, based on information in the Janes[64] study, to the acute fatality rates for all IS and HS strokes the differences between the ENGAGE trial and model outputs decrease compared with those seen in

Figure 10. However, as this adjustment affects both warfarin and edoxaban, it does not have a substantial impact on the cost effectiveness results (Section 6).

To assess the impact of the difference between the ENGAGE trial and model OS on the model results, the ERG conducted further analyses. The company model includes an adjustment factor for other-cause mortality rates for people with NVAF, which applies to all arms in the model. This was varied to minimize the differences between trial results and the model OS estimates in both arms (residual sum of squared differences), and the cost-effectiveness results were re-estimated. Using the company base case analysis as a starting point, increasing the other-cause mortality adjustment factor from 1.34 to 1.542 produced similar survival estimates between the model and trial. This increased the ICER for edoxaban compared to warfarin by £912 per QALY gained in the pairwise analysis. A second calibration was undertaken using the company base case analysis with the ERG amendment to acute stroke fatality rates as a starting point; in this case an adjustment factor of 1.477 was required to produce similar trial and model estimates, and increased the ICER by £402 in the pairwise analysis. This is the ERG's preferred amendment to reconciling model estimates of OS, with those observed in the ENGAGE trial.

5.6.6 Health-related quality of life

The ERG has various concerns about the HRQoL data used in the company's model. These relate to the:

- age-related utility decrement
- ENGAGE trial utility data
- utility estimate associated with stable AF
- post-event SE utility
- utility values for the MI and TIA health states

Age-related utility decrement

The company uses an estimate, attributed to Sullivan[72], as the source for the age-related utility decrement in the model (-0.00029 per annum). The ERG notes that this is based on data relating to a US population, although the UK tariff of values has been applied to these figures. As the data on based on the self-reported health status of a US population, they may not be generalisable to a UK population.

Data reported from a UK population are available from the study used to calculate the standard UK tariff for the EQ-5D and reported in a paper entitled "UK Population Norms for EQ-5D"[82]. The ERG has used these data to calibrate separate linear regression equations for adult males and females aged 35 and over.

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[83]). In this STA[83], the ERG used EQ-5D data from the Health Survey for England[84] and an analysis using these data yielded an estimated annual utility decrement of -0.00646. Including this estimate in the incremental analyses using the company's model does not affect the result that edoxaban is dominated by other treatments. However, it substantially increases the ICER in the deterministic (probabilistic) pairwise comparison of edoxaban versus warfarin and results in an ICER of £34,008 (£37,129) per QALY gained. Clearly, the choice of an appropriate source for populating this parameter is of critical importance to the appraisal of edoxaban. Since the Health Survey for England[84] data reflect a more representative population, this more recent analysis is preferred by the ERG for assessing this effect in model.

ENGAGE trial utility data

Although EQ-5D data were collected as part of the ENGAGE trial, the CS base case utility value for the stable AF health state has been extracted from a UK study by Khan.[71] The ERG notes that the Khan[71] study had a modest sample size of 125 patients, with a low response rate and was designed to assess the effect of an anticoagulation education programme and self-monitoring of patients with AF taking warfarin. The ERG considers that the sample was selective and may not be representative of a general AF population. The ERG acknowledges that these data meet the NICE reference case[49] criteria and were used in a previous STA[31]; however, the ERG also notes that directly collected EQ-5D data were not available for use in the aforementioned STA.[31]

Utility estimate associated with stable atrial fibrillation

The CS includes a sensitivity analysis using a utility estimate for patients with stable AF directly collected from patients in the ENGAGE trial; however this was calculated using US preference weights and therefore does not meet the NICE reference case[49] criteria. Following a request from the ERG (via the clarification process) the company provided results of an analysis of EQ-5D data collected as part of the ENGAGE trial, with the standard UK EQ-5D tariff applied to all patients in the trial and for the UK subgroup of patients. The ERG notes that the estimated average baseline utility, calculated by the company using pooled edoxaban and warfarin data from UK participants, was [redacted]

Although used in a previous STA,[31] the ERG has three concerns with the utility estimates used in the model for the stroke health states, which were extracted from a study by Gage[73]:

- They do not meet NICE reference case criteria[49] as they were elicited by presenting hypothetical scenarios of anticipated stroke to patients with AF and so are not based

on patients' self-reported health status and have not been obtained using the EQ-5D or another standardised and validated generic HRQoL instrument.

- The estimates have been calculated from the study as the difference between the value of hypothetical stroke health states and the value of 'current' health state of the patients who valued those states. The ERG considers that, as the values are for hypothetical final stroke health states and unrelated to the respondents' health state, it is inappropriate to adjust for the respondents' health state.
- The estimates assume that there is no difference in health-related utility in the acute and post-event health states. It is possible that patients' HRQoL may improve over time following a stroke as reported by Luengo-Fernandez.[85]

The ERG carried out two analyses, using alternative EQ-5D estimates, namely those reported by:

- Gage[73] without any adjustment for respondents' current health and
- Luengo-Fernandez[85] for the acute and post-event stages, for each category of mild, moderate and severe stroke.

In both the deterministic and probabilistic incremental analyses, edoxaban was more costly and less effective than at least one other treatment option.

Utility values for the MI and TIA health states

The ERG conducted analyses using alternative sources for the utility estimates for MI[76] and TIA[74]. In the CS, data for MI were sourced from a paper by Sullivan[76] which was based on data from a US population. The ERG used data from a later paper by Sullivan[72] which is based on data from a UK population (used by the company to estimate the utility associated with SE). Data for utility associated with TIA were taken from the study by Luengo-Fernandez[85] In both sensitivity analyses there was no change in the overall results, edoxaban remained dominated and there was little change to the ICERs per QALY gained.

The deterministic pairwise results of the re-analysis using alternative MI data show that the ICER for edoxaban versus warfarin is slightly reduced to £12,818 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is also reduced (£16,063 per QALY gained).

The deterministic pairwise results of the re-analysis using alternative TIA data show that the ICER for edoxaban versus warfarin is slightly reduced to £12,823 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is also reduced (£15,047 per QALY gained).

Post-event SE utility

The ERG considers that the post-event utility value used in the model has been calculated incorrectly. The source paper (Sullivan[72]) reports two regression models and the ERG believes that the company has incorrectly used the coefficient for SE from one model and a coefficient representing multiple comorbidities from the other. However, amending this discrepancy has a negligible impact on model results. The deterministic pairwise results of this analysis show that the ICER for edoxaban versus warfarin is slightly reduced to £12,823 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is also reduced (£15,171 per QALY gained).

The ERG's also carried out an analysis using an alternative utility estimate for SE. The results of this preferred approach show that there was little impact on the results. In the deterministic pairwise analysis the ICER for edoxaban versus warfarin did not change and in the incremental analysis edoxaban remained dominated.

5.6.7 Resources and costs

Warfarin cost

The cost of warfarin used in the company's model (£0.11 per day) was estimated using the list prices reported in the BNF[79]. However, warfarin is a generic product that is widely available to the NHS at discounted prices. The Department of Health's eMit database[86] provides information about prices and usage for generic drugs and pharmaceutical products. The ERG carried out an analysis using the warfarin cost estimated from figures reported in this database (£0.0375). The deterministic pairwise results of this analysis data show that the ICER for edoxaban versus warfarin is increased to £13,883 per QALY gained; the ICER for edoxaban versus warfarin in the probabilistic analysis is reduced (£16,159 per QALY gained).

Warfarin monitoring cost

The annual cost of INR monitoring for patients treated with warfarin used in the company's model is £265.03; this figure is based on the unit costs included in a previous NICE STA (apixaban[31]) and is derived from assumptions regarding the proportions of people monitored in primary and secondary care settings from a previous NICE STA (rivaroxaban[30]). The ERG notes that a simple inflation of the annual INR monitoring cost for warfarin used in the previous NICE appraisal (apixaban[31]) would yield a cost of £257.11. The ERG considers that if the lower cost had been used in the model the effect on the company's base case results would have been minimal.

Costs for acute-MI, post-MI and temporary events (i.e. other ICH, TIA, non-ICH major bleed, CRNMB) are sourced from the NHS Reference Costs 2012-13[78]. The health care resource

group (HRG) codes and methods used to estimate costs are appropriate. However, NHS Reference Costs for 2013-14[87] were released on 27 November 27 2014 and should have been used in the model. The ERG carried out an analysis using the current costs. However, this change had little impact on the company's base case cost effectiveness results (deterministic and probabilistic).

5.6.8 Cost effectiveness results

Base case results

The 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 differ between the probabilistic and deterministic analyses. In the deterministic analysis dabigatran 150mg dominates the other NOACs (is less costly and more effective), whereas in the probabilistic analysis apixaban dominates dabigatran 150mg. The ERG considers that this is due to the very small differences in QALYs between dabigatran 150mg and apixaban in all analyses. In addition the results of the probabilistic analysis are 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.

Sensitivity analyses

The sensitivity analyses carried out by the company were deterministic and reflected a series of pairwise comparisons. The impact of changing base case parameter values was presented in terms of the impact on NMB.

The ERG notes various discrepancies between the probabilistic distributions used in the model and those reported in the CS (Appendix 10.7). However, using the values reported in the CS does not change the results of the probabilistic base case analysis. In addition, the ERG has 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 reflects a lifetime horizon and so underestimates 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.

5.6.9 Subgroup analyses

Two subgroup were highlighted in the NICE scope[44], TTR on warfarin and level of stroke/thromboembolic risk. The company undertook an analysis for patients with

$CHADS_2 \geq 3$ and another based on centre time in therapeutic range (cTTR≥60%). However, very limited data specific to these subgroups were available 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 is unclear.

