NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Edoxaban

For preventing stroke and systemic embolism in adults with non-valvular atrial fibrillation

Submitted by

Daiichi Sankyo

Single technology appraisal (STA)

January 2015

Contents

Contents 2
List of tables 3
List of figures 6
Abbreviations 8
Executive summary 10
Section A – Decision problem 14
1 Description of technology under assessment 14
2 Context 20
3 Equality 29
4 Innovation 30
5 Statement of the decision problem 32
Section B – Clinical and cost effectiveness 34
6 Clinical evidence 34
7 Cost effectiveness 110
Section C – Implementation 244
8 Assessment of factors relevant to the NHS and other parties 244
9 References 251
10 Appendices ..... **Error! Bookmark not defined.**

List of tables

Table 1: Unit costs of technology being appraised ... 18
Table 2: Estimated number of patients eligible for edoxaban in England and Wales ... 23
Table 3: Eligibility criteria for RCT search ... 35
Table 4: Eligibility criteria for Non-RCT search ... 36
Table 5: List of data sources for edoxaban ... 37
Table 6: List of relevant RCTs ... 39
Table 7: Summary of methodology of ENGAGE AF-TIMI 48 ... 42
Table 8: Patient characteristics at baseline in ENGAGE AF-TIMI 48 (ITT analysis set) ... 48
Table 9: Primary and secondary outcomes of ENGAGE AF-TIMI 48 ... 50
Table 10: Definitions and summary of analysis sets in ENGAGE AF-TIMI 48 ... 52
Table 11: Summary of statistical analyses in ENGAGE AF TIMI 48 ... 54
Table 12: Quality assessment results for ENGAGE AF-TIMI 48 ... 60
Table 13: Study Drug Exposure and Duration of Study Period, safety analysis set, on-treatment period ... 62
Table 14: Discontinuation of study drug during ENGAGE AF-TIMI 48, safety analysis set, on-treatment period ... 62
Table 15: Time in Various INR Ranges for Subjects Randomised to Warfarin, safety analysis set, on-treatment period ... 63
Table 16: Overview of analysis sets in ENGAGE AF-TIMI 48 ... 63
Table 17: Primary efficacy results from ENGAGE AF-TIMI 48: Adjudicated Primary Endpoint (Stroke or SEE) ... 65
Table 18: Stroke and systemic embolism results from ENGAGE AF-TIMI 48 (mITT analysis set, on-treatment period). ... 67
Table 19: Stroke and systemic embolism results from ENGAGE AF-TIMI 48 (ITT analysis set, overall study period). ... 68
Table 20: Stroke and systemic embolism results from ENGAGE AF-TIMI 48 (mITT analysis set, overall study period). ... 69
Table 21: Secondary efficacy results from ENGAGE AF-TIMI 48 (mITT analysis set, on-treatment analysis). ... 71
Table 22: Secondary efficacy results from ENGAGE AF-TIMI 48 (ITT analysis set, overall study period). ... 72
Table 23: Secondary efficacy results from ENGAGE AF-TIMI 48 (mITT analysis set, overall study period). ... 73
Table 24: Primary efficacy (Stroke or SEE) results by centre level TTR (mITT analysis set, overall study period) ... 76
Table 25: Primary efficacy (Stroke or SEE) results by $CHADS_2$ score (mITT analysis set, overall study period) ... 77
Table 26: Summary of the trials used to conduct the NMA ... 81
Table 27: Overview of efficacy and safety outcomes by study ... 82
Table 28: NMA Risk Ratios on Composite of Stroke and Systemic Embolism, Baseline $CHADS_2$ ≥2 ... 86
Table 29: NMA Risk Ratios on other efficacy outcomes, Baseline CHADS2 ≥2 (RR; 95% CrI) ... 87
Table 30: NMA Risk Ratios on major bleeding, Baseline $CHADS_2$ ≥2 ... 88
Table 31: NMA Risk Ratios on other safety outcomes, Baseline $CHADS_2$ **≥2 (RR; 95% CrI)** ... 90
Table 32: Adjudicated bleeding events during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period). ... 96
Table 33: Adverse events during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period) ... 97
Table 34: Adverse events during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period) ... 99
Table 35: Net clinical outcome results from ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period) ... 99
Table 36: Major bleeding by centre level TTR (safety analysis set, on-treatment period) ... 101
Table 37: Major bleeding by $CHADS_2$ score (safety analysis set, on-treatment period) ... 102
Table 38: Study drug exposure, safety analysis set, HOKUSAI-VTE ... 103

Table 39: Adjudicated bleeding events (safety analysis set, on-treatment study period) event, HOKUSAI-VTE 103
Table 40: MACE and individual components (safety analysis set, on-treatment and treatment plus 30 days study periods); HOKUSAI-VTE 104
Table 41: Summary list of other cost-effectiveness evaluations 113
Table 42: CHA_2-DS_2-VAS(c) score of patient population in PREFER In AF registry 132
Table 43: Model health states and events 136
Table 44: Key features of analysis 139
Table 45: Intervention and comparators 140
Table 46: Base case scenario 143
Table 47: Availability of hazard ratios for subgroups from NMA 144
Table 48: Patient characteristics 150
Table 49: Event rates for edoxaban ($CHADS_2 \geq 2$ population) 151
Table 50: Risk adjustment factor per decade 152
Table 51: Clinical outcome hazard ratios for subgroups (comparators vs edoxaban) 153
Table 52: Definitions of the severity levels of stroke based on the rankin score 155
Table 53: Proportion of patients experiencing strokes of each severity category 155
Table 54: Risk of stroke following prior clinical events 156
Table 55: Acute event-related mortality 156
Table 56: Long-term mortality for event survivors 158
Table 57: Event-related discontinuation 159
Table 58: Assumptions used in the model 160
Table 59: Studies reporting utility values for health states used in the economic model 166
Table 60: Summary of quality-of-life values for cost-effectiveness analysis 175
Table 61: UK Costing studies identified through economic systematic review 181
Table 62: Unit costs associated with the technology in the economic model 186
Table 63: Warfarin monitoring cost 187
Table 64: List of health states and associated costs in the economic model 187
Table 65: Stroke health state costs (One off acute costs and subsequent monthly cost) 189
Table 66: Acute MI costs 189
Table 67: Monthly post MI costs 190
Table 68: List of adverse events and summary of costs included in the economic model 191
Table 69: ICH (excluding stroke) costs 191
Table 70: Transient Ischaemic Attack costs 192
Table 71: Non- Intracerebral haemorrhage major bleed cost 192
Table 72: CRNMB cost 193
Table 73: Summary of model results compared with clinical data 197
Table 74: Model outputs by clinical outcomes: total discounted costs per patient 199
Table 75: Model outputs by clinical outcomes: total discounted QALYs per patient 200
Table 76: Summary of QALY gain by health state 200
Table 77: Summary of costs by health state 203
Table 78: Number of Events (per 1,000 patients) 204
Table 79: Base-case results. 206
Table 80: Incremental base-case results for edoxaban versus NOACs 207
Table 81: Probability of being most cost-effective option, at different WTP thresholds 234
Table 82: Probability of edoxaban being cost-effective versus each comparator arm, at different WTP thresholds 234
Table 83: Data gaps for TIA hazard ratios: 0.93 236
Table 84: Data gaps for TIA hazard ratios: 0.72 236
Table 85: Data gaps for CRNMB hazard ratios: 1.19 237
Table 86: Data gaps for CRNMB hazard ratios: 1.25 237
Table 87: Subgroup analysis - patients with $CHADS_2 \geq 3$ 240
Table 88: Subgroup analysis - cTTR $\geq$ 60% 240
Table 89: Estimation of population eligible for treatment with edoxaban 245
Table 90: Current and future competitor market share 246
Table 91: Annual costs used in budget impact calculations 247
Table 92: Unit costs used in budget impact calculations 247
Table 93. Annual budget impact for NHS in England and Wales 249
Table 94: Markov trace, edoxaban ..... **Error! Bookmark not defined.**
Table 95: Markov trace, apixaban ..... **Error! Bookmark not defined.**

Table 96: Markov trace, rivaroxaban.....**Error! Bookmark not defined.**
Table 97: Markov trace, dabigatran 110mg.....**Error! Bookmark not defined.**
Table 98: Markov trace, dabigatran 150 mg.....**Error! Bookmark not defined.**
Table 99: Markov trace, warfarin.....**Error! Bookmark not defined.**
Table 100: Markov trace, edoxaban .....**Error! Bookmark not defined.**
Table 101: Markov trace, apixaban .....**Error! Bookmark not defined.**
Table 102: Markov trace, rivaroxaban.....**Error! Bookmark not defined.**
Table 103: Markov trace, dabigatran 110mg.....**Error! Bookmark not defined.**
Table 104: Markov trace, dabigatran 150 mg.....**Error! Bookmark not defined.**
Table 105: Markov trace, warfarin.....**Error! Bookmark not defined.**

List of figures

Figure 1: Targets for new anticoagulants in the coagulation pathway 15
Figure 2: Stroke risk stratification algorithm 26
Figure 3: Overall Multiplicity Adjustment Testing Procedure 56
Figure 4: Summary of study populations and analysis sets for ENGAGE AF – TIMI 48 59
Figure 5: Forest plot of primary efficacy endpoint (Stroke or SEE) in ENGAGE AF-TIMI 48 (mITT Analysis Set - On-Treatment and Overall Study Period) 65
Figure 6: Kaplan-Meier curve of primary efficacy endpoint (Stroke or SEE) for edoxaban 60mg / 30mg DR vs warfarin in ENGAGE AF-TIMI 48 (ITT analysis set, overall study period) 66
Figure 7: Subgroup analysis of primary efficacy outcome (Stroke or SEE) of ENGAGE AF-TIMI 48 –edoxaban 60 mg / 30 mg DR vs. warfarin (mITT analysis set, overall study period) 75
Figure 8: Base case network diagram 80
Figure 9: NMA Risk Ratios on Composite of Stroke and Systemic Embolism, Baseline $CHADS_2$ ≥2 87
Figure 10: NMA Risk Ratios on major bleeding, Baseline $CHADS_2$ ≥2 89
Figure 11: NMA Risk Ratios on composite of major bleeding and clinically relevant non-major bleeding, Baseline $CHADS_2$ ≥2 89
Figure 12: NMA Risk Ratios on composite of Stroke and Systemic Embolism, patients with CHADS2 score ≥ 3 91
Figure 13: NMA Risk Ratios on major bleeding, Baseline $CHADS_2$ ≥3 91
Figure 14: Risk Ratios on composite of Stroke and Systemic Embolism, patients with time in therapeutic range (TTR) ≥ 60% 92
Figure 15: Risk Ratios on major bleeding, patients with time in therapeutic range (TTR) ≥ 60% 92
Figure 16: NMA Risk Ratios on Composite of Stroke and Systemic Embolism, all patients 93
Figure 17: NMA Risk Ratios on major bleeding, all patients 93
Figure 18: Kaplan-Meier curve of major bleeding during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period). 97
Figure 19: Subgroup analysis of primary safety outcome (Major bleeding) of ENGAGE AF-TIMI 48 –edoxaban 60 mg / 30 mg DR vs. warfarin (safety analysis set, on-treatment period). 100
Figure 20: Kaplan-Meier cumulative event rate estimates for the principal safety endpoint (major plus CRNM bleeding), edoxaban vs warfarin, safety analysis set (on-treatment period); HOKUSAI-VTE 104
Figure 21: Schematic for the systematic review of economic evidence 111
Figure 22: Economic model diagram 135
Figure 23: Schematic for the systematic review of QoL evidence 165
Figure 24: Tornado diagram; Edoxaban vs apixaban 209
Figure 25: Sensitivity analysis; Apixaban total drug cost per month (Edoxaban vs apixaban) 210
Figure 26: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs apixaban) 210
Figure 27: Sensitivity analysis; Starting age (Edoxaban vs apixaban) 211
Figure 28: Sensitivity analysis; Monitoring cost per month: Edoxaban (Edoxaban vs apixaban) 212
Figure 29: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs apixaban) 212
Figure 30: Tornado diagram; Edoxaban vs rivaroxaban 213
Figure 31: Sensitivity analysis; Starting age (Edoxaban vs rivaroxaban) 214
Figure 32: Sensitivity analysis; Edoxaban, total drug cost per month (Edoxaban vs rivaroxaban) 214
Figure 33: Sensitivity analysis; Rivaroxaban, total drug cost per month (Edoxaban vs rivaroxaban) 215
Figure 34: Sensitivity analysis; Monthly monitoring cost for edoxaban (Edoxaban vs rivaroxaban) 216
Figure 35: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs rivaroxaban) 217
Figure 36: Tornado diagram; Edoxaban vs dabigatran 110mg 218
Figure 37: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs dabigatran 110mg) 218

Figure 38: Sensitivity analysis; Edoxaban total monitoring cost per month (Edoxaban vs dabigatran 110mg) 219
Figure 39: Sensitivity analysis; Starting age (Edoxaban vs dabigatran 110mg) 220
Figure 40: Sensitivity analysis; Edoxaban: Other-cause discontinuation per month (Edoxaban vs dabigatran 110mg) 220
Figure 41: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs dabigatran 110mg) 221
Figure 42: Tornado diagram; Edoxaban vs dabigatran 150mg 222
Figure 43: Sensitivity analysis; Starting age (Edoxaban vs dabigatran 150mg) 222
Figure 44: Sensitivity analysis; Dabigatran total drug cost per month (Edoxaban vs dabigatran 150mg) 223
Figure 45: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs dabigatran 150mg) 223
Figure 46: Sensitivity analysis; Edoxaban total monitoring cost per month (Edoxaban vs dabigatran 150mg) 224
Figure 47: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs dabigatran 150mg) 225
Figure 48: Tornado diagram; Edoxaban vs warfarin 226
Figure 49: Sensitivity analysis; Starting age (Edoxaban vs warfarin) 226
Figure 50: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs warfarin) .. 227
Figure 51: Sensitivity analysis; Edoxaban total monitoring cost per month (Edoxaban vs warfarin) 228
Figure 52: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs warfarin) 229
Figure 53: Sensitivity analysis; Other-cause mortality adjustment factor (Edoxaban vs warfarin) 230
Figure 54: Edoxaban vs. apixaban 231
Figure 55: Edoxaban vs. rivaroxaban 231
Figure 56: Edoxaban vs. dabigatran 110mg 232
Figure 57: Edoxaban vs. dabigatran 150 mg 232
Figure 58: Edoxaban vs. warfarin 233
Figure 59: Cost-effectiveness acceptability curve (probability of being most cost-effective option) 233
Figure 60: Cost-effectiveness acceptability curve (pairwise comparison of the probability of edoxaban being cost-effective compared to each comparator) 234
Figure 61: Schematic for the systematic review of RCT clinical evidence ..... **Error! Bookmark not defined.**
Figure 62: Schematic for the systematic review of non RCT clinical evidence ..... **Error! Bookmark not defined.**
Figure 63 A) Incidence of major and CRNM bleeding events by edoxaban dose group; B) Edoxaban plasma exposure by dosing regimen ..... **Error! Bookmark not defined.**

Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial Fibrillation
AHA	American Heart Association
ALT	Alanine transaminase
AMI	acute myocardial infarction
aPTT	Activated partial thromboplastin time
AST	aspartate transaminase
BD	Twice daily
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CHADS	Congestive heart failure, Hypertension, Age, Diabetes, Stroke
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum concentration observed
CrCl	Creatinine clearance
CRNM	Clinically Relevant Non-Major
CRNMB	Clinically Relevant Non-Major bleed
CSED	Common Study End Date
CVD	Cardiovascular disease
DS	Daiichi Sankyo
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
ER	Emergency Room
ESC	European Society Of Cardiology
ETP	Endogenous thrombin potential
FDA	Food and Drug Administration
GPRD	General Practice Research Database
Hgb	Haemoglobin
HIV	Human immunodeficiency virus
HR	Hazard Ratio
INR	International Normalized Ratio
Kg	Kilogram
LAA	Left Atrial Appendage
LFT	Liver function test
LV	Left Ventricle
Mg	Milligrams
MI	Myocardial Infarction
ML/min	Millilitre per minute
NMA	Network meta-analysis
NOAC	Non-VKA Oral Anticoagulants
NVAF	Non-valvular atrial fibrillation

NYHA	New York Heart Association
OAC	Oral anticoagulants
OD	Once daily
ONS	Office for National Statistics
OR	Odds Ratio
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
P-gp	P-glycoprotein
PT	Prothrombin time
RCT	Randomised clinical trial
RFT	Renal function test
SBP	Systolic Blood Pressure
SLSR	South London Stroke Register
SMC	Scottish Medicine Consortium
SmPC	Summary of Product Characteristics
SPAF	Stroke Prevention in Atrial Fibrillation
SPC	Summary of product characteristics
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TIA	Transient Ischaemic Attack
TTR	Time in Therapeutic Range
ULN	Upper limit of normal
VKA	Vitamin K antagonists
WBC	White blood cell count

Executive summary

Atrial fibrillation (AF) is the most common cardiac arrhythmia caused by irregular electrical signals generated throughout the atria of the heart. It is characterised by loss of synchronous atrial mechanical activity, which 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 cardioembolic stroke and peripheral embolisation). [1]

AF is associated with an approximately five-fold increase in the risk of stroke and a two-fold increase in the risk of all-cause mortality. [2;3] At least 15% to 20% of all ischaemic strokes occur in patients with AF, and this risk of ischaemic stroke increases with age. [4]

The prevalence of AF was estimated at 1.76% in England, according to the GRASP-AF registry [5], and 1.85% in Wales, according to data from the National Health Service (NHS) Quality and Outcomes Framework for 2012/2013. [6] AF occurs more frequently in men than in women and rarely affects people aged less than 50 years.

The current standard of care, according to national treatment guidelines, includes the use of vitamin K antagonist (VKAs; e.g. warfarin) and non-VKA oral anticoagulants (NOACs), such as the direct thrombin inhibitor dabigatran etexilate, and direct factor Xa inhibitors rivaroxaban and apixaban. [7] Warfarin is still the most commonly prescribed anticoagulant in the UK, and while it is an effective, suitable means of stroke prevention in patients with atrial fibrillation, it has a number of recognised limitations. This results in a significant proportion of patients at high risk of stroke that receive suboptimal treatment (e.g. being out of warfarin's narrow therapeutic range), or remain untreated, due to contraindications, drug-drug or drug-food interactions, and/or poor adherence. [5] A recent national stroke audit revealed that only 36% of patients with known AF are taking anticoagulants when they are admitted to hospital with a stroke. [8] It is clear that this is still an area of unmet need.

Clinical evidence for edoxaban

Edoxaban tosylate (brand name: LIXIANA®; henceforth edoxaban) offers another valuable treatment option for stroke prevention in AF. Edoxaban is an oral, highly selective, rapidly-acting, potent, competitively reversible, direct inhibitor of Factor Xa. The Marketing Authorisation Application for edoxaban was submitted to the EMA in January 2014 for approval as a treatment for the prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).[1] The addition of edoxaban as a treatment option in England and Wales will provide patients with an alternative

[1] It has also been submitted for approval for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults. This second indication will be separately appraised by NICE.

treatment for stroke prevention in atrial fibrillation with a once-daily dosage, a rapid onset of action, minimal food and drug interactions and no requirement for routine anticoagulation monitoring.

The primary source of evidence for the efficacy of edoxaban is its pivotal trial, ENGAGE AF-TIMI 48. This was a phase III, randomised, double-blind, double-dummy, non-inferiority study designed to evaluate the benefits and risks of edoxaban for stroke or systemic embolism in patients with non-valvular atrial fibrillation (21,105 patients were enrolled at 1393 centres in 46 countries, including 31 centres in the UK).

Two regimens, high-dose edoxaban (60mg or dose-reduced 30mg; i.e. 60 mg / 30 mg DR) and low-dose edoxaban (30mg or dose-reduced 15mg; i.e. 30 mg / 15 mg DR) once daily were compared with warfarin (international normalised ratio [INR] 2.0–3.0) in patients at moderate-to-high risk of stroke, with a mean $CHADS_2$ score of 2.8.

Patients at increased risk of bleeding due to higher drug exposure, specifically those with body weight ≤60 kg, creatinine clearance 30–50 mL/min, or concomitant treatment with selected P-gp inhibitors, had their dose reduced by 50%. The dose could be reduced either at randomisation or during the study if any of these conditions were met. A median time in therapeutic range (TTR; i.e. INR 2.0–3.0) of 68.4% was achieved in the warfarin arm, indicating that edoxaban was compared with very well-controlled warfarin therapy.

To reflect the anticipated indication, only data from the high-dose arm (60 mg / 30 mg DR) are discussed in this submission and included in the cost-effectiveness analysis. However, it should be noted that both once-daily regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes in the pivotal ENGAGE AF-TIMI 48 study. [9]

In the primary efficacy analysis of ENGAGE AF-TIMI 48, edoxaban 60 mg / 30 mg DR was non-inferior to well-controlled warfarin for the prevention of stroke or systemic embolism in patients with NVAF, with a numerical 21% reduction in risk ($p<0.001$ for non-inferiority) in the mITT on-treatment population. Moreover, edoxaban significantly reduced the risk of haemorrhagic stroke compared with well-controlled warfarin (46% risk reduction; $p<0.001$). Prespecified subgroup analyses demonstrate a consistent pattern across patient groups; the hazard ratios for the comparison of the high-dose edoxaban (60 mg / 30 mg DR) arm versus the warfarin arm on the primary efficacy endpoint was frequently 1.0 or less.

Edoxaban once-daily was associated with a significantly lower rate of the primary safety endpoint of major bleeding than well-controlled warfarin in the safety on-treatment population; risk reduction was 20% ($p<0.001$). Edoxaban also significantly reduced the risk of several bleeding outcomes compared with well-controlled warfarin, including fatal bleeding, life-threatening bleeding, the composite of major bleeding and clinically relevant non-major bleeding and minor bleeding. Analyses of major bleeding in a broad range of patient subgroups indicated that treatment with edoxaban was associated with a lower risk of bleeding than well-controlled warfarin in the majority of patient subgroups in ENGAGE AF-TIMI 48.

Analyses of major bleeding in a wide variety of patient subgroups in the safety on-treatment population found that there was a broadly consistent reduction in major bleeding across the majority of subgroups vs. well controlled warfarin.

Edoxaban demonstrated a favourable risk-benefit profile compared with well-controlled warfarin for net clinical outcome, a composite of efficacy and safety events, including stroke, systemic embolism, major bleeding, and death (HR 0.89; 95% CI 0.83–0.96; p=0.003). Furthermore, cardiovascular mortality was significantly reduced with edoxaban versus well-controlled warfarin (14% risk reduction; p=0.013).

In case of life-threatening bleeding, complications that can arise during the course of treatment with any anticoagulant, the effects of edoxaban have been shown to be reversed by 4-factor prothrombin complex concentrate. Edoxaban is currently the only NOAC to include such guidance in its SmPC based on clinical data.

Indirect comparison of edoxaban with other NOACs

In the absence of head-to-head data, a network meta-analysis (NMA) was conducted to estimate the relative efficacy and safety of edoxaban versus dabigatran, rivaroxaban, and apixaban. The NMA data should be interpreted with caution because of significant differences in patient characteristics and trial design that exist between the four pivotal phase III trials comparing individual non-VKA OACs with warfarin. However, results from the NMA were generally consistent with the results of direct comparison of the NOACs versus warfarin in the individual pivotal studies.

Compared to other NOACs, results from the NMA suggest that, among patients with $CHADS_2$ score ≥2, [redacted]

Cost-effectiveness analysis

A Markov model was developed to assess the cost-effectiveness of edoxaban versus the currently available OACs used for stroke prevention in atrial fibrillation. The model was based on those previously assessed by NICE in the appraisals of the other NOACs, and simulated the course of disease in hypothetical cohorts of patients with AF. Base case analyses used data from ENGAGE AF-TIMI 48 to compare edoxaban with warfarin, and used estimates from the NMA to compare edoxaban with apixaban, dabigatran (both doses; 110 mg twice daily [BID] and 150 mg twice daily [BID]) and rivaroxaban.

Edoxaban represents a cost-effective use of NHS resources. In the base case analysis (patients with $CHADS_2$ ≥2, mirroring the pivotal trial population), the incremental cost-effectiveness ratio (ICER) for edoxaban vs. warfarin was £12,881

per QALY gained. Consideration of subgroups of interest to NICE, which included time in therapeutic range on warfarin and level of stroke/thromboembolic risk, indicated that edoxaban was also cost-effective vs. warfarin in these patient groups; the ICERs were £7,012 per QALY gained for patients with $CHADS_2 \geq 3$, and £20,376 per QALY gained in the cTTR≥60% subgroup. This model is conservative, and does not account for disutility associated with patients taking warfarin.

Compared to other NOACs, edoxaban was found to be dominant compared to rivaroxaban, less effective and less costly vs. dabigatran 110 mg BD and dominated vs. apixaban and dabigatran 150 mg BD. The full incremental analysis showed that edoxaban, dabigatran 110 mg BID, apixaban and rivaroxaban are strictly dominated by dabigatran 150 mg BID. It should be noted that the required dose of dabigatran (110 mg BID or 150 mg BID) is dependent on individual patient characteristics, so the results of the discrete comparisons with the separate doses are not individually representative of the cost-effectiveness in the total UK AF population.

The results of the one-way and probabilistic sensitivity analyses support this finding of cost-effectiveness and show that conclusions are robust to alternative assumptions about model inputs. The deterministic sensitivity analysis shows that, for all comparators, the cost of treatment, monitoring cost, and patients starting age are among the top five variables with the largest effect on the results. Clinical effectiveness did not have such an influence on the base case results; the exceptions were mortality associated with major non-ICH bleeding (which has the greatest effect on the cost-effectiveness of edoxaban vs. rivaroxaban), and acute mortality for CRNM and major non-ICH bleeding (for the comparison of edoxaban vs. warfarin). Utility values in the model had little effect on the results; only the utility of stable AF appeared in the top 10 variables.