5.6.10 Other inconsistencies identified by the ERG

1. There is some confusion in the labelling of the dabigatran comparators in the original and revised CS and in the company's response to clarification.
2. The regimen including dose reduction implemented in the model is incorrectly labelled in parts of the CS (the labels for "Dabigatran 150mg" and "Dabigatran 110mg" should be reversed in Tables 62 and 82)."
3. The company use a reference by Janes[64] to estimate the risk of stroke; however, the data described in that paper are not specific to patients with AF.
4. The HRs from the NMA for warfarin, for the $CHADS_2 \geq 2$ and $CHADS_2 \geq 3$ populations, that are reported in Table 51 are not those used in the model; however the values actually used in the model are consistent with results from the NMA.
5. The CS includes a pre-inflation cost of £4,078 (CS, Table 65) for acute SE; however, a figure of £3,958, which is compatible with the stated source, is implemented in the model.
6. The monthly cost of warfarin monitoring following an event-related discontinuation of therapy should be £22.09, not £3.26 (which is the cost of warfarin acquisition). The ERG considers that the impact, on deterministic and probabilistic base case results, of correcting this error is likely to be minimal.
7. Luengo-Fernandez[77] reports a mean cost per person for resource use for 90 days post-stroke; however, this cost is applied to a model cycle of 30 days. The ERG considers that use of the correct cost would have had a minimal impact on the company's base case cost effectiveness results (deterministic and probabilistic).

5.7 Conclusions of the cost effectiveness section

The company developed a de novo economic model. Deterministic (probabilistic) results generated by the model show that the ICER for the pairwise comparison of edoxaban with warfarin is £12,881 (£16,871) per QALY gained. The fully incremental analyses show that edoxaban is dominated (less effective and more costly than at least one other alternative) in base case analyses (deterministic and probabilistic) and that this result is robust to various amendments.

The ERG notes 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 is between rivaroxaban and warfarin (£3455) and the biggest difference in lifetime QALYs is between apixaban and warfarin (0.205, i.e. 75 days).

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

- The incremental analysis is based upon the company's NMA. Analysis by the ERG has shown that 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 HRQoL with increasing age are based on data from a US population and significantly underestimate this impact when compared with data from a UK population.
- The model overestimates OS when the outputs are compared with data from the ENGAGE trial.
- The company conducted sub-group analyses as requested in the NICE scope. As limited data were available to the company to inform the subgroup analyses, much of the data on relative effectiveness is the same as that used in the base case analyses. The robustness of the results of the subgroup analyses therefore depend on the robustness of the assumption of no differences in relative treatment effects between these groups.

The ERG has reviewed the decision model submitted by the company and notes that it appears 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 is more expensive and less effective that at least one of the alternative treatments when full incremental analyses are carried out. The largest change to base case was as a result of using the ERG's preferred age-adjusted HRQoL values, i.e. adjustments relating to a UK rather than a US population. However, when all of the ERG's preferred values are used in the model the resultant pairwise deterministic (probabilistic) ICERS for the comparison of edoxaban with warfarin are £49,305 (£34,553). 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 £37,000 and £50,000, and the probabilistic results to between £45,000 and £60,000.

6 IMPACT ON THE ICER OF ADDITIONAL ANALYSES UNDERTAKEN BY THE ERG

The cost effectiveness results generated as a result of model amendments and corrections implemented by the ERG to examine issues described in section 5 of this report are displayed in Table 47 (deterministic incremental analysis) and Table 48 (probabilistic incremental analysis). The changes feature up to 16 revisions which use the ERG's preferred alternative parameter values or formulae.

The changes carried out by the ERG are listed below and further details of their implementation are reported in Appendix 8 of this ERG report. Further details on the costs and QALY estimates for each comparator following the amendments are provided in Appendix 9.

The analyses are detailed in Appendix 8 and include:

R1. Correcting an error in the cell reference for the utility estimate for post-SE (change estimate from 0.74 to 0.68)

R2. Employing an alternative utility estimate for the SE state based on regression coefficients from a single regression model (Updated value = 0.69)[72]

R3. Using HRs in the incremental analysis for warfarin from the company's NMA rather than HR from the ENGAGE trial data.

R4. Using an alternative utility estimate for the MI state based on UK data reported by Sullivan (updated value = 0.663)[72]

R5. Using an alternative utility estimate for the TIA state based on the study by Luengo-Fernandez[85] (updated decrement = -0.086)[85]

R6. Using the company's utility values for mild, moderate and severe stroke states without the adjustment for respondents' own health (updated values: 0.76, 0.39, 0.11 respectively)[73]

R7. Using alternative utility values for stroke states based on the study by Luengo-Fernandez[75] (updated values for acute mild, moderate and severe stroke states: 0.63, 0.40, and 0.03 respectively. Post-event mild, moderate and severe stroke states: 0.63, 0.46 and 0.28)[85]

R8. Assuming all patients receiving dabigatran 150mg switch treatment at age 80 years to dabigatran 110mg

R9. Assuming all patients discontinue treatment following HS

R10. Applying the acute stroke fatality rate to all stroke events (mild stroke change to 16.8% (IS) and 31.6% (HS) from 0%)

R11. Use case fatality rates for mild, moderate and severe acute stroke sourced from ENGAGE trial data

R12. Amend age adjusted utility decrement per year (change from -0.00029 to -0.00646)

R13. Warfarin daily cost sourced from eMIT as per NICE reference case (change from 0.11 to 0.04 per day)

R14. Amendments to reflect a distribution of different starting ages, each with different gender distribution

R15. Applying ENGAGE trial hazard rates for HS

R16. Reconcile OS estimates by adjusting other cause mortality adjustment factor and using trial data for acute stroke case fatality rates for mild, moderate and severe stroke

The ERG also carried out four analyses in which multiple parameters were changed. The pairwise analysis excluded the amendment to use the warfarin hazard ratios from the NMA. The amendments are labelled C, D, E and F and results presented in Table 47 to Table 52:

- Analysis C: ERG sourced utility values for SE (R2), warfarin hazard ratios from NMA (R3), alternative utility values for MI (R4), TIA (R5) and ERG sourced utility values for acute and post stroke health states (R7).
- Analysis D: ERG sourced utility values for SE (R2), warfarin hazard ratios from NMA (R3), alternative utility values for MI (R4), TIA (R5) and ERG sourced utility values for acute and post stroke health states (R7), assumption regarding method used to switch patient medication from dabigatran 150mg to 110mg at age 80 (R8), assumption regarding treatment discontinuation after HS (R9), amendment to age adjusted utility decrement per year (R12), change in daily cost warfarin (R13), plus applying the ENGAGE trial HR for HS (R15).
- Analysis E: All the amendments introduced in analysis D plus applying the amendment to the probabilities of acute stroke fatality from the trial (R15)
- Analysis F: All the amendments introduced in analysis D plus applying the amendment to reconcile the model and ENGAGE trial OS estimates (R16) and the age/gender distribution over time (R14).

Table 47 ERG analyses: incremental deterministic results (incremental cost per QALY gained)

Scenario/revision		Comparator					
		Edoxaban	Apixaban	Rivaroxaban	Dabigatran 110mg	Dabigatran 150mg	Warfarin
A	**CS deterministic base case**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£7,645**	**-**
B	**CS probabilistic base case**	**Dominated**	**£13,036**	**Dominated**	**Dominated**	**Extendedly Dominated**	**-**
R1	CS base case-corrected utility for SE*	Dominated	£15,275	Dominated	Dominated	£12,210	-
R2	CS base case - alternative utility value for SE	Dominated	£15,531	Dominated	Dominated	£13,365	-
R3	Hazard ratio for Warfarin from NMA	Dominated	£14,960	Dominated	Dominated	£14,273	-
R4	Alternative utility value for MI	Dominated	£21,363	Dominated	Dominated	£12,052	-
R5	Alternative utility value for TIA	Dominated	£23,933	Dominated	Dominated	£11,565	
R6	Corrected utility values for mild, moderate and severe stroke	Dominated	£15,275	Dominated	Dominated	£12,210	-
R7	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	Dominated	£16,132	Dominated	Dominated	£12,691	-
R8	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	Dominated	Dominated	Dominated	Dominated	£10,570	-
R9	Discontinuation rate medication following HS set at 100%	Dominated	£12,543	Dominated	Dominated	Extendedly Dominated	-
R10	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	Dominated	£15,050	Dominated	Dominated	£12,756	-
R11	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	Dominated	£15,793	Dominated	Dominated	£13,486	-
R12	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	Dominated	Dominated	Dominated	Dominated	£19,428	-
R13	Warfarin daily cost sourced from eMIT as per NICE reference case	Dominated	£12,902	Dominated	Dominated	Extendedly Dominated	**-**

Table 47 ERG analyses: incremental deterministic results (incremental cost per QALY gained) continued

Scenario/revision		Comparator					
		Edoxaban	Apixaban	Rivaroxaban	Dabigatran 110mg	Dabigatran 150mg	Warfarin
R14	Change in age and gender distribution over time	Dominated	Dominated	Dominated	Dominated	£4,976	-
R15	Apply ENGAGE trial hazard rates for HS	Dominated	Dominated	Dominated	Dominated	£10,323	-
R16	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	Dominated	Dominated	Dominated	Dominated	£8,080	-
C	R2+R3+R4+R5+R7	Dominated	Dominated	Dominated	Dominated	£7,841	-
D	**R2+R3+R4+R5+R7+R8+R9+R12+R13+R15**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£21,997**	**-**
E	**R2+R3+R4+R5+R7+R8+R9+R11+R12+R13+R15**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£23,436**	**-**
F	**R2+R3+R4+R5+R7+R8+R9+R12+R13+R14+R15+R16**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£15,084**	**-**

*Base case used for model amendments R2-R14

Table 48 ERG analyses: incremental probabilistic results

Scenario/revision		Comparator					
		Edoxaban	Apixaban	Rivaroxaban	Dabigatran 110mg	Dabigatran 150mg	Warfarin
A	**CS deterministic base case**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£7,645**	**-**
B	**CS probabilistic base case**	**Dominated**	**£13,036**	**Dominated**	**Dominated**	**Extendedly Dominated**	**-**
R1	CS base case-corrected utility for SE*	Dominated	£15,275	Dominated	Dominated	£12,210	-
R2	CS base case - alternative utility value for SE	Dominated	£15,531	Dominated	Dominated	£13,365	-
R3	Hazard ratio for Warfarin from NMA	Dominated	£14,960	Dominated	Dominated	£14,273	-
R4	Alternative utility value for MI	Dominated	£21,363	Dominated	Dominated	£12,052	-
R5	Alternative utility value for TIA	Dominated	£23,933	Dominated	Dominated	£11,565	
R6	Corrected utility values for mild, moderate and severe stroke	Dominated	£15,275	Dominated	Dominated	£12,210	-
R7	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	Dominated	£16,132	Dominated	Dominated	£12,691	-
R8	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	Dominated	Dominated	Dominated	Dominated	£10,570	-
R9	Discontinuation rate medication following HS set at 100%	Dominated	£12,543	Dominated	Dominated	Extendedly Dominated	-
R10	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	Dominated	£15,050	Dominated	Dominated	£12,756	-
R11	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	Dominated	£15,793	Dominated	Dominated	£13,486	-
R12	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	Dominated	£33,313	Dominated	Dominated	£28,308	-
R13	Warfarin daily cost sourced from eMIT as per NICE reference case	Dominated	£12,902	Dominated	Dominated	Extendedly Dominated	**-**

Table 49 ERG analyses: incremental probabilistic results continued

	Scenario/revision	Comparator					
		Edoxaban	**Apixaban**	**Rivaroxaban**	**Dabigatran 110mg**	**Dabigatran 150mg**	**Warfarin**
R14	Change in age and gender distribution over time	Dominated	Dominated	Dominated	Dominated	£8,045	-
R15	Apply ENGAGE trial hazard rates for HS	Dominated	Dominated	Dominated	Dominated	£10,323	-
R16	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	Dominated	£20,549	Dominated	Dominated	£13,763	-
C	R2+R3+R4+R5+R7	Dominated	£13,358	Dominated	Dominated	Extendedly Dominated	-
D	**R2+R3+R4+R5+R7+R8+R9+R12+R13+R15**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£34,553**	**-**
E	**R2+R3+R4+R5+R7+R8+R9+R11+R12+R13 +R15**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£40,994**	**-**
F	**R2+R3+R4+R5+R7+R8+R9+R12+R13+R14+R15+R16**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£24,202**	**-**

Table 50 ERG analyses: pairwise deterministic results (edoxaban versus warfarin)

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
A	**CS deterministic base case**	£15,957	6.52	£13,413	6.32	£2,544	0.20	£12,881
R1	CS base case-corrected utility for SE*	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R2	Alternative utility value for SE	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R3	HR for warfarin from NMA	£15,957	6.51	£13,403	6.32	£2,554	0.19	£13,287
R4	Alternative utility value for MI	£15,957	6.51	£13,413	6.31	£2,554	0.20	£12,818
R5	Alternative utility value for TIA	£15,957	6.51	£13,413	6.32	£2,554	0.20	£12,823
R6	Corrected utility values for mild, moderate and severe stroke	£15,957	6.53	£13,413	6.34	£2,554	0.20	£12,951
R7	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,809
R8	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
R9	Discontinuation rate medication following HS set at 100%	£15,927	6.51	£13,385	6.32	£2,542	0.20	£12,813
R10	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
R11	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
R12	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
R13	Warfarin daily cost sourced from eMIT as per NICE reference case	£15,957	6.51	£13,203	6.32	£2,754	0.20	£13,883
R14	Change in age and gender distribution over time	£18,365	6.92	£15,806	6.66	£2,558	0.26	£10,010
R15	Apply ENGAGE trial hazard rates for HS	£15,957	6.51	£13,078	6.35	£2,879	0.17	£17,137
R16	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	£15,35	6.24	£12,904	6.06	£2,430	0.18	£13,735

Table 51 ERG analyses: pairwise deterministic results (edoxaban versus warfarin) continued

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
C	R2+R4+R5+R7	£15,957	6.51	£13,413	6.31	£2,544	0.20	£12,811
D	**R2+R4+R5+R7+R8+R9+R12+R13+R15**	**£15,927**	**2.34**	**£12,847**	**2.38**	**£3,080**	**0.06**	**£49,305**
E	**R2+R4+R5+R7+R8+R9+R11+R12+R13+R15**	**£15,539**	**2.33**	**£12,360**	**2.27**	**£3,179**	**0.06**	**£50,102**
F	**R2+R4+R5+R7+R8+R9+R12+R13+R14+R15 +R16**	**£17,735**	**2.57**	**£14,679**	**2.49**	**£3,055**	**0.08**	**£36,966**

Table 52 ERG analyses: pairwise probabilistic results (edoxaban versus warfarin)

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
A	**CS deterministic base case**	**£15,957**	**6.52**	**£13,413**	**6.32**	**£2,544**	**0.20**	**£12,720**
B	**CS probabilistic base case**	**£15,471**	**6.72**	**£12,868**	**6.56**	**£2,603**	**0.16**	**£16,269**
R1	CS base case-corrected utility for SE*	£15,404	6.74	£12,825	6.57	£2,579	0.17	£15,171
R2	Alternative utility value for SE	£15,462	6.73	£12,832	6.58	£2,630	0.15	£17,533
R3	HR for warfarin from NMA	£15,389	6.76	£12,753	6.62	£2,636	0.14	£18,829
R4	Alternative utility value for MI	£15,432	6.75	£12,862	6.59	£2,570	0.16	£16,063
R5	Alternative utility value for TIA	£15,474	6.75	£12,916	6.58	£2,558	0.17	£15,047
R6	Corrected utility values for mild, moderate and severe stroke	£15,476	6.73	£12,975	6.56	£2,501	0.17	£14,712
R7	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	£15,397	6.76	£12,784	6.6	£2,613	0.16	£16,331
R8	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	£15,382	6.75	£12,807	6.58	£2,575	0.17	£15,147
R9	Discontinuation rate medication following HS set at 100%	£15,428	6.74	£12,844	6.58	£2,584	0.16	£16,150
R10	Apply acute stroke fatality rates to all IS and HS strokes in the model	£15,466	6.74	£12,873	6.58	£2,593	0.16	£16,206
R11	Use trial data on acute stroke case fatality rates for all IS and HS stroke	£15,317	6.73	£12,643	6.58	£2,674	0.15	£17,827
R12	Age adjusted utility decrement per year changed from -0.00029 to -0.00646	£15,478	2.42	£12,879	2.35	£2,599	0.07	£37,129
R13	Warfarin daily cost sourced from eMIT as per NICE reference cost	£15,557	6.74	£12,810	6.57	£2,747	0.17	£16,159
R14	Change in age and gender split over time	£17,794	7.20	£15,233	7.00	£2,561	0.20	£12,805
R15	Apply ENGAGE trial hazard rates for HS	£15,532	6.73	£12,587	6.60	£2,945	0.13	£22,654
R16	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	£14,717	6.43	£12,201	6.29	£2,516	0.14	£17,971

Table 53 ERG analyses: pairwise probabilistic results (edoxaban versus warfarin) continued

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
C	R2+R4+R5+R7	£15,381	6.76	£12,715	6.62	£2,666	0.14	£19,043
D	**R2+R4+R5+R7+R8+R9+R12+R13+R15**	**£15,381**	**2.44**	**£12,334**	**2.39**	**£3,047**	**0.05**	**£60,940**
E	**R2+R4+R5+R7+R8+R9+R11+R12+R13+R15**	**£15,375**	**2.43**	**£12,345**	**2.38**	**£3,030**	**0.05**	**£60,600**
F	**R2+R4+R5+R7+R8+R9+R12+R13+R14+R15+R16**	**£17,122**	**2.69**	**£13,998**	**2.62**	**£3,124**	**0.07**	**£44,629**

7 END OF LIFE

The company has not put forward a case for edoxaban to be considered under the NICE End of life criteria. The ERG considers this to be appropriate.

8 OVERALL CONCLUSIONS

8.1 Conclusions of the clinical effectiveness section

The company provided a detailed submission that fully addressed the NICE scope[44].

8.1.1 Direct evidence

The key clinical evidence for the efficacy and safety of edoxaban was derived from the ENGAGE trial, which was considered to be of good quality. The ENGAGE trial included a substantial follow-up period of 2.8 years (median) and the data collected were fully mature. In addition, the trial included a well-controlled warfarin arm as a comparator to edoxaban. Trial evidence suggests that, treatment with edoxaban is non-inferior to treatment with warfarin for the prevention of stroke or SE in patients with NVAF who have a $CHADS_2$ ≥2. The results of the trial were driven largely by a reduction in HS events in patients treated with edoxaban. The safety data demonstrate that patients treated with edoxaban experienced statistically significantly fewer major bleeding events than patients treated with warfarin. However, there were statistically significantly greater numbers of GI bleeds in patients treated with edoxaban compared with patients treated with edoxaban. The HRQoL data that were provided as part of the clarification process are difficult to interpret due to the low response rate and incomplete analysis.

At 2.8 years (median) the duration of follow-up in the ENGAGE trial is substantial when compared with trials of other NOACS. However, it is worth noting that patients with NVAF are normally treated with anticoagulants for their lifetime.

At the time of the submission of this ERG report, the EMA had not published any opinion relevant to the marketing authorisation for edoxaban. Therefore, no European Public Assessment Report was available and the EMA's view of the efficacy of edoxaban compared with warfarin is unknown.

<u>Patient subgroups</u>

In clinical practice in England and Wales, the current NICE guideline[24] recommends that anticoagulation is considered for men with a CHA_2DS_2-VASc score of 1 and is offered to men and women with a CHA_2DS_2-VASc score ≥2 or above, taking their bleeding risk into account. The ERG considers NICE's guideline[24] encompasses patients with a lower risk of

stroke (i.e. similar to a $CHADS_2$ =1). The ENGAGE trial, however, only included patients with a $CHADS_2$ ≥2. It is currently unclear whether results from the ENGAGE trial can be generalised to those with a $CHADS_2$=1, i.e. patients at lower risk of stroke and SE.

The company presented an analysis of patients by renal function as measured by creatinine clearance. The results of the company's subgroup analysis suggest that, for patients with normal renal function (CrCL≥80 mL/min), the risk of experiencing a primary outcome event was higher in the edoxaban arm than in the warfarin arm. However, the ERG acknowledges that the company presents reasonable arguments which suggest that the detected subgroup difference may be a spurious result.

The ERG notes that the outcomes for the pre-specified subgroup that included Turkey and Israel favoured warfarin over edoxaban. However, the results of the company's post-hoc analyses of outcomes for countries in the European Economic Area plus Switzerland favoured edoxaban. The ERG considers that the latter finding should be treated with caution as the analysis was not pre-specified and may be the result of a data-mining exercise.

The ERG is aware that in clinical practice, there are patients with NVAF who undergo treatment with cardioversion. The company has not provided any outcome results for patients treated with cardioversion; however, a trial (PROBE[43]) is underway. If patients in clinical practice who are treated with edoxaban need to switch to an alternative anticoagulation treatment for cardioversion, then this would be a limitation of edoxaban treatment.