Therefore, the use of edoxaban in accordance with its licensed indication represents a clinically effective and cost-effective allocation of NHS resources. It provides a once-daily option for patients with NVAF, supported by robust efficacy and safety data.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Lixiana®

Approved name: Edoxaban tosylate

Therapeutic class: Oral anticoagulant (B01A – antithrombotic agent)

1.2 What is the principal mechanism of action of the technology?

Factor Xa is a serine protease that converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin and thus plays a central role in formation of a cross-linked thrombus. [10-12] Factor Xa is the primary site of amplification as one molecule of Factor Xa catalyses the formation of ~1000 thrombin molecules. [11] Factor Xa has been shown to activate clotting over a much wider concentration range than thrombin in preclinical studies, suggesting that Factor Xa inhibitors may have a wider therapeutic window than thrombin inhibitors. [11]

Edoxaban tosylate (henceforth edoxaban) is an oral, highly selective, rapidly-acting, potent, competitively reversible, direct inhibitor of Factor Xa that can inhibit thrombin generation, and produces sustained inhibition of anticoagulation for up to 24 h. [13]

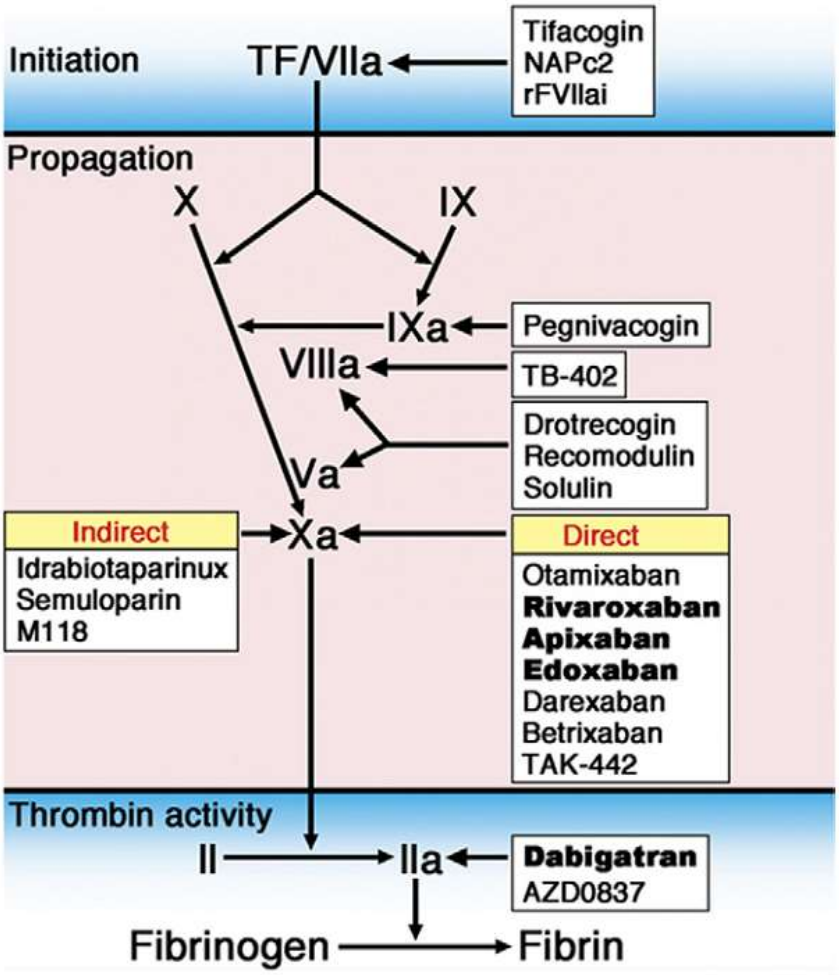
Edoxaban produces rapid onset of pharmacodynamic (PD) effects within 1 - 2 hours, which corresponds with peak edoxaban exposure (Cmax). The PD effects measured by anti-factor Xa assay are predictable and correlate with the dose and the concentration of edoxaban. As a result of FXa inhibition, edoxaban also prolongs clotting time in tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests are expected at the therapeutic dose; however, these changes are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of edoxaban. [14]

Approximately 40–59% of edoxaban is bound to plasma proteins [13] and it is a substrate for the P-glycoprotein (P-gp) transporter; [15] however, a very limited proportion of edoxaban (<4%) is metabolised by the cytochrome P450. [16]

Clinical pharmacology studies of edoxaban have shown it has a predictable and consistent pharmacokinetic (PK) profile. The elimination half-life of edoxaban is approximately 10-14 h in healthy subjects, with an absolute bioavailability of approximately 63%. [17] Approximately 50% of the absorbed edoxaban dose undergoes renal elimination. [18], meaning around 35% is eliminated in the urine. [17]

Figure 1 below, taken from De Caterina 2012 [19] represents the coagulation pathway and the different targets for several oral and parenteral anticoagulants (licenced or in development), including edoxaban.

Figure 1: Targets for new anticoagulants in the coagulation pathway



Source: Adapted from De Caterina 2012 [19]

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Edoxaban tosylate does not currently have a UK marketing authorisation for preventing stroke and systemic embolism in people with atrial fibrillation. European Medicines Agency (EMA) filing occurred on 7th January 2014. Positive Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in February 2015 and EMA marketing authorisation in May 2015.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for

example, exceptional circumstances/conditions to the marketing authorisation).

Discussions with the regulator are ongoing. To date, the main issues discussed have related to: the efficacy and safety in subgroups; the reversibility of edoxaban effect; the Risk Minimisation Plan; bleeding risk; and drug interactions. The most up-to-date SmPC available at the time of submission has been provided, which reflects the outcome of these discussions.

As Daiichi Sankyo does not have access to the draft EPAR, we are unable to provide a copy at this time. A version will be provided when available.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Edoxaban is anticipated to be indicated for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults.

It is also expected to be indicated for the prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

In the ongoing edoxaban clinical development programme, there is one ongoing study that is estimated to report within the next 12 months:

EDOXABAN VS WARFARIN IN SUBJECTS UNDERGOING CARDIOVERSION OF ATRIAL FIBRILLATION (ENSURE-AF) is a Prospective, Randomized, Open-label, Blinded endpoint Evaluation (PROBE) parallel group study comparing edoxaban (DU-176b) with enoxaparin/warfarin followed by warfarin alone in subjects undergoing planned electrical cardioversion of non-valvular atrial fibrillation. The estimated completion date is August 2015.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Daiichi Sankyo intends to launch edoxaban shortly after UK marketing authorisation is granted. We anticipate edoxaban will be available in the UK from May 2015.

In January 2015, the US FDA approved edoxaban to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF), with the following limitation of use: edoxaban should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischaemic stroke compared to warfarin at the highest dose studied (60 mg).

The US FDA also approved edoxaban for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Approval was obtained in Japan in September 2014 for the prevention of stroke and systemic embolism in patients with NVAF and for the treatment and recurrence prevention of VTE (DVT and PE).

Edoxaban was approved in Japan in April 2011, for the prevention of VTE after major orthopaedic surgery and was launched in July 2011 under the name LIXIANA™.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Daiichi Sankyo plans to submit edoxaban for appraisal by the Scottish Medicines Consortium (SMC) in March 2015, with a decision expected in July 2015.

Additionally, Daiichi Sankyo plans to submit edoxaban for the treatment of VTE including DVT and PE, and prevention of recurrent VTE in adults for appraisal by NICE in February 2015.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1: Unit costs of technology being appraised

Pharmaceutical formulation	Edoxaban tosylate is supplied as 60 mg, 30 mg, and 15 mg tablets
Acquisition cost (excluding VAT)	£2.10 per tablet (15mg, 30mg, 60mg)
Method of administration	Oral
Doses	The recommended dose is 60 mg Lixiana once daily, or 30 mg in specific patient groups (See Dose adjustments) The 15mg dose is available as a transition dose only. The draft SmPC includes detailed instructions for use of the 15mg transition dose in patients needing to switch from edoxaban to a VKA.
Dosing frequency	Once daily
Average length of a course of treatment	Therapy with edoxaban in NVAF patients should be continued indefinitely.
Average cost of a course of treatment	The provisional annual cost is £766.50 for edoxaban once daily.
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	Therapy with edoxaban in NVAF patients should be continued indefinitely.
Dose adjustments	The recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: • Moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 mL/min) • Body weight ≤ 60 kg • Concomitant use of the following P-gp inhibitors: cyclosporine, dronedarone, erythromycin, ketoconazole

Abbreviations: CrCl; creatinine clearance; kg: kilogram; mg, milligrams; mL/min: millilitre per minute; P-gp: P-glycoprotein.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

The use of edoxaban is not subject to any additional tests or investigations for patient selection compared to routine clinical practice as, prior to starting NOACs, renal function (RFT) and liver function tests (LFT) must be checked.

However treatment with edoxaban requires the lower (30mg) dose in patients with moderate to severe renal failure (CrCL 15-50 mL/min). As a result, the assessment of renal function may be required; however these tests are not above and beyond what would normally be assessed for these patients. According to ESC guidelines for the management of atrial fibrillation, assessment of renal function (by CrCl) is mandatory for all NOACs. [20] Indeed, renal function should be assessed annually in patients with normal (CrCl ≥80 mL/min) or mild (CrCl 50–79 mL/min) renal impairment, and perhaps 2–3 times per year in patients with moderate (i.e. creatinine clearance 30–49 mL/min) renal impairment. [20] The NICE clinical guideline on the management of atrial fibrillation also notes that the clinical features of the patient should be evaluated prior to choosing an appropriate anticoagulant. [7]

No additional monitoring is therefore required because of edoxaban.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

There is no general need for monitoring of patients on edoxaban over and above usual clinical practice, as recommended by NICE with regard to the use of currently available Non-VKA Oral Anticoagulants (NOACs) [21]. Therefore, it is anticipated there will be a reduction in the need for anticoagulation monitoring compared to warfarin.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There is no requirement to administer other therapies at the same time as edoxaban.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Natural history of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia caused by irregular electrical signals generated throughout the atria of the heart. This supraventricular arrhythmia characterised by loss of synchronous atrial mechanical activity 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). [1]

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. The longer AF persists, the more difficult it is to restore and maintain sinus rhythm. [1]

ESC classification distinguishes five types of AF based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF. [20]

In 90% of cases, AF occurs in patients with underlying heart disease. [22] The majority of patients with AF have hypertension. Other common cardiac abnormalities include ischaemic heart disease, mitral valve disease, hypertrophic cardiomyopathy, and dilated cardiomyopathy. Less common causes of AF that can trigger the development of atrial fibrosis include: restrictive cardiomyopathies such as amyloidosis, constrictive pericarditis, cardiac tumours, and severe pulmonary hypertension.

Non-valvular AF has been defined by the ACC/AHA/ESC Guidelines in 2001 as cases in which the rhythm disturbance occurs in the absence of rheumatic mitral stenosis or a prosthetic heart valve. [23] and is the most frequently AF type diagnosed in UK based on the PREFER AF registry (98.1% of AF patients). [24]

Clinical features of atrial fibrillation

AF is often asymptomatic, and it is not unusual for a patient to first become aware of AF during a routine physical examination. When symptoms occur, they are commonly associated with rapid ventricular rate. [25] If symptoms occur, the, most common symptoms of AF are palpitations, fatigue, dyspnoea, effort intolerance, and light-headedness. [26] 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. [2]

Because most cases of AF are associated with other medical conditions, a detailed medical history assessing the presence of angina, hyperthyroidism, or lung disease is important. A previous history of stroke or TIA, hypertension, diabetes, heart failure

or rheumatic fever may indicate that a patient with AF is at increased risk of thromboembolism. [2]

Risk factors for stroke in atrial fibrillation

Patients with AF have a substantial risk of stroke and systemic thromboembolism compared with age-matched people in sinus rhythm. This risk depends on comorbidities and demographic factors, and ranges from less than 1% to more than 20% per year. [27] The important independent prognostic factors for an increased risk of AF-related stroke are increasing age, a history of previous TIA or stroke, hypertension, diabetes mellitus, and evidence of moderate to severe left ventricular systolic dysfunction.

The complexity of the factors that influence thromboembolic risk in patients with AF necessitated the development of risk stratification schemes (i.e. $CHADS_2$ and CHA_2DS_2-VASc score) to identify the subgroup of patients who will benefit from anticoagulation.[25;28]

The risk factors measured by the $CHADS_2$ scoring system are congestive heart failure (1 point allocated), hypertension (1 point), age as or over 75 years (1 point), diabetes mellitus (1 point), and previous stroke or TIA (2 points), while the CHA_2DS_2-VASc scoring algorithm includes additional stroke risks (i.e., presence of vascular disease (1 point), age 65-74 years (1 point), and female gender (1 point)) and an extra point is allocated to the risk factor “age as or over 75 years”. [29] NICE guidelines recommend oral anticoagulation in patients with a $CHADS_2$-VASc score of 1 or greater. [7]

AF is associated with an approximately five-fold increase in the risk of stroke and a two-fold increase in the risk of all-cause mortality. [2;3] At least 15% to 20% of all ischaemic strokes occur in patients with AF, and this risk of ischaemic stroke increases with age. [4] Not only is the stroke risk higher in patients with AF, but also, the risk of stroke recurrence is higher compared to non-AF patients.[30] Strokes are significantly more severe, and more likely to be fatal, in patients with AF compared with those without AF. In the EuroHeart Failure Survey including 10,701 patients hospitalised for heart failure, death related to stroke was higher in AF patients (11%) compared to non-AF patients (4%).[31] Moreover, in non-fatal cases, strokes in AF patients are associated with greater functional disability compared to non-AF patients.[30-32]

Prevalence of AF

The prevalence of AF was estimated at 1.76% in England according to the GRASP-AF registry [5] and 1.85% in Wales according to data from the National Health Service (NHS) Quality and Outcomes Framework for 2012/2013. [6] 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 based on data from the General Practice Research Database (GPRD). [33;34] The prevalence of AF is estimated to at least double in the next 50 years as the average age of populations within Europe increases. [28]

Overall, prevalence of AF in patients with associated cardiovascular disease (CVD) is higher compared to that in the overall population.[35] The explanation for this is that

these conditions are responsible for structural and electrophysiological changes in the heart, which can lead to development of AF.[36;37] The presence of underlying CVD, both chronic (e.g. heart failure and hypertension) and acute (e.g. acute coronary syndrome (ACS) or acute myocardial infarction (AMI)), has a large effect on the prevalence and incidence of AF.

In the UK, the annual incidence of stroke was estimated at approximately 152,000 with a rate 25% higher in men than women. [38]

Prevention of stroke related AF

Oral anticoagulants, including vitamin K antagonists (VKAs) and the NOACs are the mainstay of stroke prevention in AF.[39] However, based on the Sentinel Stroke National Audit Programme of the Royal College of Physicians, only 36% of patients admitted with stroke to hospitals in England, Wales and Northern Ireland in the first 3 months of 2013, received an anticoagulant. [7] This shortfall in the prescribing of anticoagulants could be explained by perceived risk of anticoagulation. Indeed, VKAs are associated with several limitations including a high variability of effect due to several drug-drug and drug-food interactions, a narrow therapeutic window, and a slow onset of action.

The addition of edoxaban to the prescribing schedule in England and Wales will provide patients with an alternative treatment for stroke prevention in atrial fibrillation (SPAF) with a once-daily dosage, a rapid onset of action, minimal food and drug interactions and no requirement for routine anticoagulation monitoring.

Economic burden

Estimates of the economic burden posed by AF and stroke prevention in Europe are critical in light of an ageing population and constrained public finances. The costs of AF are driven by the consequences of AF-related complications such as strokes, hospitalisations, [40;41] and loss of productivity.[42]

A study which included 3000 patients who had suffered a stroke from the South London Stroke Register (SLSR), estimated the cost of stroke care in UK to be around £9 billion a year with the total annual direct care cost estimated to be approximately 49% and hospitalisations 10% of this total.[43]

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The marketing authorisation is anticipated to cover the population of patients with non-valvular atrial fibrillation at risk of stroke and systemic embolism.

According to the GRASP-AF registry, the AF prevalence rate was estimated at 1.76% per year in England, which corresponds to an estimated 985,813 patients diagnosed with AF each year (assuming a total number of registered patients in practices at 56,012,096). [5]

In Wales, there were 58,787 patients registered and diagnosed with AF in 2012/2013, which corresponds to a prevalence rate of 1.85%. [44]

Estimates suggest that at least 75% of AF is non-valvular [45] and 78.8% of patients are at risk of stroke (i.e., with a $CHADS_2$ risk score ≥1) [46]. Assuming these rates, the number of patients eligible for treatment with edoxaban is estimated at 582,615 in England and 34,743 in Wales.

Table 2: Estimated number of patients eligible for edoxaban in England and Wales

	Rate	England	Wales
Number of AF patients		985,813	58,787
Number of NVAF patients	75%	739,360	44,090
Number of NVAF patients at risk of stroke	78.80%	582,615	34,743

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

The life expectancy of people with AF is reduced compared to the life expectancy of the general population within England and Wales. According to information from the Office for National Statistics (ONS) on life expectancy in the general population, at the age of 65, men have a life expectancy of a further 18 years in England, 17.5 years in Wales; and women a further 20.6 years in England, 20.2 years in Wales. [47]

Data from the Framingham heart study showed an effect of AF on life expectancy; the median survival of patients with AF aged 55-64 years was 12.6 years for men and 12.1 years for women. [48]

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE Technology Appraisal Guidance

NICE has issued technology appraisal guidance on dabigatran etexilate (TA 249), rivaroxaban (TA 256) and apixaban (TA 275). [49-51]

Dabigatran etexilate was recommended in March 2012 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 (NYHA) class 2 or above,
- age 75 years or older; or
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

Rivaroxaban was recommended in May 2012 as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:

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

Apixaban was recommended in January 2013 as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:

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

NICE clinical guidelines

In addition to these technology appraisals, NICE has recently published new guidelines for the management of atrial fibrillation, (CG180), including recommendations about the treatment of AF with anticoagulants [7]:

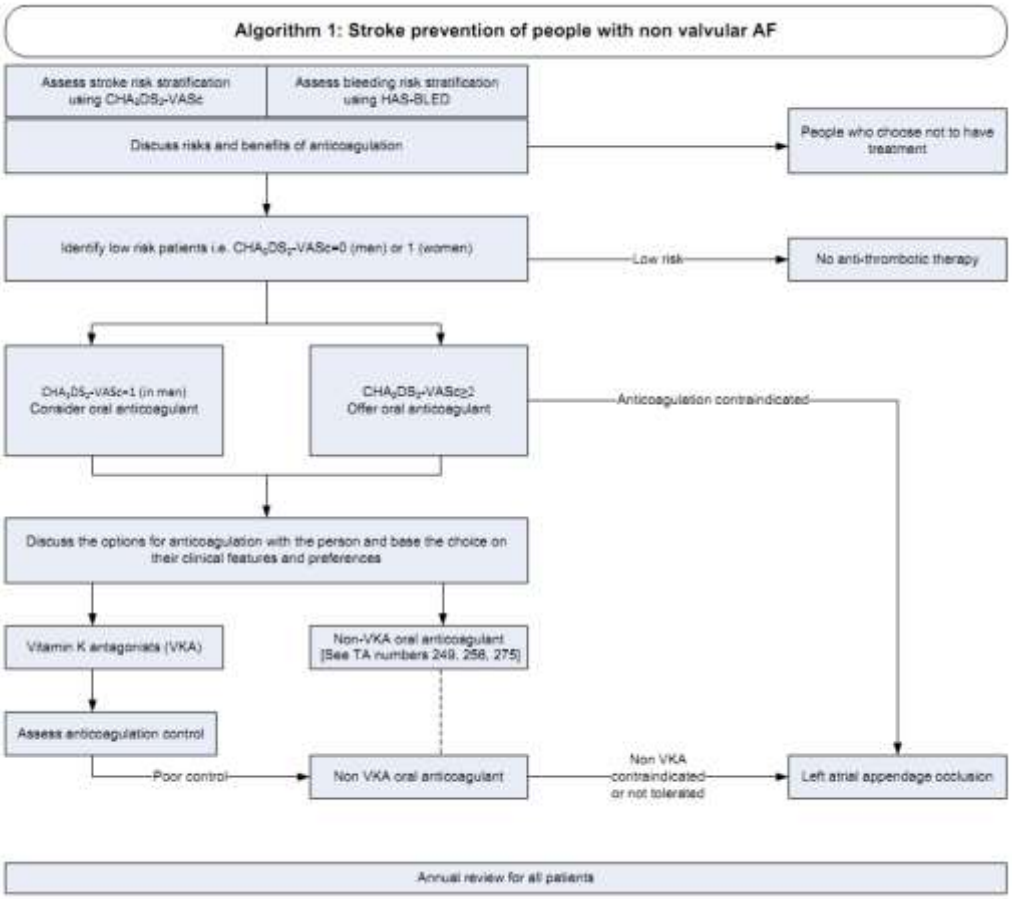
- Anticoagulation therapy may be achieved with apixaban, dabigatran etexilate, rivaroxaban or vitamin K antagonists. It recommends that the options for anticoagulation should be discussed with the patient and the choice based on their clinical features and preferences. The NICE guideline makes no recommendations 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 vitamin K antagonists shown by any of the following:
    - Two International Normalised Ratio (INR) values higher than 5 or one INR value higher than 8 within the past 6 months,
    - Two INR values less than 1.5 within the past 6 months,
    - Time in Therapeutic Range (TTR) less than 65% (the calculation is over a maintenance period of at least 6 months).

- If poor anticoagulation control with vitamin K antagonists cannot be improved, the clinician should evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the patient.
- This guideline (which supersedes the previous NICE guideline on the management of atrial fibrillation) now recommends that aspirin monotherapy should not be prescribed to people with atrial fibrillation solely on account of stroke prevention.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The current clinical pathway of care for patients with NVAF in England and Wales is shown in Figure 2. It is anticipated that edoxaban would offer an alternative pharmacotherapy to other NOACs (apixaban, dabigatran etexilate, rivaroxaban) and warfarin within the existing pathway for adult patients with NVAF.

Figure 2: Stroke risk stratification algorithm



Source: NICE Guidance CG180 [7]

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

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.

Minor changes in plasma concentration can lead to major clinical issues, such as development of a hypercoagulable state or bleeding due to over-anticoagulation. As a result, VKA dosing must be guided by INR monitoring.[52] An INR between 2.0 and 3.0 is recommended for most patients with NVAF who receive warfarin.[23;53] A recent multinational meta-analysis/meta-regression study which included VKA study groups from Europe/UK, Asia, Israel and North America, showed that only 61% of patients spent their time within the therapeutic range (INR 2-3).[54] Studies have shown that increasing the percentage of time a patient spends within a therapeutic INR range decreases their likelihood of stroke and bleeding.

INR monitoring induces burden for the patient and impacts patient's quality of life. In a quality of life questionnaire validation study conducted on patients with DVT, the 'hassle with monitoring' domain was significantly correlated with the SF-36 general health and mental health domains, indicating that mandatory visits to the clinic for

blood monitoring have a negative impact on patient perception of general health and emotional distress.[55] 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.

One of the many problems with anticoagulation with VKAs is the high inter-individual and intra-individual variation in INRs.[28] 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. More than 120 drug and food interactions have been reported for warfarin.[56] Drug-drug interactions occur with drugs that compete with the cytochrome 2C9 (CYP2C9). Some drugs also interfere with the intestinal absorption of VKAs.[56]

VKAs are also characterised by a slow onset of action as it can take three to seven days to reduce endogenous levels of vitamin K-dependent coagulation factor activity and reach therapeutic levels of anticoagulation.

Even though VKAs are recommended in the clinical guidelines, these agents are under prescribed in clinical practice. This underuse is driven by safety and convenience issues associated with the use of VKAs.[57] as shown in a survey of senior UK hospital physicians, experience of bleeding events and fear of bleeding appeared to reduce prescription of oral anticoagulation therapy.[58]

NVAF treatment approach has been evolving in recent years with the entry of NOACs. 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. This is especially true now that the updated NICE AF guidelines recommend that aspirin monotherapy should not be prescribed to people with atrial fibrillation solely on account of stroke prevention. [7]

In this context, patients with AF who need chronic anticoagulation for the prevention of stroke need a safe, efficient simple treatment that provides appropriate protection, particularly for challenging groups such as fragile patients and those with comorbidities. Furthermore, patients need a treatment option that provides them with reassurance through clear dosing guidance.

2.7 Please identify the main comparator(s) and justify their selection.

The main comparators, as defined in the final scope, are the interventions recommended to prevent stroke in the AF guidelines in UK [7]: vitamin K antagonist (VKAs; e.g. warfarin), and non-VKA oral anticoagulants such as the direct thrombin inhibitor dabigatran etexilate and direct factor Xa inhibitors rivaroxaban and apixaban.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Edoxaban, like all anticoagulants, increases the risk of bleeding. As there is no specific antidote for bleeds while on any of the non-VKA oral anticoagulants, the edoxaban SPC recommends in case of bleeding to promptly evaluate any signs or symptoms of blood loss and discontinue edoxaban in patients with clinically significant active bleeding.

A number of reversal agents are currently under development. These include the 4-factor prothrombin complex concentrate (4F-PCC) which has been investigated recently in a phase I trial. The study demonstrated that, for life-threatening bleedings that cannot be controlled, the administration of a 4F-PCC at 50 iU/kg reverses the effects of edoxaban 30 minutes after completing the infusion. [59]

The SmPC states that for life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 iU/kg has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion.

Recombinant factor VIIa (r-FVIIa) can also be considered. However, there is limited clinical experience with the use of this product in individuals receiving edoxaban.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The main resource use to the NHS associated with edoxaban is the acquisition cost of the drug. No additional costs are anticipated to arise based on location of care, staff usage, administration costs, monitoring or tests. As INR monitoring is unnecessary with edoxaban, a reduction in INR monitoring required with warfarin treatment is expected. No additional laboratory testing is expected to be recommended compared to other NOACs.

2.10 Does the technology require additional infrastructure to be put in place?

Edoxaban does not require additional infrastructure to be put in place.

3 Equality

3.1 Identification of equality issues

There are no equality issues surrounding the use of edoxaban in stroke prevention in non-valvular atrial fibrillation.

3.1.1 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

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 [60]: unpredictable PK and PD; 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.

By contrast, the currently NICE-recommended NOACs have predictable PK/PD, have minimal interactions with other drugs compared to VKAs, and do not require INR monitoring. However, rivaroxaban is also associated to several limitations, including: the need to be administered with a meal; and the use of an initiation dose which differs from its maintenance dose. [61] Similarly, dabigatran is limited by its need to be taken twice daily; its association with dyspepsia; and that the tablets are not stable outside of their blister pack, so they cannot be added to any pill organiser, which is 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. [62]

Edoxaban may provide a convenient alternative to comparators without compromising efficacy or safety. Like the other NOACs, edoxaban does not require any INR monitoring; it has predictable PK/PD, and has minimal interactions with other drugs. By contrast, it can be taken with or without food, is once-daily and is stable outside its blister pack. Furthermore, that the dose of edoxaban 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-gp inhibitors) provides a very simple dosing regimen both for physician and patient.