8.1.2 Indirect evidence

There are no trials that directly compare the use of edoxaban with the use of apixaban, dabigatran or rivaroxaban in patients with NVAF. However, the pivotal trials for each of these trials use warfarin as a comparator arm; this facilitated a network and the company concluded that trials were sufficiently similar to allow a NMA to be undertaken.

The base case NMA included inputs that related to the patient population with $CHADS_2$ ≥2. However, across all four trials,[25,27,28,88] only results relating to the primary efficacy outcome (the composite endpoint of stroke and SE) and the primary safety endpoint (major bleeding) were available for the $CHADS_2$ ≥ 2 population. The results suggest that in terms of the primary endpoint, edoxaban [redacted] Whilst, in terms of major bleeding, results suggest that edoxaban [redacted]

[redacted]

Where parameter values were required to populate the company's economic model, but were unavailable from patients with a $CHADS_2$ ≥2, two additional assumptions were included in the NMA methods. Where available, data from whole trial populations (not just $CHADS_2$ ≥2) were included and, where such evidence was not available, a HR equal to 1 was assumed.

The ERG has considerable concern in relation to the validity of the results from the company's NMA. For results from NMA to be reliable, the included trials need to be similar (in terms of study population, design, outcome measures, and also effect modifies [e.g. age, disease severity, duration of follow-up]) and the HRs linking values for outcome measures within, and between, trials need to be proportional. Violation of the proportional hazards assumption violates the theory of transitivity that underpins a NMA, i.e. if A is better than B and B is better than C then A must be better than C.

The company has shown that, by and large, the included trials are similar. However, the results of the additional analyses of ENGAGE trial data undertaken by the ERG show that the assumption of proportional hazards in terms of HS does not hold. Furthermore, the results of exploratory analyses carried out by the ERG, using warfarin data from all four included trials,[25,27,28,88] show that, in terms of the primary outcome, the assumption of proportional hazards again does not hold. The results of the ERG's analysis of major bleeding data from the warfarin arms of ENGAGE and [27]also show that the assumption of proportional hazards does not hold; comparable data were not available from RE-LY[25] and ROCKET-AF.[28]

The impact of these violations of the proportional hazards assumption on the size of NMA outputs is not known. However, it should be noted that these violations mean that the mathematics used to generate the output HRs has been fundamentally compromised and, therefore, reliable HR estimates have not been generated.

8.2 Economic model/cost effectiveness issues

The economic model submitted by the company addressed the decision problem outlined in the NICE scope and included all key comparators. The results of the incremental analyses show that edoxaban is not cost-effective as it is dominated (less effective and more costly) by other alternative treatments. This result was robust to various sensitivity analyses conducted by the company and ERG.

The results of the economic analysis are driven by the results of the NMAs. The ERG has serious concerns about the robustness of these results given that the assumption of proportionality required for these analyses does not hold. In addition, the ERG notes that the trials for one of the NMAs used in the economic analysis included different populations; the trials of apixaban and dabigatran included patients with $CHADS_2$ ≥1 whereas the trials of edoxaban and rivaroxaban were limited to patients with $CHADS_2$ ≥2. Given these concerns about the NMA, the ERG has significant concerns about the robustness of the results of the incremental analysis.

The ERG had concerns about some of the data inputs included in the economic model. Whilst the results were robust to sensitivity analyses exploring the impact of many alternative data sources and assumptions, the results were sensitive to the choice of data to inform deterioration in HRQoL with increasing age. In the CS, this was based on data from a US population. The ERG considers that data from a UK population would be more appropriate. A sensitivity analysis conducted by the ERG found that use of UK data for this parameter substantially increased the ICER for edoxaban compared to warfarin to £34,008 in the pairwise analysis. Including this amendment alongside other preferred ERG sources of data in the deterministic pairwise comparison with warfarin increased the ICER for edoxaban 49,305. Additional analyses conducted by the ERG to explore alternative approaches to reconciling the model outputs with the ENGAGE trial and the age/gender distribution over time led to ICERs of approximately £37,000 and £50,000. The results of the incremental analyses did not change, in that edoxaban remained dominated (was more costly and less effective) by other treatments included in the model.

The manufacturer presented results of subgroup analyses as requested by the NICE scope. Edoxaban was dominated by other treatment options in both subgroup analyses. The ERG notes that the data available to the company to inform these analyses were limited and hazard ratios for many of the comparisons and events were limited to those used in the company base case. The robustness of these results therefore depends on the robustness of the assumption of no difference in relative treatment effects between subgroups. The ERG notes a lack of data to inform this.

8.3 Implications for research

Due to the paucity of long-term evidence for both the continued benefit and safety of treatment with NOACs, close monitoring and surveillance of patients undergoing treatment with NOACs is necessary.

In addition, access to, support and best use of currently available clinical data from patient registries and hospital audits should be encouraged in order to explore the substantial uncertainty around key clinical issues for patients with NVAF.

A multiple technology appraisal would allow direct trial evidence to be used to determine the relative cost effectiveness of approved NOACS

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10 APPENDICES

Appendix 1

Inclusion and exclusion criteria for the ENGAGE trial

Inclusion criteria

- Subjects had to satisfy all of the following criteria to be included in the study:
- Male or female subjects with age ≥21 years;
- Able to provide written informed consent;
- History of AF documented by any electrical tracing (routine 12-lead electrocardiogram [ECG], Holter monitor [continuous ECG recording] rhythm strip, intracardiac electrocardiogram, or pacemaker or implantable cardiac defibrillator interrogation) within the prior 12 months and for which anticoagulation therapy was indicated and planned for the duration of the study;
    - Subjects with AF included subjects with paroxysmal, persistent, or permanent AF and subjects with or without previous VKA (including warfarin) experience (it was anticipated that approximately 40% of subjects would be VKA-naive);(VKA experienced was defined as current users as well as former users who took VKA for greater than 2 months. VKA naive was defined by the complement of VKA experienced for those subjects with e-CRF data present)
- Subjects had a $CHADS_2$ index score ≥2. The $CHADS_2$ scoring was performed by assigning 1 point each for a history of congestive heart failure (CHF), hypertension, age ≥75 years, or diabetes mellitus; and by assigning 2 points for history of stroke or TIA.

Exclusion criteria

Subjects who met any of the following criteria were disqualified from entering the study:

- Transient AF secondary to other reversible disorders (e.g., thyrotoxicosis, cardiac or thoracic surgery, pneumonia, severe anaemia);
- Subjects with moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves and/or valve repair could have been included);
    - However, subjects with AF and valvular heart diseases such as mitral valve prolapse, mitral valve regurgitation, and aortic valve disease were allowed in the study;
- Subjects with a history of left atrial appendage exclusion (either by surgery or by a procedure);
- Subjects with intracardiac mass or left ventricular thrombus;
- Subjects for whom discontinuation of chronic anticoagulation therapy was considered if a planned pharmacologic, electrical, or surgical therapy were to be successful in converting the subject to normal sinus rhythm and maintaining that rhythm;

- Subjects with any contraindication for anticoagulant agents;
- Subjects with conditions associated with high risk of bleeding such as past history of intracranial (spontaneous or traumatic), or spontaneous intraocular, spinal, retroperitoneal, or intra-articular bleeding; overt gastrointestinal (GI) bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy within the previous 10 days; active infective endocarditis; uncontrolled hypertension (blood pressure [BP] above 170/100 mmHg); or haemorrhagic disorder including known or suspected hereditary or acquired bleeding or coagulation disorder;
- Subjects who were receiving dual antiplatelet therapy (e.g., aspirin plus thienopyridine such as ticlopidine or clopidogrel) or were anticipated to receive such therapy unless all but 1 of the antiplatelet medications could have been safely stopped prior to randomisation and while receiving study drug;
- Subjects who were receiving chronic cyclosporine therapy;
- Subjects who were receiving prohibited concomitant medications (fibrinolytics, non-study anticoagulants other than those used as a bridge to/from study drug, chronic oral or parenteral non-aspirin non-steroidal anti-inflammatory drug (NSAID) (use of NSAIDs via other routes were not restricted) use for ≥4 days/week, and potent P-gp inhibitors as defined for this study;
- Subjects with acute MI, stroke, acute coronary syndrome (ACS), or percutaneous coronary intervention (PCI) within the previous 30 days;
- Subjects with active liver disease or persistent (confirmed by repeat assessments at least a week apart) elevation of liver enzymes/bilirubin:
    - Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2 times the upper limit of normal (ULN);
    - Total bilirubin (TBL) ≥1.5 times the ULN (however, subjects whose elevated TBL was due to known Gilbert's syndrome could have been included in the study);
- Subjects with severe renal insufficiency (calculated CrCL <30 mL/min);
- History of testing positive for Hepatitis B antigen or Hepatitis C antibody before randomisation;
- Any other clinically relevant laboratory abnormality as judged by the Investigator;
- Subjects with a known history of testing positive for human immunodeficiency virus (HIV);
- Subjects with haemoglobin (Hgb) <10 g/dL or platelet count <100,000 cells/ µl or white blood cell count (WBC) <3000 cells / µl;
- Subjects with pre-planned invasive procedures (other than routine endoscopy) or surgeries in which bleeding was anticipated during the study period;

- Subjects who received any investigational drug or device within 30 days prior to randomisation, or planned to receive such investigational therapy during the study period;
- Subjects previously randomised in an edoxaban study;
- Females of childbearing potential including the following:
    - Females with a history of tubal ligation;
    - Females less than 2 years postmenopausal;
- Subjects with the following diagnoses or situations:
    - Active malignancy (diagnosed within 5 years) except for adequately treated non-melanoma skin cancer or other non-invasive or in-situ neoplasm (e.g., cervical cancer in situ);
    - Treatment with cancer therapy (drugs, radiation, and/or surgery) within the last 5 years;
    - Significant active concurrent medical illness or infection;
    - Life expectancy <12 months;
- Subjects who were unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the Investigator to be unlikely to complete the study);
- Subjects with a known drug or alcohol dependence within the past 12 months as judged by the Investigator.