Lastly, as described above in Section 2.8, the administration of a 4-factor prothrombin complex concentrate (PCC) has been shown to reverse the effects of edoxaban in the case of uncontrolled bleeding. Edoxaban is currently the only NOAC to include such guidance in its SmPC based on clinical data.

4.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The use of edoxaban may result in potential convenience benefits, since INR monitoring is not required, as is the case with VKAs. Poor compliance may eventually lead to undesired health outcomes such as stroke/recurrence.

Edoxaban may also lead to improved health-related benefits due to the absence of lifestyle limitations on account of the absence of significant drug-drug or drug-food

interactions, and its ease of use as a once-daily medication. Once daily regimens of medication do enhance patient adherence and compliance to therapy. [63]

For reasons presented above (monitoring, compliance, lifestyle changes), warfarin has been shown to have an impact on quality-of-life. A study has estimated that warfarin was associated with a disutility of 0.012, compared with NOACs. [64]

These consequences were not considered in the base case model but were taken into account in a sensitivity analysis. As a result, the costs per QALY for edoxaban in the base case analysis are likely to be conservative estimates.

4.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Data are taken from peer-reviewed publications [63;64], the ENGAGE AF-TIMI 48 clinical study report and the summary of product characteristics for edoxaban.

5 Statement of the decision problem

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.	As per NICE scope	N/A

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	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.		
Subgroups to be considered	If evidence allows, consideration will be given to subgroups defined by: • time in therapeutic range on warfarin. • level of stroke/thromboembolic risk.	As per NICE scope	
Special considerations, including issues related to equity or equality	None	N/A	N/A

Abbreviations: N/A, not applicable

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1 **Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.**

Two systematic reviews were conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of edoxaban and relevant comparators as outlined in the scope.

1. Randomised controlled trial (RCT) evidence on the efficacy and safety of edoxaban and relevant comparators for stroke prevention in patients with non-valvular atrial fibrillation (NVAF)
2. Non-RCT evidence on the efficacy and safety of edoxaban for stroke prevention in patients with non-valvular atrial fibrillation (NVAF).

The RCT systematic review was also conducted to inform a network meta-analysis (NMA).

The searches were supplemented by hand searching the bibliographies of relevant review articles and conference proceedings.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for atrial fibrillation, pharmacological intervention(s) of interest, and clinical trial design.

The search strategy for RCT evidence is provided in Section **Error! Reference source not found.** (Appendix 2) and for non-RCT evidence in Section **Error! Reference source not found.** (Appendix 6).

6.2 Study selection

6.2.1 **Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.**

Studies identified were initially assessed based on title and abstract (i1). Papers not meeting the inclusion criteria were excluded, and allocated a “reason code” to document the rationale for exclusion (e1). Papers included after this stage were then assessed based on the full text (i2). Further papers were excluded, yielding the final data set for interrogation (i3). The final included data set consisted of clinical studies for edoxaban (i4).

The full text of the final data set was also screened for studies suitable for the NMA (i5).

Inclusion and exclusion selection criteria for the RCT search are detailed in Table 3 for non-RCT search in Table 4.

Table 3: Eligibility criteria for RCT search

	Description	Justification
Inclusion criteria		
Population	Adults (≥18 years) with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism	Consistent with scope
Interventions	• Warfarin • Apixaban • Rivaroxaban • Dabigatran • Edoxaban	Consistent with scope
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	Consistent with scope
Study design	RCTs	Non-RCT studies were identified through a separate search
Exclusion criteria		
Population	Subjects <18 y, patients with valvular/rheumatic AF	
Interventions	Studies not investigating edoxaban or relevant comparator	
Outcomes	Studies not reporting the outcomes listed in the scope	
Study design	Non-RCT	Non-RCT studies were identified through a separate search

Abbreviations: AF, atrial fibrillation; RCT, randomised controlled trial

Table 4: Eligibility criteria for Non-RCT search

	Description	Justification
Inclusion criteria		
Population	Adults (≥18 years) with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism	Consistent with scope
Interventions	Edoxaban	Consistent with scope
Comparators	No restriction on comparator	Consistent with scope
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	Consistent with scope
Study design	Non- RCTs including cohort studies (prospective, retrospective), case-control studies, cross-sectional studies	RCT studies were identified through a separate search
Exclusion criteria		
Population	Subjects <18 y, patients with valvular/rheumatic AF	
Interventions	Studies not investigating edoxaban or relevant comparator	
Comparators	No restriction on comparator	
Outcomes	Studies not reporting the outcomes listed in the scope	
Study design	RCTs	RCT studies were identified through a separate search

Abbreviations: AF, atrial fibrillation; RCT, randomised controlled trial

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The schematic for the systematic review of RCT evidence is shown in **Error! Reference source not found.** (in Appendix 2, section **Error! Reference source not found.**).The systematic review was conducted between 28th April and 8th May 2014.

Following assessment and exclusion of studies based on title, abstract and full text, 52 publications satisfied the selection criteria.

An update of the systematic review, using the same search strategy, was conducted between the 24th November and 03rd December 2014 (with a date restriction of 2014 to present). The update identified a further 18 records. Aditionally, 27 abstracts were found after conference proceeding search.

In total 97 records, of which 4 relevant peer-reviewed articles investigated the intervention of interest (edoxaban):

- ENGAGE AF-TIMI 48 [9]
- DU176b-PRT018 (NCT00504556) [65]
- DU176b-C-J226 (NCT00806624) [66]
- DU176b-C-J225 (NCT00829933) [67]

A total of 4 studies, including one edoxaban RCT, one dabigatran RCT, one rivaroxaban RCT and one apixaban RCT were identified for inclusion in the NMA, further details of which are reported in Section 6.7.

The schematic for the systematic review of non-RCT evidence is shown in **Error! Reference source not found.** (in Appendix 6, section **Error! Reference source not found.**). The systematic review was conducted between 30th April and 8th May 2014. Following assessment and exclusion of studies based on title, abstract and full text no records for non-RCTs were identified.

An update of the systematic review, using the same search strategy, was conducted between the 24th November and 03rd December 2014 (with a date restriction of 2014 to present). No records were identified.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

In total the systematic review identified four RCTs in the population of interest.

Data for edoxaban within this submission are reported from the following sources. ENGAGE AF-TIMI 48 is reported in Section 6.5. Data from DU176b-C-J225, DU176b-C-J226J226 and DU176b-PRT018PRT018 are reported in Section **Error! Reference source not found.**.

Table 5: List of data sources for edoxaban

Trial name	Trial number	Data source
ENGAGE AF-TIMI 48 (NCT00781391)	DU176b-C-U301	• CSR [68] • Publication – Giugliano 2013 [9]
NCT00504556	DU176b-PRT018	• Publication – Weitz 2010 { Weitz J, 2010 280 /id
NCT00829933	DU176b-C-J225	• Publication – Yamashita 2012 [67]
NCT00806624	DU176b-C-J226	• Publication – Chung 2011 [66]

Abbreviations: CSR, clinical study report.

Complete list of relevant RCTs

6.2.4 **Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.**

The systematic review of clinical evidence identified four RCTs of edoxaban in the population of interest to this submission (Table 6).

Table 6: List of relevant RCTs

Study no. (acronym)	Intervention	Active control/ comparator	Population	Number of patients	Trial duration	Primary study ref.
Primary Phase III RCTs						
ENGAGE AF-TIMI 48 (DU176b-C-U301)	• Edoxaban 30 mg/15 mg DR OD • Edoxaban 60 mg/30 mg DR OD	• Warfarin	Adult patients ≥ 21 years old with NVAF with a $CHADS_2$ score of 2 or more	N= 21,105	Median follow-up of 2.8 years	[68]
Phase II RCTs						
DU176b-C-J225	• DU-176b low dose OD • DU-176b intermediate dose OD • DU-176b high dose OD	• Warfarin	Adult patients ≥ 21 years old with NVAF with at least one of the risk factors for embolism	N=536	12 weeks	[67]
DU176b-C-J226	• DU-176b low dose OD • DU-176b high dose OD	• Warfarin	Adult patients aged 18 to 80 years, with NVAF with a $CHADS_2$ score of 1 or more	N=235	12 weeks	[66]
DU176b-PRT018	• Edoxaban 30 mg OD • Edoxaban 60 mg OD • Edoxaban 30 mg BD • Edoxaban 60 mg BD	• Warfarin	Adult patients aged 18 to 80 years, with persistent NVAF with a $CHADS_2$ score of 2 or more	N=1,146	3 months	[65]

Abbreviations: BD, Twice daily; OD, once daily

6.2.5 **Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.**

One primary Phase III study compares the intervention with one of the named comparators in the decision problem:

- ENGAGE AF-TIMI 48 compared both once-daily high-dose edoxaban (60mg or dose-reduced 30mg; i.e. 60 mg / 30 mg DR) and once-daily low-dose edoxaban (30mg or dose-reduced 15mg; i.e. 30 mg / 15 mg DR) to warfarin (target INR 2.0-3.0).

For patients randomised to either the 60mg or the 30mg group, the dose was halved if any of the following characteristics were present at the time of randomisation or during the study: estimated creatinine clearance of 30 to 50 ml per minute, a body weight of 60 kg or less, or the concomitant use of verapamil, quinidine or dronedarone. Indeed, PK modelling and simulation showed that patients with low body weight, moderate-to-severe renal dysfunction, or concomitant use of a potent P-glycoprotein inhibitor should have the edoxaban dose reduced by 50%. [9]

The Phase III ENGAGE AF-TIMI 48 is reported in full in this submission. A summary of the largest Phase II dose-ranging study with any NOAC in patients with AF (DU176b-PRT018) is provided as supporting evidence in section **Error! Reference source not found.** and thereferences for the phase II studies DU176b-C-J225, DU176b-C-J226 are provided in Table 6.

6.2.6 **When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.**

No identified studies were excluded from further discussion.

List of relevant non-RCTs

6.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.**

No relevant non-RCTs were identified.

6.3 Summary of methodology of relevant RCTs

6.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

Please note that in the sections below, once-daily high-dose edoxaban (60mg, including those dose-reduced to 30mg) will be referred to as edoxaban 60 mg / 30 mg DR and once-daily low-dose edoxaban (30mg, including those dose-reduced to 15mg) as 30 mg / 15 mg DR.

Methods

6.3.2 **Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.**

The methodology of the primary Phase III RCT is summarised in Table 7.

Table 7: Summary of methodology of ENGAGE AF-TIMI 48

Study no. (acronym)	ENGAGE AF-TIMI 48
Study objective	To demonstrate non-inferiority of a once-daily high-dose of edoxaban (60 mg / 30 mg DR) and also a once-daily low-dose of edoxaban (30 mg / 15 mg DR) compared with warfarin (INR target range 2.0–3.0), for the prevention of stroke and SEE in patients with NVAF with a $CHADS_2$ score of 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 the Interactive Response Technology System (IXRS). • Randomisation stratified by $CHADS_2$ risk score (stratum 1: $CHADS_2$ risk score 2 and 3; stratum 2: $CHADS_2$ risk 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 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

Study no. (acronym)	ENGAGE AF-TIMI 48
Interventions, N randomised	• 30 mg edoxaban OD (or 15 mg OD for subjects requiring dose adjustments) plus placebo-to-match warfarin, N= 7034 • 60 mg edoxaban OD (or 30 mg 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
Permitted concomitant medications	• Use of aspirin ≤ 100 mg daily • Use of a single antiplatelet therapy with any antiplatelet agent • Use of open-label VKA in case of a clinical indication for dual antiplatelet therapy(study drug should be temporarily interrupted) • Use of NSAIDs by all routes other than oral/parenteral • Topical use of strong P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin, and clarithromycin. • Use of specified concomitant medications (e.g., verapamil, quinidine, dronedarone) with study drug was to be handled by reducing the dosage regimen of edoxaban or placebo-to-match
Disallowed concomitant medications	• Anticoagulants, other than the assigned study drugs, by any route (with the exception of parenteral agents used as a bridge when starting or resuming study drug), fibrinolytic agents, dual antiplatelet therapy such as aspirin plus a thienopyridine (ticlopidine or clopidogrel), aspirin plus any other non-aspirin antiplatelet therapy, and any 2 non-aspirin antiplatelet medications taken together. • Chronic use of oral or parenteral NSAIDS including both cyclooxygenase-1 and cyclooxygenase-2 inhibitors other than aspirin for ≥ 4 days/week. • Use of the following P-gp inhibitors ritonavir, nelfinavir, indinavir, saquinavir, and cyclosporine • Systemic use of the P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin, and clarithromycin required study drug treatment temporary interruption. The subject was to restart study drug after completing treatment with these medications. • Other investigational drugs or devices
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 SEE
Secondary efficacy	• Time to first occurrence of:

Study no. (acronym)	ENGAGE AF-TIMI 48
endpoints	○ Composite outcome of stroke, SEE and CV mortality, as well as each component separately ○ MACE, defined as a composite of non-fatal MI, non-fatal stroke, non-fatal SEE and death due to CV cause or bleeding, as well as each component separately ○ Composite outcome of stroke, SEE and all-cause mortality, as well as each component separately
Additional efficacy endpoint	• Other efficacy endpoints were analysed based on ITT, mITT, and PP analysis sets with no correction for multiplicity: ○ Composite of adjudicated stroke, adjudicated SEE, and Investigator reported TIA, as well as each individual component ○ Investigator reported VTE, including both PE and DVT, as well as each individual component ○ Incidence of hospitalisation due to CV condition including hospitalisations for bleeding; ○ Severity of strokes (modified Rankin scale performed 1 month following stroke onset); ○ Number of adjudicated and Investigator reported strokes and SEEs (1 subject can have multiple strokes and SEEs).
Principal safety endpoint	Adjudicated major bleeding during treatment, in line with the modified International Societyon Thrombosis and Haemostasis (ISTH) definition
Secondary safety outcomes	Adjudicated major or clinically relevant non-major (CRNM) bleeding. A CRNM bleeding event was specifically defined in ENGAGE AF-TIMI 48 as a clinically overt bleeding visualized by examination or radiologic imaging and requiring medical attention.
Other safety outcomes	• Bleeding events: fatal, CRNM, minor, life-threatening, intracranial, gastrointestinal, bleeding during 30-day transition period • All-cause mortality; adverse events; assessment of liver function; clinical laboratory tests • Net clinical outcome defined as the adjudicated composite endpoint of stroke, SEE, major bleeding, and all-cause mortality
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]

Abbreviations: CRNM: Clinically Relevant Non-Major, CV: Cardiovascular, DVT: Deep vein thrombosis, INR: International normalized ratio, ISTH: International Society on Thrombosis and Haemostasis, IXRS: Interactive Voice and Web Response System, MI: Myocardial infarction, NSAIDs: Non-steroidal anti-inflammatory drugs, NVAF: Non-valvular atrial fibrillation, OD: once-daily, P-gp: P-glycoprotein, PE: Pulmonary embolism, SEE: Systemic embolic event, TIA: Transient ischaemic attack, VKA: Vitamin K antagonists, VTE: Venous thromboembolic event.