Subjects with any condition that, in the opinion of the Investigator, would have placed the subject at increased risk of harm if he/she participated in the study

Appendix 2

Cumulative hazard plots from the ENGAGE trial – IS and SE

[redacted]

Cumulative hazard plot for ischaemic stroke: ENGAGE trial

[redacted]

Cumulative hazard plot for SE; ENGAGE trial

Appendix 3

Additional safety data reported by the company

Additional safety data are provided in the CS from two sources. The first is a published paper[52] describing the initial 6 months of post-marketing experience of edoxaban in Japan following the approval of edoxaban for the prevention of VTE after orthopaedic surgery. The second source of safety data is the HOKUSAI-VTE[89] trial that compares edoxaban with warfarin for the treatment of symptomatic VTE. The ERG notes that neither data source includes patients with NVAF.

Post-marketing data from Japan

The company summarises the post-marketing data from Japan (at 6 months):

- A total of 67 AEs reported in 56 patients
- 51 bleeding events in 42 patients
- 15 serious AEs in 14 patients – all bleeding events
- The majority of bleeding events experienced by patients aged ≥75 years or who had a CrCl ≥50 mL/min.

It is stated in the CS that these findings are consistent with the known safety profile of edoxaban.

The ERG notes from the published paper[52] describing the Japanese data that the 20,000 people included in the database were treated with edoxaban.

HOKUSAI-VTE trial

The safety analyses for the non-inferiority HOKUSAI-VTE[89] trial (edoxaban 60mg with warfarin for the treatment of VTE) are presented in Table 38, Table 39 and Table 40 of the CS.

The mean duration of treatment in the trial was 251 days for patients in the edoxaban arm and 250 days for patients in the warfarin arm. Table 39 of the CS lists the bleeding events recorded during the trial. This is replicated here. The ERG notes that for the outcome of major bleeding, no statistically significant difference is reported for edoxaban versus warfarin. For all other bleeding outcomes, edoxaban was found to be statistically significantly superior to warfarin. The CS reports that the reduction in major/CRNM bleeding in the edoxaban arm compared with the warfarin arm was in evidence throughout the on-treatment study period.

Adjudicated bleeding events HOKUSAI-VTE trial

Bleeding Outcome	Warfarin (N=4122) n (%/year)	Edoxaban (N=4118) n (%/year)	Edoxaban vs Warfarin HR (95% CI) p-value (superiority)
Major bleeding	66 (1.6%)	56 (1.4%)	0.84 (0.59 to 1.21) p=0.352
Major or clinically relevant non-major bleeding	423 (10.3%)	349 (8.5%)	0.81 (0.71 to 0.94) p=0.004
Clinically relevant non-major bleeding	368 (8.9%)	298 (7.2%)	0.80 (0.68 to 0.93) p=0.004
[redacted]	[redacted]	[redacted]	[redacted]
Any bleeding	1056 (25.6%)	895 (21.7%)	0.82 (0.75 to 0.90) p<0.001

Source: CS, Table 39

Table 40 of the CS reports the results for the composite outcome of non-fatal MI, non-fatal stroke, non-fatal SE and CV death (MACE) and its constituents. The ERG agrees with the company's summary that similar numbers of events were experienced by patients in both arms of the HOKUSAI-VTE trial.

Appendix 4

Risk of bias assessments for the 4 trials included in the network meta-analysis

Study question reference	Support for judgement	Judgement (Low risk/High risk/Unclear risk/NA)	ERG comment
ARISTOTLE trial			
Random sequence generation (selection bias)	Have not mentioned the way of generating random sequence.	Unclear risk	Low risk At the time of enrolment, each subject was assigned a unique sequential subject number via IVRS. Subjects were randomised 1:1 to apixaban or warfarin via IVRS. Randomisation was stratified by investigative site and prior warfarin/VKA status (experienced or naive). Subjects were randomised in blocks of 2. (Taken from ERG report for TA275)
Allocation concealment (selection bias)	Quote: 'The 2 sets of tablets each subject receives are distinguishable by color and size, but active apixaban tablets match placebo apixaban tablets and active warfarin tablets match placebo warfarin tablets to ensure blinding of the patient and investigator.' 'An algorithm was provided to manage temporary discontinuations of the study drug around the time of interventional procedures while maintaining concealment of the group assignments.' The concealment bias should have been avoided.	Low risk	Low risk Method of randomisation ensures that treatment allocation could not be predicted
Blinding of participants and personnel (performance bias)	Quote: 'To maintain blinding, study medications are packaged using a double-dummy design.' 'INRs were monitored with the use of a blinded, encrypted, point-of-care INR device. An algorithm was provided to guide the adjustment of the warfarin does. ' The performance bias should have been avoided by this.	Low risk	Low risk
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Quote: 'This system processes the information in a blinded manner and returns either a true INR value (if a subject is receiving warfarin) or a sham INR value (if a subject is receiving apixaban). Although investigators will need to obtain open label INR values when clinically indicated, efforts will be made to minimize non study INR assessments'. 'The primary and secondary efficacy and safety outcomes were adjudicated on the basis of pre-specified criteria by a clinical-events committee whose members were not aware of study-group assignments.' From this, the blinding of outcome	Low risk	Low risk

	assessment should have been done.		
Blinding of outcome assessment (detection bias) (Mortality)	Quote: 'The primary and secondary efficacy and safety outcomes were adjudicated on the basis of pre-specified criteria by a clinical-events committee whose members were not aware of study-group assignments.' The detection bias should be avoided by this means.	Low risk	Low risk
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks)	Hard to tell which is short-term outcome	Unclear risk	Unclear risk
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks)	Quote: 'Data on vital status at the end of the trial were missing for 380 patients (2.1%). The absence of data on vital status was due to withdrawal of consent in the case of 92 patients in the apixaban group (1.0%) and 107 patients in the warfarin group (1.2%) and was due to loss to follow-up in the case of 35 patients in the apixaban group (0.4%) and 34 in the warfarin group (0.4%).' "The absence of data on vital status was due to withdrawal of consent in the case of 92 patients in the apixaban group (1.0%) and 107 patients in the warfarin group (1.2%) and was due to loss to follow-up in the case of 35 patients in the apixaban group (0.4%) and 34 in the warfarin group (0.4%)" Plus there is no intermediate outcome report, there might be high risk in terms of incomplete data	High risk	Low risk The number of patients lost to follow-up was similar in each arm. All losses were accounted for.
Selective reporting (reporting bias)and what was found	The authors report on all primary outcomes that they set out to measure	Low risk	Low risk
ROCKET AF trial			
Random sequence generation (selection bias)	Quote: 'Randomisation was performed with the use of a central 24-hour, computerised, automated voice-response system.' The random sequence generation was done scientifically.	Low risk	Low risk
Allocation concealment (selection bias)	Quote: 'Patients were randomly assigned to receive fixed dose rivaroxaban (20 mg daily or 15 mg daily in patients with a creatinine clearance of 30 to 49 ml per minute) or adjusted-dose warfarin (target international normalised ratio [INR], 2.0 to 3.0).' The allocation should avoid bias.	Low risk	Low risk Method of randomisation ensures that treatment allocation could not be predicted
Blinding of participants and personnel (performance bias)	Quote: 'A point-of-care device was used to generate encrypted values that were sent to an independent study monitor, who provided sites with either real INR values (for patients in the warfarin group in order to adjust the dose) or sham values (for patients	Low risk	Low risk

	in the rivaroxaban group receiving placebo warfarin) during the course of the trial. Sham INR results were generated by means of a validated algorithm reflecting the distribution of values in warfarin-treated patients with characteristics similar to those in the study population.' The blinding in terms of performance bias should be sufficient		
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Quote: 'An independent clinical end-point committee applied protocol definitions to adjudicate all suspected cases of stroke, systemic embolism, myocardial infarction, death, and bleeding events that contributed to the pre-specified end points.' The independent party should be able to help avoid outcome bias	Low risk	Low risk
Blinding of outcome assessment (detection bias) (Mortality)	Quote: 'An independent clinical end-point committee applied protocol definitions to adjudicate all suspected cases of stroke, systemic embolism, myocardial infarction, death, and bleeding events that contributed to the pre-specified end points.' The independent party should be able to help avoid outcome bias	Low risk	Low risk
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Quote: As pre-specified in the statistical-analysis plan, we analysed the trial data in a variety of ways because we anticipated that some patients would discontinue the study treatment and we wished to evaluate both non-inferiority and superiority.' Therefore the problem of incomplete data should be addressed	Low risk	Low risk
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Quote: 'As pre-specified in the statistical-analysis plan, we analysed the trial data in a variety of ways because we anticipated that some patients would discontinue the study treatment and we wished to evaluate both non-inferiority and superiority.' Therefore the problem of incomplete data should be addressed	Low risk	Low risk
Selective reporting (reporting bias)	Authors have reported on all of the key outcomes that they set out to measure	Low risk	Low risk
RE-LY trial			
Random sequence generation (selection bias)	Quote: 'The patients were randomised by a central randomisation service, through an interactive voice response system (IVRS) located at the Coordinating Centre at Population Health Research Institute (PHRI) in Hamilton, Canada'. This random sequence generation should be done.	Low risk	Low risk
Allocation concealment (selection bias)	Quote: 'Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered, in an un-blinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an	Low risk	Low risk Method of randomisation ensures that treatment allocation could not be predicted

	international normalised ratio (INR) of 2.0 to 3.0, with the INR measured at least monthly.' The capsules with different dosage should be able to make sure the allocation concealment.		
Blinding of participants and personnel (performance bias)	Blinding was only done with dabigatran but not warfarin	High risk	High risk
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Quote: 'An international team of adjudicators reviewed documents in local languages after blinding, or documents were translated by an independent group and were centrally blinded. Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments. All transient ischaemic attacks were reviewed to ensure that strokes had not been missed. To detect possible unreported events, symptom questionnaires were regularly administered to patients, and adverse-event and hospitalisation reports were scrutinised for unreported primary or secondary outcomes.' The patients reported outcomes have avoided bias	Low risk	Low risk
Blinding of outcome assessment (detection bias) (Mortality)	Quote: 'An international team of adjudicators reviewed documents in local languages after blinding, or documents were translated by an independent group and were centrally blinded. Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments.' Detection bias should be avoided. Mortality is not addressed specifically, but should be included.	Low risk	Low risk
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Quote: 'The median duration of the follow-up period was 2.0 years, and complete follow-up was achieved in 99.9% of patients, with 20 patients lost to follow-up.'	Low risk	Low risk
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Quote: 'The median duration of the follow-up period was 2.0 years, and complete follow-up was achieved in 99.9% of patients, with 20 patients lost to follow-up.'	Low risk	Low risk
Selective reporting (reporting bias)	Authors have reported on all of the key outcomes that they set out to measure	Low risk	Low risk
ENGAGE AF-TIMI 48 trial			
Random sequence generation (selection bias)	Quote: 'Randomisation was performed with the use of a central, 24-hour, interactive, computerised response system.'	Low risk	Low risk

Allocation concealment (selection bias)	Quote: 'Each patient received two sets of study drugs: either active edoxaban and a placebo matching warfarin, or a placebo matching edoxaban and active warfarin.'	Low risk	Low risk Method of randomisation ensures that treatment allocation could not be predicted
Blinding of participants and personnel (performance bias)	Quote: 'The INR was measured at least monthly with the use of an encrypted point-of-care device. To maintain blinding, sham INR values were generated for patients who were randomly assigned to edoxaban.'	Low risk	Low risk
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Quote: 'An independent clinical end-point committee, whose members were unaware of the study assignment, adjudicated all deaths and suspected cerebrovascular events, systemic embolic events, myocardial infarctions, bleeding events, and hepatic events.' The detection bias should be avoided	Low risk	Low risk
Blinding of outcome assessment (detection bias) (Mortality)	Quote: 'An independent clinical end-point committee, whose members were unaware of the study assignment, adjudicated all deaths and suspected cerebrovascular events, systemic embolic events, myocardial infarctions, bleeding events, and hepatic events.' Mortality is one of the outcomes	Low risk	Low risk
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Quote: 'Premature permanent discontinuation of the study drugs occurred in 2417 patients, 2415 patients, and 2309 patients in the three groups, respectively. Complete information on the primary end point was ascertained for 99.5% of the total 56,346 patient-years of potential follow-up.' Complete information should be sufficient.	Low risk	Low risk
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Quote: 'Premature permanent discontinuation of the study drugs occurred in 2417 patients, 2415 patients, and 2309 patients in the three groups, respectively. Complete information on the primary end point was ascertained for 99.5% of the total 56,346 patient-years of potential follow-up.' Complete information should be sufficient.	Low risk	Low risk
Selective reporting (reporting bias)	The authors report on all primary outcomes that they set out to measure	Low risk	Unclear risk The trial protocol states that outcomes for patients undergoing cardioversion were to be reported. These outcomes do not appear to be reported.

Appendix 5

Data inputs for the base case network meta-analysis

Data inputs for the base case network meta-analysis (patients with $CHADS_2$ score ≥2)

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CRNM=clinically relevant non-major bleeding; N/A=not available; SE=systemic embolism
Source: Data files provided as part of the company's clarification response

Data inputs for the secondary network meta-analysis (patients with $CHADS_2$ ≥3)

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SE=systemic embolism
Source: Data files provided as part of the company's clarification response

Data inputs for the secondary network meta-analysis (patients with cTTR ≥60%)

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cTTR=centre-level time in therapeutic range; N/A=not available; SE=systemic embolism
Source: Data files provided as part of the company's clarification response

Data inputs for the secondary network meta-analysis (all patients unrestricted by $CHADS_2$ score)

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SE=systemic embolism
Source: Data files provided as part of the company's clarification response

Appendix 6

Baseline event rates used in the economic model (Edoxaban arm, CHADS2≥2 population)

Event	Annual event	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
Source: CS, Table 49

Appendix 7

Only a limited selection of model results are displayed in the CS. Further base case deterministic and base case model results, generated by the ERG, are included in this section.

Pairwise and incremental cost effectiveness results, as well as NMB rankings are displayed in tables x and y for the base case deterministic and probabilistic cost effectiveness analyses respectively. Cost effectiveness frontiers for the deterministic and probabilistic analyses are displayed in Figure A and Figure B respectively.

Deterministic base case results

	Edoxaban	Dabigatran 150mg	Apixaban	Dabigatran 110mg	Rivaroxaban	Warfarin
Total costs	£15,957	£15,563	£15,940	£16,074	£16,744	£13,413
Total QALYs	6.516	6.600	6.588	6.515	6.437	6.318
Incremental costs vs warfarin	£2,544	£2,150	£2,527	£2,661	£3,332	£0
Incremental QALYs vs warfarin	0.198	0.281	0.269	0.196	0.118	0.000
ICER vs warfarin	**£12,881**	**£7,645**	**£9,383**	**£13,565**	**£28,180**	**-**
NMB Rank @ £20,000/QALY	3	1	2	4	6	5
NMB Rank @ £30,000/QALY	3	1	2	4	5	6
Incremental costs vs edoxaban	£0	-£394	-£17	£117	£787	-
Incremental QALYs vs edoxaban	0.000	0.084	0.072	-0.001	-0.079	-
ICER vs edoxaban	**-**	**-£4,703**	**-£237**	**-£89,542**	**-£9,933**	**-**
	-	**Dominant**	**Dominant**	**Dominated**	**Dominated**	**-**

Dominant=increased benefits at reduced cost; Dominated=reduced benefits at increased cost; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; QALY=quality adjusted life year
Source: Company's model

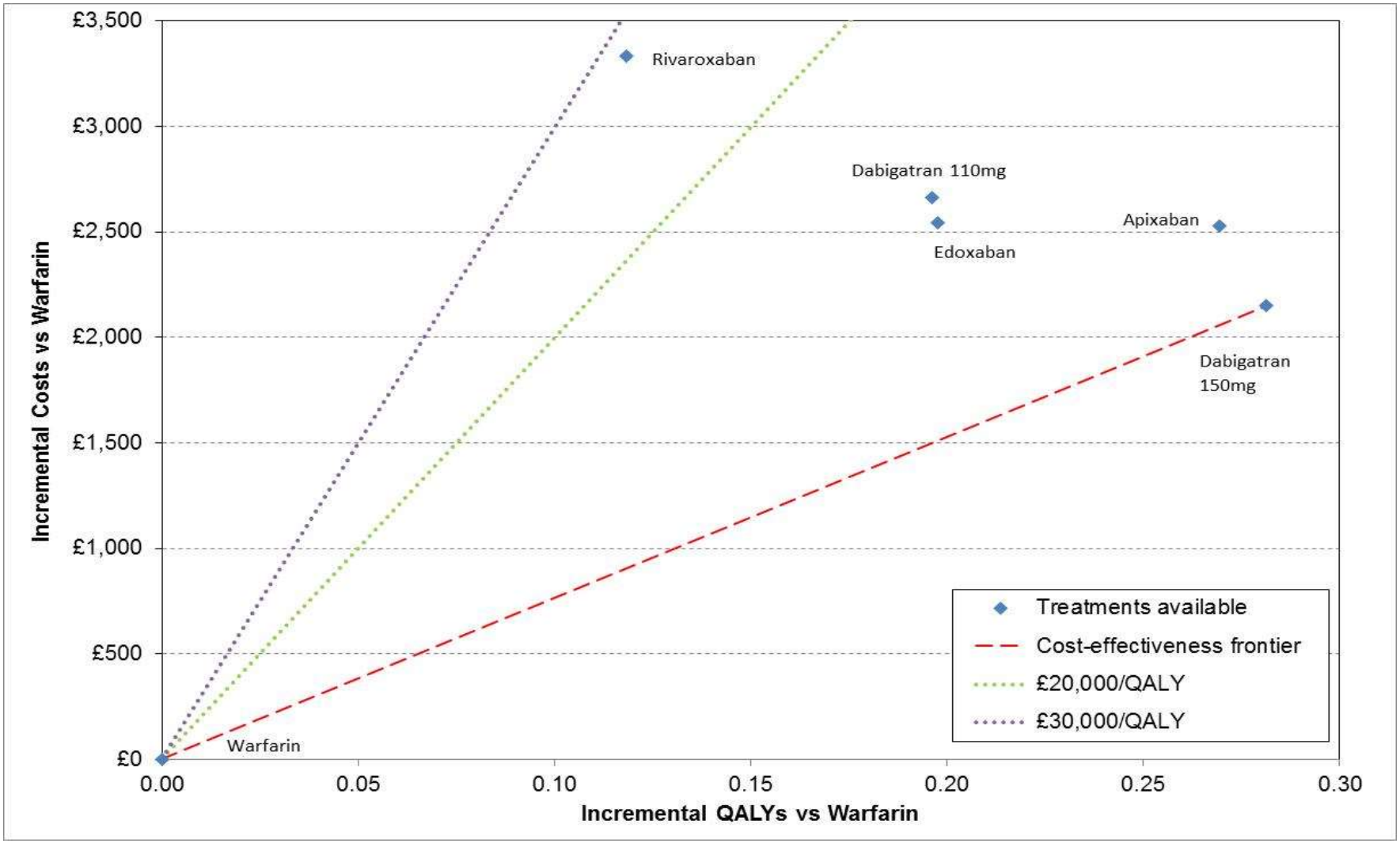

Figure A Cost effectiveness frontier (deterministic analysis)

Source: Company's model

Probabilistic base case results

	Edoxaban	Dabigatran 150mg	Apixaban	Dabigatran 110mg	Rivaroxaban	Warfarin
Total costs	£15,451	£15,293	£15,531	£15,732	£16,313	£12,868
Total QALYs	6.718	6.750	6.769	6.663	6.654	6.564
Incremental costs vs warfarin	£2,583	£2,425	£2,662	£2,863	£3,444	£0
Incremental QALYs vs warfarin	0.153	0.185	0.204	0.098	0.089	0.000
ICER vs warfarin	**£16,871**	**£13,073**	**£13,036**	**£29,162**	**£38,558**	**-**
NMB Rank @ £20,000/QALY	3	2	1	4	6	5
NMB Rank @ £30,000/QALY	3	2	1	4	6	5
Incremental costs vs edoxaban	£0	-£158	£80	£280	£861	-
Incremental QALYs vs edoxaban	0.000	0.032	0.051	-0.055	-0.064	-
ICER vs edoxaban	**-**	**-£4,886**	**£1,555**	**-£5,107**	**-£13,509**	**-**
	-	**Dominant**		**Dominated**	**Dominated**	-

Dominant=increased benefits at reduced cost; Dominated=reduced benefits at increased cost; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; QALY=quality adjusted life year
Source: Company's model