Participants

6.3.3 **Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.**

The inclusion and exclusion criteria for the relevant RCTs are summarised as follows:

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.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

The reporting of ENGAGE AF-TIMI 48 results will focus on the high-dose edoxaban arm (i.e. those randomised to 60mg, including those dose-reduced to 30mg; 60 mg / 30 mg DR), since this arm represents the licensed dosing and posology.

Population datasets definitions are presented in Table 10.

Patient characteristics of the ITT dataset at baseline for edoxaban 60 mg / 30 mg DR and warfarin arms are summarised in Table 8.

All demographic and baseline characteristics were comparable among the treatment groups. Overall, the majority of patients were male (62%) with a median age of 72

years-old. The percentage of patients aged ≥75 years was approximately 40%. The mean $CHADS_2$ score was 2.8 and approximately 53% of patients had a $CHADS_2$ score ≥3, indicating the patient population was at moderate-to-high risk of stroke.

Table 8: Patient characteristics at baseline in ENGAGE AF-TIMI 48 (ITT analysis set)

Characteristic	Edoxaban (60 mg / 30 mg DR) (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,		

Characteristic	Edoxaban (60 mg / 30 mg DR) (N=7035)	Warfarin (N=7036)
n (%)	2070 (29.4)	2092 (29.7)
Aspirin	174 (2.5)	164 (2.3)
Thienopyridine	866 (12.3)	827 (11.8)
Amiodarone	2078 (29.5)	2176 (30.9)
Digoxin or digitalis preparation		

Abbreviations: $CHADS_2$, Congestive heart failure or left ventricular dysfunction, Hypertension, Aged ≥75 years (doubled), Diabetes, Stroke/transient ischaemic attack (doubled); CrCl, creatinine clearance; ITT, intention-to-treat; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Outcomes

6.3.5 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.**

The outcomes investigated in ENGAGE AF-TIMI 48, the measures used to assess those outcomes and their relevance with reference to the decision problem are presented in Table 9.

Table 9: Primary and secondary outcomes of ENGAGE AF-TIMI 48

Primary outcome(s) and measures	Secondary outcome(s) and measures	Outcome definitions	Reliability/validity/ current use in clinical practice
Efficacy			
Time to the first adjudicated stroke (ischaemic or haemorrhagic) or SEE	• Time to first occurrence of: ○ Composite outcome of stroke, SEE and CV mortality ○ MACE, ○ Composite outcome of stroke, SEE and all-cause mortality • Adjudicated composite endpoint of disabling stroke, SEE, life-threatening bleeds/ICH, and all-cause mortality • Composite of adjudicated stroke, adjudicated SEE, and Investigator reported TIA, as well as each individual component • Investigator reported VTE, including both PE and DVT, as well as each individual component • Incidence of hospitalisation due to CV condition including hospitalisations for bleeding; • Severity of strokes (modified Rankin scale performed 1 month following stroke onset); • Number of adjudicated and Investigator reported strokes and SEEs (1 subject can have multiple strokes and SEEs).	• A stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery that is not due to an identifiable non-vascular cause (i.e., brain tumour or trauma), and that either lasts at least 24 hours or results in death within 24 hours of onset. • An SEE is defined as an arterial embolism resulting in clinical ischaemia, excluding the CNS, coronary and pulmonary arterial circulation. • Both stroke and SEE are defined in greater detail in the CEC charter. • MACE is defined as a composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding	The primary and secondary efficacy endpoints were defined in the Clinical Events Committee (CEC) charter and were adjudicated by an independent CEC. The key endpoints are well defined clinical outcomes and the definitions of these outcomes are well accepted by the Regulatory and Medical community.
Safety			
Adjudicated	• Adjudicated Major or CRNM bleeding;	• Bleeding was based on published guidance from the ISTH, with minor modifications for Hgb decrease and	Bleeding events were adjudicated by an

Primary outcome(s) and measures	Secondary outcome(s) and measures	Outcome definitions	Reliability/validity/ current use in clinical practice
Major bleeding	• Bleeding events: fatal, CRNM, minor , life-threatening, intracranial, gastrointestinal, bleeding during 30-day transition period;	blood transfusion requirements. ○ Major bleeding: ○ Clinically overt bleeding accompanied by a decrease in haemoglobin of ≥ 2 g/dL and/or transfusion of ≥ 2 units of packed red blood cells ○ Bleeding that occurred in a critical site ○ Bleeding that was fatal ○ CRNM bleeding – clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to either: ○ Hospital admission ○ Physician guided medical or surgical treatment • Minor bleeding – clinically overt bleeding that did not satisfy the criteria for major bleeding or CRNM	independent CEC based on the definition of Major and CRNM bleeds described in the CEC charter
Other outcome measures			
Net clinical outcome	• All-cause mortality; adverse events; assessment of liver function; clinical laboratory tests.	• Net clinical outcome is defined as the composite of stroke, SEE, major bleeding, and all-cause mortality	

Abbreviations: CEC, Clinical Events Committee; CNS, Central Nervous System; CRNM, Clinically Relevant Non-Major; CV, Cardiovascular; DVT, Deep vein thrombosis; ISTH, , International Society on Thrombosis and Haemostasis; PE, Pulmonary embolism; SEE, Systemic embolic event; TIA, Transient ischaemic attacks; VTE, Venous thromboembolic event

Statistical analysis and definition of study groups

6.3.6 **State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT**

Definitions of populations analysed and observation periods in ENGAGE AF-TIMI 48 are provided in Table 10.

Table 10: Definitions and summary of analysis sets in ENGAGE AF-TIMI 48

Population	Abbreviation	Definition
Intent-to-treat Analysis Set	ITT	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 Analysis Set	mITT	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 Analysis Set	PP	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 PP 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	SAS	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

Population	Abbreviation	Definition
		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	**Abbreviation**	**Definition**
On-treatment period	OT	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) [2] visit, the subject was not considered at risk after the CSED Visit for primary statistical analyses.
Overall study period	OS	The time from the reference date (randomisation date or initial dose of study drug date) to the CSED visit

To fulfil FDA and EMA requirements, the efficacy analyses were performed within several analysis sets. The primary efficacy analyses, which tested whether both dose regimens of edoxaban were non-inferior to warfarin, were performed with the use of a Cox proportional-hazards model that included treatment arms and the two randomisation stratification factors, and was performed in the mITT population for the on-treatment period. To satisfy non-inferiority, the upper boundary of the one-sided 97.5% confidence interval for the hazard ratio of the primary efficacy endpoint comparing edoxaban with warfarin could not exceed 1.38, which was an estimate that preserved at least 50% of the benefit of warfarin over placebo.

If the high-dose edoxaban (60 mg /30 mg DR) dosing regimen met the pre-specified criteria for non-inferiority, it was then compared with warfarin in a prespecified test of superiority in the ITT population. All primary endpoint events that occurred during the overall study period were considered in the analysis with a 97.5% confidence interval and hazard ratio boundary of 1.38 for superiority. If non-inferiority with warfarin was observed with the low-dose edoxaban (30 mg / 15 mg DR) arm, it was also compared with warfarin in an analogous, but exploratory, test of superiority in the ITT population.

[2] The CSED is an actual calendar date at which time it is projected that the study will have accrued the required number of primary endpoint events.

Details of hypotheses and statistical analyses are provided in Table 11.

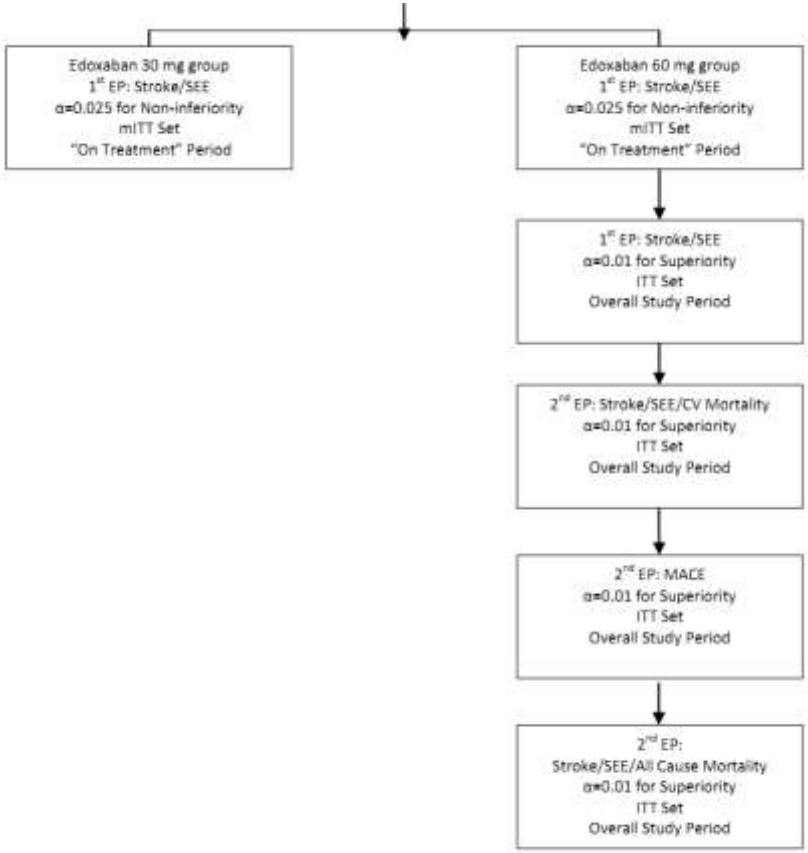
Table 11: Summary of statistical analyses in ENGAGE AF TIMI 48

Study no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ENGAGE AF-TIMI 48	• The primary objective was to determine if edoxaban was non-inferior to warfarin for the composite endpoint of stroke and SEE. If non-inferiority was established for the edoxaban 60 mg /30 mg DR group, the edoxaban 60 mg /30 mg DR group was compared with warfarin for superiority. • Secondary objectives were to determine if edoxaban was superior to warfarin with regard to: ○ the composite clinical outcome of stroke, SEE,	A multiplicity adjustment testing procedure (Figure 3) was followed to adjust for multiple comparisons/multiplicity in efficacy analyses. Once a test criterion is not satisfied, all subsequent tests below that level should be considered hypothesis generating. • The primary efficacy endpoint, time to the first occurrence of stroke/SEE, was first compared concurrently between each of the 2 edoxaban groups and warfarin group using the mITT Analysis Set in the on-treatment period for non-inferiority. In order to control the study-wise type-I error rate of two-sided α=0.05 for non-inferiority, each of these 2 comparisons were performed at the statistical significance level of two-sided α=0.025, respectively. • If the non-inferiority of the edoxaban 60 mg /30 mg DR group over warfarin group was statistically significant, the primary efficacy endpoint and secondary efficacy endpoints were compared between the edoxaban 60 mg /30 mg DR group and warfarin group using the ITT analysis set for the overall study period for superiority at a significance level of α=0.01. . • Other efficacy endpoints were analysed for exploratory purposes based on the ITT, mITT and PP Analysis sets with no multiplicity adjustment. • For the primary efficacy variable, the time to first event was analysed using the Cox proportional hazards model including treatment groups and the following 2 (randomisation)	• A total of at least 448 events were required for a 2 group comparison (warfarin versus 1 of the edoxaban dose groups) for the study to have >90% power to reject at least 1 of the 2 null hypotheses (1 for each edoxaban treatment group [60 mg and 30 mg groups]) of inferiority. Consequently, a total of at least 448 events were required for each of the following treatment group combinations for the mITT analysis set: ○ Events in warfarin group plus edoxaban 60 mg /30 mg DR group ○ Events in warfarin group plus edoxaban 30 mg/ 15 mg DR group • With anticipated median follow-up time of 2 years and the revised projected, blinded, aggregate annualised event rate of approximately 1.7% per	All of the non-inferiority and superiority analyses were performed on observed endpoints only. No missing endpoints were imputed. Data on subjects who did not reach the primary endpoint were censored.