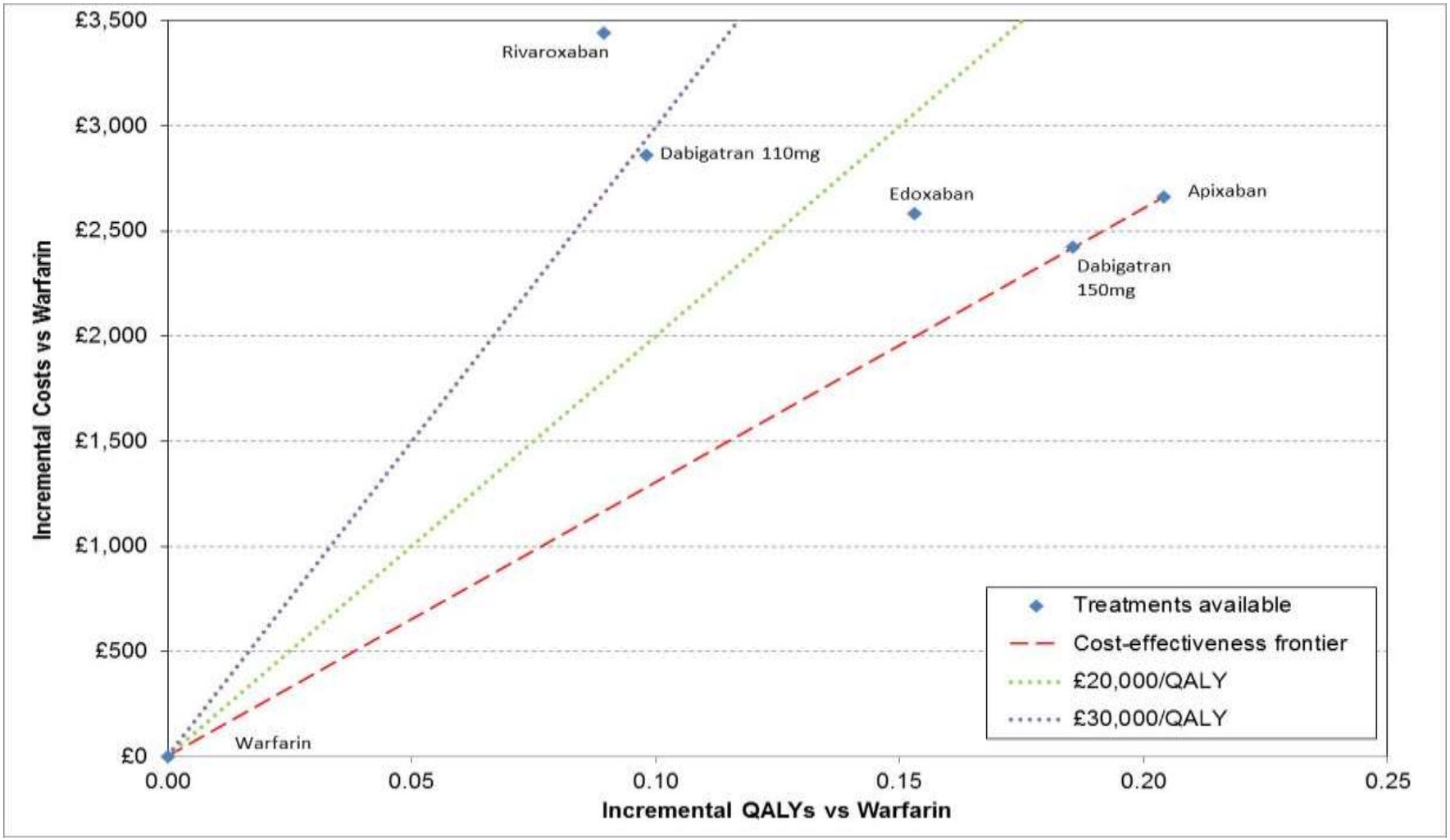

Figure B Cost effectiveness frontier (probabilistic analysis)

Source: Company's model

Appendix 8

Implementation of ERG decision model amendments

Implementation of analysis with different gender weights per starting age

- Create worksheet ‘Age Sex’
- Label Cell A2 Age and Cell B2 Male
- Input age (25-95 years in 5 year age bands) in cells A4:A18 for males
- Input age (25-95 years in 5 year age bands) in cells A19:A33 for females
- Input percentage males (set at 100%) in cells B4:B18
- Input percentage females (set at 0%) in cells B19:B33
- Set up E2:P2 to reference costs and QALYs cells for each comparator‘
    - Set E2= ‘Results Summary’ D31
    - Set F2= ‘Results Summary’ D45
    - Set G2= ‘Results Summary’ E31
    - Set H2= ‘Results Summary’ E45
    - Set I2= ‘Results Summary’ F31
    - Set J2= ‘Results Summary’ F45
    - Set K2= ‘Results Summary’ G31
    - Set L2= ‘Results Summary’ G45
    - Set M2=‘Results Summary’ H31
    - Set N2= ‘Results Summary’ H45
    - Set O2=‘Results Summary’ I31
    - Set P2= ‘Results Summary’ I45

- Amend cycle length in model in cell C28 in ‘Live’ worksheet for lifetime (max 911 cycles)
- Copy formula from rows 373 to 725 for all cells in the following worksheets
    - ‘Patients Edox’
    - ‘Patients Apix’
    - ‘Patients Riv’
    - ‘Patients Dab110’
    - ‘Patients Dab150’
    - Patients Warf’
    - ‘Costs Edox’
    - ‘Costs Apix’
    - ‘Costs Riv’
    - ‘Costs Dab110’
    - ‘Costs Dab150’
    - Costs Warf’
    - ‘QALYs Edox’
    - ‘QALYs Apix’
    - ‘QALYs Riv’
    - ‘QALYs Dab110’
    - ‘QALYs Dab150’
    - ‘QALYs Warf’

Run macro:

```
Sub GetICER()
Dim i As Integer
Application.ScreenUpdating = False
Sheets("Age Sex").Select
Range("A4").Activate

   For i = 1 To 30
   Set m = ActiveCell
   m.Range("A1:B1").Select
```

```
    Selection.Copy
    Range("A2:B2").Select
    Selection.PasteSpecial Paste:=xlPasteValuesAndNumberFormats, Operation:= _
        xlNone, SkipBlanks:=False, Transpose:=False
    Range("E2:P2").Select
    Application.CutCopyMode = False
    Selection.Copy
    m.Offset(0, 4).Range("A1").Select
    Selection.PasteSpecial Paste:=xlPasteValuesAndNumberFormats, Operation:= _
        xlNone, SkipBlanks:=False, Transpose:=False
    m.Offset(1, 0).Range("A1").Select
    Next i

Sheets("Age Sex").Select
    Range("A2").Value = 71      'Adjust this value to model default starting age
    Range("B2").Value = 0.6229    'Adjust this value to model default gender split
Sheets("Age Sex").Select
      Range("A39").Activate

Application.ScreenUpdating = True
    End Sub
```

Implementation of ERG estimated hazard ratios for warfarin relative to edoxaban for HS (sourced from Kaplan Meier analysis)

1. Estimate live event rates using K-M data

On Sheet 'Live'

Add following formula to cell O58

[redacted]

Add following formula to cell O58

[redacted]

Add following formula to cell P79

[redacted]

Add following formula to cell Q79

[redacted]

Add following formula to cell R79

[redacted]

Add following formula to cell P79

[redacted]

Add following formula to cell Q79

[redacted]

Add following formula to cell R79

[redacted]

2. Implement live event rates in ’Patients Warf’ worksheet

Create range Mod_9 (binary variable taking value 0 or 1)

On Sheet ‘Patients Warf’,

Modify formula in cell J14 as follows:

[redacted]

Modify formula in cell K14 as follows:

[redacted]

Modify formula in cell L14 as follows:

[redacted]

[redacted]

Implementation of other model amendments

Other model amendments implemented by the ERG are activated by a series of modification logic switches; these take the value 0 when the original model logic is active, and positive integer values (1, 2,…..,n) when alternative values or assumptions are active. The logic switches are labelled Mod_1 to Mod_8. The changes are listed in the table below. To carry out the changes, create a range of Mod_1 to Mod_8 values (binary values taking values 0 or 1) and modify cell formulae as per the revised formulae column.

Sensitivity Analyses revised formulae

Sheet	Cell (Base Case Values)	Revised formulae	Cell (PSA Inputs)	Revised formula (Standard Deviation/ Standard Error)
Alternative hazard ratio for warfarin Hazard ratio (use value from NMA rather than ENGAGE trial)	Worksheet- 'Clinical Outcomes' Cell C92	=IF(Mod_1=1,1,TRUE)	Not Applicable	
Alternative utility value for systemic embolism (SE)	Worksheet- 'Utilities' F19, F24	=IF(Mod_2=1, 0.688, 0.68)	No change	
Alternative utility value for MI	Worksheet- 'Utilities' G19, G24	=IF(Mod_3=1, 0.633, 0.683)	No change	
Alternative utility decrement for TIA	Worksheet- 'Utilities' I19	=IF(Mod_4=1, -0.132, -0.103)	No change	
Correction of implementation of mild stroke utility value (acute and post)	Worksheet- 'Utilities' D19, E19, D24, E24	=IF(Mod_5=1,0.76, 0.72)	No change	
Correction of implementation of moderate stroke utility value (acute and post)	Worksheet- 'Utilities' D20, E20, D25, E25	=IF(Mod_5=1,0.39, 0.35)	No change	
Correction of implementation of moderate stroke utility value (acute and post)	Worksheet- 'Utilities' D21, E21, D26, E26	=IF(Mod_5=1,0.11, 0.07)	No change	
Alternative utility value for acute mild stroke period	Worksheet-'Utilities' D19, E19	=IF(Mod_6=1,0.628, 0.72)	E117, E120	=IF(Mod_6=1,0.014,0.0299)
Alternative utility value for acute moderate stroke period	Worksheet-'Utilities' D20, E20	=IF(Mod_6=1,0.398, 0.35)	E118, E121	=IF(Mod_6=1,0.037,0.0299)
Alternative utility value for acute severe stroke period	Worksheet-'Utilities' D21, E21	=IF(Mod_6=1,0.028, 0.07)	E119, E122	=IF(Mod_6=1,0.057,0.0299)
Alternative utility value for post mild stroke period	Worksheet-'Utilities' D24, E24	=IF(Mod_6=1,0.628, 0.72)	E130, E133	=IF(Mod_6=1,0.019,0.0299)

Sheet	Cell (Base Case Values)	Revised formulae	Cell (PSA Inputs)	Revised formula (Standard Deviation/ Standard Error)
Alternative utility value for post moderate stroke period	Worksheet-'Utilities' D25, E25	=IF(Mod_6=1,0.458, 0.35)	E131, E134	=IF(Mod_6=1,0.056,0.0299)
Alternative utility value for post severe stroke period	Worksheet-'Utilities' D26, E26	=IF(Mod_6=1,0.278, 0.07)	E132, E135	=IF(Mod_6=1,0.104,0.0299)
Discontinuation rates medication after HS set at 100%	Worksheet-'Intervention Costs' D40 E40 F40 G40 E46 G46	 =IF (Mod_7=1, 0, 20%) =IF (Mod_7=1, 0, 20%) =IF (Mod_7=1, 0, 60%) =IF (Mod_7=1, 100, 0%) =IF (Mod_7=1, 0, 50%) =IF (Mod_7=1, 100, 50%)	No change	
Change in method of switching change in medication from dabigatran 150mg to dabigatran 110mg at age 80	Worksheet- 'Patients Dab150" Range: E14-E373	=IF(AND(Mod_8=1,D14<80),1, IF(AND(Mod_8=1,D14>=80),0, NORMDIST(80,D14,9.42,TRUE)))	No change	
Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	Worksheet- 'Mortality' I13	=IF (Mod_10=1, 16.8%, 0%)	No change	
Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	Worksheet- 'Mortality' I13	=IF (Mod_10=1, 31.6%, 0%)	No change	
Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	Worksheet- 'Mortality' Range H13 H14 H15	=IF (Mod_11=1, 21%, 16.8%)	H68 H69 H70 I68 I69 I70	=IF (Mod_11=1,99, 0) =IF (Mod_11=1,99, 85) =IF (Mod_11=1,99, 85) =IF (Mod_11=1,372, 0) =IF (Mod_11=1,372, 421) =IF (Mod_11=1,372, 421)

Sheet	Cell (Base Case Values)	Revised formulae	Cell (PSA Inputs)	Revised formula (Standard Deviation/ Standard Error)
Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	Worksheet- 'Mortality' Range I13 I14 I15	=IF (Mod_11=1, 48.2%, 31.6%)	H71 H72 H73 I71 I72 I73	=IF (Mod_11=1,67, 0) =IF (Mod_11=1,67, 30) =IF (Mod_11=1,67, 30) =IF (Mod_11=1,72, 65) =IF (Mod_11=1,72, 65) =IF (Mod_11=1,72, 65)
Age adjusted utility decrement per year changed from -0.00029 to -0.00646	Worksheet –'Utilities' D32	=IF (Mod_12=1, -0.00646, -0.00029)	No change	
Warfarin daily cost sourced from eMIT as per NICE reference cost	Intervention Costs D16	=IF (Mod_13=1, 0.04, 0.11)	No change	
Overall survival adjustment: amend other cause mortality adjustment factor	Worksheet- Mortality H21	=IF(mod_14=1, 1.54165,1.34)	No change	

Appendix 9

ERG probabilistic sensitivity analyses results (Mean costs and QALYs)

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
A	**CS deterministic base case**	**15,957**	**6.52**	**15,940**	**6.59**	**16,744**	**6.44**	**16,074**	**6.51**	**15,563**	**6.60**	**13,413**	**6.32**
B	**CS probabilistic base case**	**15,471**	**6.72**	**15,531**	**6.77**	**16,313**	**6.65**	**15,732**	**6.66**	**15,293**	**6.75**	**12,868**	**6.56**
R1	CS base case-corrected utility for SE*	15,404	6.74	15,489	6.79	16,274	6.68	15,723	6.68	15,261	6.77	12,825	6.57
R2	CS base case - alternative utility value for SE	15,462	6.73	15,557	6.78	16,342	6.67	15,741	6.68	15,292	6.77	12,832	6.58
R3	Hazard ratio for Warfarin from NMA	15,389	6.76	15,480	6.81	16,260	6.70	15,672	6.71	15,231	6.79	12,753	6.62
R4	Alternative utility value for MI	15,432	6.75	15,525	6.80	16,316	6.69	15,652	6.70	15,244	6.79	12,862	6.59
R5	Alternative utility value for TIA	15,474	6.75	15,547	6.80	16,367	6.68	15,731	6.69	15,279	6.79	12,916	6.58
R6	Corrected utility values for mild, moderate and severe stroke	15,476	6.73	15,565	6.77	16,377	6.66	15,769	6.68	15,305	6.76	12,975	6.56
R7	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	15,397	6.76	15,482	6.81	16,250	6.70	15,252	6.80	15,252	6.80	12,784	6.60
R8	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	15,382	6.75	15,477	6.80	16,252	6.68	15,609	6.71	15,138	6.81	12,807	6.58
R9	Discontinuation rate medication following HS set at 100%	15,428	6.74	15,509	6.79	16,271	6.68	15,762	6.68	15,312	6.77	12,844	6.58
R10	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	15,466	6.74	15,552	6.79	16,363	6.67	15,753	6.69	15,333	6.77	12,873	6.58

ERG probabilistic sensitivity analyses results (Mean costs and QALYs) continued

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
R11	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	15,317	6.73	15,401	6.78	16,176	6.67	15,578	6.69	15,177	6.77	12,643	6.58
R12	Age adjusted utility decrement per year changed from -0.00029 to -0.00646	15,478	2.42	15,568	2.44	16,384	2.39	15,805	2.39	15,350	2.43	12,879	2.35
R13	Warfarin daily cost sourced from eMIT as per NICE reference cost	15,557	6.74	15,619	6.79	16,450	6.67	15,818	6.68	15,377	6.77	12,810	6.57
R14	Change in age and gender split over time	17,794	7.20	17,852	7.26	18,851	7.12	18,087	7.15	17,447	7.27	15,233	7.00
R15	Apply ENGAGE trial hazard rates for HS	15,532	6.73	15,602	6.78	16,433	6.66	15,807	6.68	15,340	6.77	12,587	6.60
R16	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	14,717	6.43	14,789	6.48	15,548	6.38	15,031	6.39	14,568	6.47	12,201	6.29
C	R2+R3+R4+R5+R7	15,381	6.76	15,460	6.82	16,230	6.70	15,677	6.71	15,247	6.80	12,715	6.62
D	**R2+R3+R4+R5+R7+R8+R9+R12+R13+R15**	**15,381**	**2.44**	**15.455**	**2.46**	**16,274**	**2.42**	**15,669**	**2.42**	**15,164**	**2.47**	**12,334**	**2.39**
E	**R2+R3+R4+R5+R7+R8+R9+R11+R12+R13 +R15**	**15,375**	**2.43**	**15,448**	**2.46**	**16,239**	**2.41**	**15,650**	**2.41**	**15,121**	**2.46**	**12,345**	**2.38**
F	**R2+R3+R4+R5+R7+R8+R9+R12+R13+R14+R15+R16**	**17,122**	**2.69**	**17,164**	**2.72**	**18,133**	**2.65**	**17,452**	**2.66**	**16,763**	**2.72**	**13,998**	**2.62**

ERG deterministic sensitivity analyses results (Mean costs and QALYs)

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
A	**CS deterministic base case**	**15,957**	**6.52**	**15,940**	**6.59**	**16,744**	**6.44**	**16,074**	**6.51**	**15,563**	**6.60**	**13,413**	**6.32**
B	**CS probabilistic base case**	**15,451**	**6.72**	**15,531**	**6.77**	**16,313**	**6.65**	**15,732**	**6.66**	**15,293**	**6.75**	**12,868**	**6.56**
R1	CS base case-corrected utility for SE*	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R2	CS base case - alternative utility value for SE	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R3	Hazard ratio for Warfarin from NMA	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R4	Alternative utility value for MI	15,957	6.51	15,940	6.58	16,744	6.43	16,074	6.51	15,563	6.59	13,413	6.31
R5	Alternative utility value for TIA	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R6	Corrected utility values for mild, moderate and severe stroke	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R7	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R8	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,469	6.62	13,413	6.32
R9	Discontinuation rate medication following HS set at 100%	15,927	6.51	15,911	6.59	16,711	6.43	16,060	6.51	15,550	6.60	13,385	6.32
R10	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	15,726	6.47	15,724	6.55	16,493	6.39	15,874	6.48	15,398	6.57	13,110	6.27

ERG deterministic sensitivity analyses results (Mean costs and QALYs) continued

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
R11	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	15,556	6.46	15,566	6.53	16,306	6.37	15,743	6.46	15,287	6.56	12,871	6.25
R12	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	15,957	2.34	15,940	2.38	16,744	2.31	16,074	2.34	15,563	2.38	13,413	2.27
R13	Warfarin daily cost sourced from eMIT as per NICE reference cost	15,957	6.51	15,940	6.59	16,744	6.43	15,940	6.59	15,563	6.60	13,203	6.32
R14	Change in age and gender distribution over time	18,365	6.92	18,315	7.01	19,275	6.82	18,492	6.93	17,720	7.05	15,806	6.66
R15	Apply ENGAGE trial hazard rates for HS	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,078	6.35
R16	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	15,335	6.24	15,309	6.24	16,090	6.17	15,461	6.24	14,948	6.31	12,904	6.06
C	R2+R3+R4+R5+R7	15,957	6.51	15,940	6.58	16,744	6.43	16,074	6.51	15,563	6.59	13,403	6.32
D	**R2+R3+R4+R5+R7+R8+R9+R12+ R13+R15**	**15,927**	**2.34**	**15,911**	**2.37**	**16,711**	**2.31**	**16,060**	**2.33**	**15,456**	**2.38**	**13,010**	**2.27**
E	**R2+R3+R4+R5+R7+R8+R9+R11+ R12+R13 +R15**	**15,539**	**2.33**	**15,549**	**2.37**	**16,287**	**2.30**	**15,734**	**2.33**	**15,197**	**2.38**	**12,520**	**2.27**
F	**R2+R3+R4+R5+R7+R8+R9+R12+ R13+R14+R15+R16**	**17,735**	**2.57**	**17,674**	**2.61**	**18,613**	**2.53**	**17,893**	**2.57**	**17,066**	**2.64**	**14,679**	**2.49**