Study no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	and cardiovascular (CV) mortality, as well as each component separately, ○ major adverse cardiovascular event (MACE), ○ the composite clinical outcome of stroke, SEE, and all-cause mortality, ○ Major bleeding as well as Major plus Clinically Relevant Non-Major (CRNM) bleeding.	stratification factors as covariates: ○ 1. The dichotomised $CHADS_2$ score ($CHADS_2$ 2-3 versus 4-6); ○ 2. The dichotomised dose-adjustment factor (e.g., full dose versus reduced dose in a given treatment group). • Secondary efficacy and key safety endpoints were analysed using these 2 (randomisation) stratification factors as covariates if Cox proportional hazards model was used.	subject year, a total of approximately 20,500 subjects (6,833 in each of the 3 treatment groups) was planned to be randomised. • The final sample size was event driven. The sample size or the duration of follow-up may have required adjustment based on the actual versus anticipated primary endpoint annualised event rate and drop-out rate.	

Abbreviations: CEC, Clinical Events Committee; CNS, Central Nervous System; CRNM, Clinically Relevant Non-Major; CV, Cardiovascular; DVT, Deep vein thrombosis; ISTH, , International Society on Thrombosis and Haemostasis; PE, Pulmonary embolism; SEE, Systemic embolic event; TIA, Transient ischaemic attacks; VTE, Venous thromboembolic event

Figure 3: Overall Multiplicity Adjustment Testing Procedure



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

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-planned subgroup analyses

Pre-planned subgroup analyses were performed for the subgroups of clinical interest on the primary efficacy outcome and key safety outcomes.

The subgroups were based on characteristics including but not limited to:

- Age (≥75 versus <75 years);
- Gender (male versus female);
- $CHADS_2$ scores (≤ 3 versus, ≥ 4);
- Dose adjustment factor (dose adjusted: yes/no) and also by:
    - body weight ≤60 kg versus >60 kg,
    - calculated CrCL 30 to 50 mL/min versus >50 mL/min,
    - Concomitant use of verapamil/quinidine at randomisation (yes/no);
- VKA-naïve versus VKA-experienced;
- Geographic region/country;
- Race (Caucasian, Black, Asian, other);
- Ethnicity (Hispanic/Latino versus Not) (US 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 agents (statins, others) (yes/no);
- Concomitant angiotensin converting enzyme (ACE) or angiotensin II receptor blockers (ARB) inhibitors (yes/no);
- Concomitant amiodarone or dronedarone (yes/no);
- Concomitant diuretics (yes/no);
- Center-level INR-TTR for warfarin subjects (e.g., <60% versus ≥60%, <median versus ≥median)

Where applicable, each subgroup was analysed using a Cox proportional hazard model including treatment, and the 2 stratification variables (i.e., dichotomised $CHADS_2$ score and dichotomised dose-adjustment factor) as covariates. The estimated HR and two-sided 95% CI were calculated to assess the treatment effect within each of the subgroups.

Pre-planned pooled analyses

No pooled analyses were planned.

Post-hoc analyses

After closer inspection of the ENGAGE AF-TIMI 48 pre-specification for the regional subgroups, it was noted that the Western Europe subgroup included the following countries: Belgium, Denmark, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, United Kingdom. As Turkey and Israel would not usually be included in a definition of Western Europe, and owing to the likelihood of differences in patient characteristics and standards of care in these countries, an alternative post-hoc regional analysis of the primary efficacy results was performed for the Western Europe subgroup.

Comparative data for the European Economic Area (EEA) and Switzerland (CH) “EEA+CH” subgroup vs. “non-EEA+CH” were calculated, to clarify whether there was truly a differential effect on efficacy across geographical regions.

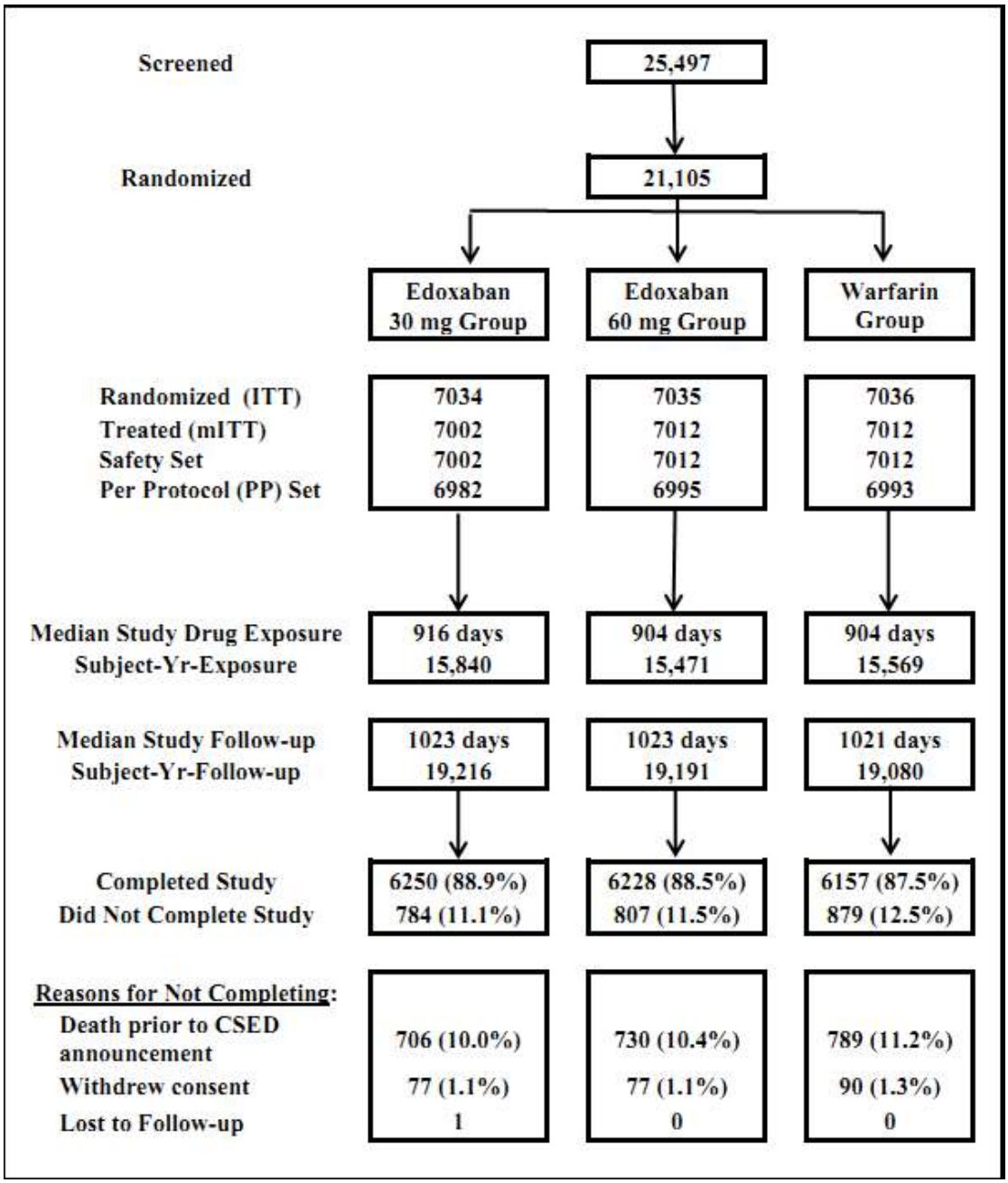
Participant flow

6.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

The CONSORT flow chart showing the numbers of patients who were eligible to enter ENGAGE AF-TIMI 48, and who were randomised and allocated to each treatment are presented in Figure 4.

A total of 25,497 subjects signed informed consent and were screened for eligibility for entry into the study. Of these screened subjects, 4,392 subjects were never randomised to receive study drug because protocol eligibility criteria for randomisation were not met (2523 subjects), the Investigator’s decision (619 subjects), the subject’s decision (1245 subjects), or because the reason was not available (5 subjects). A total of 21,105 subjects (83% of screened) were randomised and assigned to the edoxaban 30 mg/ 15 mg DR, edoxaban 60 mg /30 mg DR, or warfarin treatment groups (7034, 7035, and 7036, respectively)

Figure 4: Summary of study populations and analysis sets for ENGAGE AF – TIMI 48



Abbreviation: ITT: Intention to treat, mITT: modified intention to treat, PP: Per Protocol, CSED: common study end date.

6.4 Critical appraisal of relevant RCTs

6.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.**

- **Was the method used to generate random allocations adequate?**

- **Was the allocation adequately concealed?**
- **Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?**
- **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**
- **Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?**
- **Is there any evidence to suggest that the authors measured more outcomes than they reported?**
- **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

6.4.2 **Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.**

A complete quality assessment of ENGAGE AF-TIMI 48 is provided in Section 10.3.

6.4.3 **If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.**

Critical appraisal of ENGAGE AF-TIMI 48 is presented in Table 12. A complete quality assessment of ENGAGE AF-TIMI 48 is provided in Section **Error! Reference source not found.**

Table 12: Quality assessment results for ENGAGE AF-TIMI 48

Study no. (acronym)	ENGAGE AF-TIMI 48
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

6.5 Results of the relevant RCTs

6.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.**

6.5.2 **The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.**

6.5.3 **For each outcome for each included RCT, the following information should be provided.**

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**
- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**
- **Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.**

6.5.4 **ENGAGE AF-TIMI 48**

The reporting of ENGAGE AF-TIMI 48 results will focus on the high-dose edoxaban arm (i.e. those randomised to 60mg, including those dose-reduced to 30mg [60 mg / 30 mg DR], since this arm represents the licensed dose.

Treatment overview

Study drugs

The exposure to study drug and overall study period follow-up for treated subjects (Safety analysis set) is presented in Table 13. The number of days exposed to study drug includes the total number of days the subject took study drug and does not include days when study drug was interrupted. A subject may have had multiple periods of drug use if they temporarily interrupted and resumed study drug during the study. The overall study period

for treated subjects includes all study days (including study drug interruption days) from the initial dose of study drug until CSED Visit (or last contact date if no CSED Visit).

Both subject-year exposure on study drug and subject-year follow-up during the study were comparable among the treatment groups (median follow up was 904 days [2.8 years]; the longest of all of the pivotal studies of NOACs in this indication). Overall, subjects received study drug more than 80% of the time during the study period in all 3 treatment groups (Table 13).

Table 13: Study Drug Exposure and Duration of Study Period, safety analysis set, on-treatment period

	Edoxaban 60 mg / 30 mg DR (N=7012)	Warfarin (N=7012)
Study Drug Exposure		
Mean (SD) (days)	805.9 (390.82)	811.0 (383.14)
Median (days)	904.0	904.0
Subject-Year Exposure	15,470.96	15,569.23
Overall Study Period		
Mean (SD) (days)	999.6 (249.94)	993.9 (254.15)
Median (days)	1023.0	1021.0
Subject-Year Follow-Up	19,190.99	19,080.37
Percentage of Exposed Days		
Mean (SD)	80.3 (32.51)	81.4 (31.27)

Discontinuations

The percentage of patients who discontinued study drug was comparable between the edoxaban 60 mg / 30 mg DR, and the warfarin treatment groups (34.4%, and 34.5%, respectively). Discontinuations due to AEs were reported in 17.2%, and 16.7% of patients in both groups, respectively (Table 14).

Table 14: Discontinuation of study drug during ENGAGE AF-TIMI 48, safety analysis set, on-treatment period

Outcome	Edoxaban 60 mg / 30 mg DR (N=7012)	Warfarin (N=7012)
Permanently discontinued study drug at any time, n (%)	2415 (34.4)	2417 (34.5)
Reason for discontinuation, n (%)		
AE or suspected endpoint event	1204 (17.2)	1168 (16.7)
Death	194 (2.8)	214 (3.1)
Investigator decision	317 (4.5)	318 (4.5)
Patient decision	522 (7.4)	551 (7.9)
Patient refused routine follow-up	169 (2.4)	161 (2.3)

Abbreviations: AE, adverse event.

Measurements of treatment compliance

Edoxaban (or matching edoxaban placebo for the warfarin group) compliance was assessed by percentage of doses taken (≥80% versus <80%) at each compliance visit (every 3 months). In the edoxaban group, at least 98% of subjects were more than 80% compliant at all compliance visits.

Warfarin compliance was assessed by the percentage of time subjects' INR was within the range of 2.0 – 3.0. The percentage of time within the therapeutic range, as well as the percentage of time outside of therapeutic range for the mITT analysis set on-treatment period is summarised in Table 15. The median time in therapeutic range (2-3) was 68.4% (mean 64.9%).

Table 15: Time in Various INR Ranges for Subjects Randomised to Warfarin, safety analysis set, on-treatment period[3]

	Percent Time in INR Range								
	<1.5	**1.5-2.0**	**<2**	**2-3**	**>3**	**≥4**	**>5**	**≥8**	**1.8-3.2**
Overall (N=6897)									
Mean (SD)	6.10 (13.8)	22.70 (13.3)	22.80 (18.9)	64.90 (18.7)	12.40 (10.3)	1.80 (4.5)	0.30 (2.3)	0.00 (0.8)	78.40 (18.1)
Median	1.9	21	17.7	68.4	10.8	0.4	0	0	83.1

Abbreviations: INR = International Normalised Ratio, SD = Standard Deviation, TTR = Time in Therapeutic Range.

Datasets analysed

Dataset definitions have previously been described in Table 10. The number of patients in the datasets presented in this submission for ENGAGE AF-TIMI 48 is detailed in Table 16.

Table 16: Overview of analysis sets in ENGAGE AF-TIMI 48

Analysis set, n (%)	**Edoxaban 60 mg / 30 mg DR**	**Warfarin**
ITT (Randomised)	7035 (100.0)	7036 (100.0)
Never Received Study Drug	23 (0.3)	24 (0.3)
mITT (Received at least one dose of study drug)	7012 (99.7)	7012 (99.7)
Dosed But Excluded From Per Protocol	17 (0.2)	19 (0.3)
Per Protocol	6995 (99.4)	6993 (99.4)
Safety	7012 (99.7)	7012 (99.7)

Abbreviations: ITT=Intent to Treat (randomised subjects), mITT=Modified Intent to Treat (treated subjects).

[3] Percent Time in INR range is defined by the percentage of days the subjects have been within the specified range. Percent Time in Therapeutic Range (TTR) is calculated as the mean percentage in the range 2-3.
Note: N = Number of subjects with at least 1 INR recorded beyond Day 7.
Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.
Note: Analyses of INR use a linear interpolation method to impute INR for study days that do not have an actual INR value.
Note: All categories above are not mutually exclusive.

Primary efficacy results

Time to the first adjudicated stroke (ischaemic or haemorrhagic) or SEE

Results for the comparisons between edoxaban and warfarin for the time to the first occurrence of stroke or SEE are presented in **Table 17** and **Figure 5**.

Data for the comparison on a number of analysis sets and observation periods are available:

- The primary efficacy analysis for non-inferiority was done on the mITT analysis set (on treatment period). The mITT analysis set overall study period is also shown, as this data set was a key input into the network meta-analysis (as described in section 6.7).
- The ITT analysis set (overall study period) was used for the superiority tests in the primary efficacy analysis.

Edoxaban (60 mg / 30 mg DR) was non-inferior to well-controlled warfarin (median TTR = 68.4%) in the prevention of stroke or SEE in patients with NVAF for the mITT analysis set (on-treatment and overall study period).

Adjudicated stroke or SEE occurred in 182 subjects in the edoxaban 60 mg / 30 mg DR group (1.18% per year), and 232 subjects in the warfarin group (1.50% per year). Compared to patients in the warfarin group, the HR for the primary endpoint in the edoxaban 60 mg / 30 mg DR group was 0.79 (97.5% CI: 0.63-0.99; p<0.001 for non-inferiority).

In the prespecified superiority analysis that was performed in the ITT analysis set (overall study period), the annualised rate of the primary endpoint was 1.80% in the warfarin group, as compared with 1.57% in the edoxaban 60 mg /30 mg DR group (HR vs. warfarin, 0.87; 97.5% CI, 0.73-1.04; P = 0.08 for superiority).

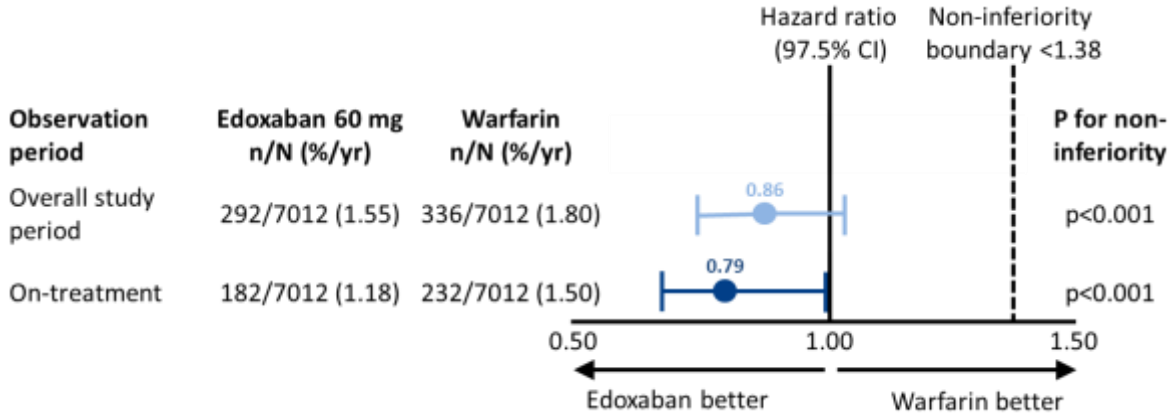
In the mITT overall study period, adjudicated stroke or SEE occurred in 292 subjects in the edoxaban 60 mg /30 mg DR group (1.55% per year), and 336 subjects in the warfarin group (1.80% per year). Compared to warfarin-treated subjects, the HR in the edoxaban 60 mg /30 mg DR group was 0.86 (97.5% CI: 0.72-1.03; p<0.001 for non-inferiority).

Table 17: Primary efficacy results from ENGAGE AF-TIMI 48: Adjudicated Primary Endpoint (Stroke or SEE)

Stroke or SEE	Warfarin, n (%/y)	Edoxaban 60 mg / 30 mg DR, n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [97.5% CI]; p-value
Stroke or SEE (mITT on-treatment period)	232 (1.50)	182 (1.18)	0.79 [0.63-0.99]; p<0.001 for non-inferiority; p=0.02 for superiority[4]
Stroke or SEE (ITT overall study period)	337 (1.80)	296 (1.57)	0.87 [0.73-1.04]; p=0.08 for superiority
Stroke or SEE (mITT overall study period)	336 (1.80)	292 (1.55)	0.86 [0.72-1.03]; p<0.001 for non-inferiority

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

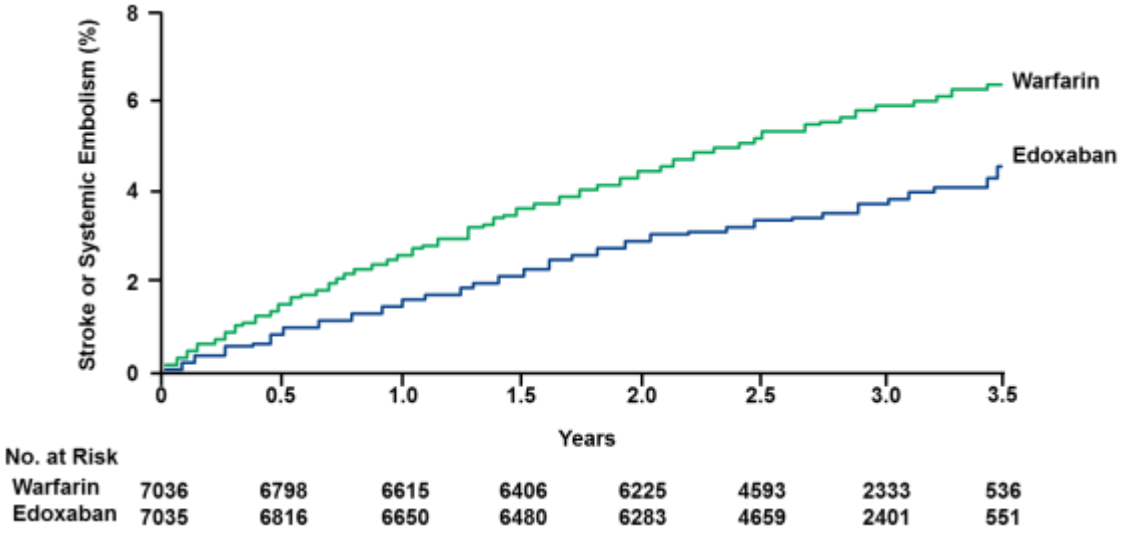
Figure 5: Forest plot of primary efficacy endpoint (Stroke or SEE) in ENGAGE AF-TIMI 48 (mITT Analysis Set - On-Treatment and Overall Study Period)



[4] Not the prespecified test for superiority, as outlined in the statistical plan; see Figure 3 in Section 6.3.6

Figure **6** shows presents the Kaplan-Meier plot for primary events in the ITT analysis set for the edoxaban 60 mg / 30 mg DR arm compared with the warfarin arm, from shortly after randomisation to the end of the follow-up period. There were no significant differences between edoxaban and warfarin for stroke or SEE. Numerically fewer subjects in the edoxaban 60 mg /30 mg DR group experienced stroke or SEE than the warfarin group (1.57% and 1.80% per year, respectively), with a HR of 0.87 (97.5% CI: 0.73, 1.04).

Figure 6: Kaplan-Meier curve of primary efficacy endpoint (Stroke or SEE) for edoxaban 60mg / 30mg DR vs warfarin in ENGAGE AF-TIMI 48 (ITT analysis set, overall study period)



Components of the primary endpoint (stroke or SEE) and subcomponents of stroke

The event rate and hazard ratio for the components of the primary endpoint (stroke and SEE), as well as subcomponents of stroke (ischaemic, haemorrhagic, fatal and disabling) are summarised for the mITT analysis set on-treatment period in Table 18, for the ITT analysis set overall study period in Table 19 and for the mITT analysis set overall study period in Table 20.

For the mITT on-treatment period, the HR for any stroke and ischaemic stroke was respectively 0.80 (95% CI: 0.66-0.98) and 0.94 (95% CI: 0.746-1.193) for the edoxaban 60 mg /30 mg DR group compared with the warfarin group.

Table 18: Stroke and systemic embolism results from ENGAGE AF-TIMI 48 (mITT analysis set, on-treatment period).

Efficacy Outcome	Warfarin (N=7036), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7035), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value
Any stroke	219 (1.41)	174 (1.13)	0.80 [0.66-0.98]; p=0.03
Haemorrhagic stroke	76 (0.49)	40 (0.26)	0.53 [0.36-0.78]; p=0.00
Ischaemic stroke	144 (0.93)	135 (0.87)	0.94 [0.75-1.19]; p=0.63
Disabling stroke	41 (0.26)	35 (0.23)	0.86 [0.55-1.35]; p=0.51
Fatal stroke	43 (0.28)	45 (0.29)	1.05 [0.70-1.60]; p=0.80
SEE	13 (0.08)	8 (0.05)	0.62 [0.26-1.50]; p=0.29
First TIA	69 (0.44)	82 (0.53)	1.20 [0.87-1.65]; p=0.26

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

In the ITT analysis set (overall study period), an analysis of haemorrhagic stroke events found that the edoxaban 60 mg / 30 mg DR arm had nearly half the rate of the warfarin arm (0.26% vs. 0.47%; p<0.001). Edoxaban 60 mg / 30 mg DR arm had a similar rate of stroke, ischaemic stroke, disabling and also fatal stroke compared with the warfarin arm.

Table 19: Stroke and systemic embolism results from ENGAGE AF-TIMI 48 (ITT analysis set, overall study period).

Efficacy Outcome	**Warfarin (N=7036), n (%/y)**	**Edoxaban 60 mg / 30 mg DR (N=7035), n (%/y)**	**Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value**
Any stroke	317 (1.69)	281 (1.49)	0.88 [0.75-1.03]; p=0.11
Haemorrhagic stroke	90 (0.47)	49 (0.26)	0.54 [0.38-0.77]; p<0.001
Ischaemic stroke	235 (1.25)	236 (1.25)	1.00 [0.83-1.19]; p=0.97
Disabling stroke	57 (0.30)	54 (0.28)	0.94 [0.65-1.36]; p=0.74
Fatal stroke	86 (0.45)	80 (0.42)	0.92 [0.68-1.25]; p=0.61
SEE	23 (0.12)	15 (0.08)	0.65 [0.34-1.24]; p=0.19
First TIA	95 (0.50)	106 (0.56)	1.11 [0.84-1.47]; p=0.45

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

Results for the mITT overall study period were consistent with those in the ITT overall study period.

Table 20: Stroke and systemic embolism results from ENGAGE AF-TIMI 48 (mITT analysis set, overall study period).

Efficacy Outcome	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value
Any stroke	316 (1.69)	278 (1.48)	0.87 [0.74-1.02]; p=0.09
Haemorrhagic stroke	90 (0.48)	49 (0.26)	0.54 [0.38-0.77]; p=0.00
Ischaemic stroke	234 (1.25)	233 (1.24)	0.99 [0.82-1.18]; p=0.90
Disabling stroke	57 (0.30)	53 (0.28)	0.92 [0.64-1.34]; p=0.67
Fatal stroke	86 (0.45)	79 (0.41)	0.91 [0.67-1.24]; p=0.56
SEE	23 (0.12)	14 (0.07)	0.60 [0.31-1.17]; p=0.14
First TIA	95 (0.50)	106 (0.56)	1.11 [0.84-1.47]; p=0.45

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

Secondary efficacy analysis

The analysis of the 3 composite secondary efficacy endpoints of stroke, SEE, and CV mortality; MACE; and stroke, SEE, and all-cause mortality are summarised in Table 21 for the mITT analysis set on-treatment period,

Table **22** for the ITT analysis set overall study period and in Table 23 for the mITT analysis set overall study period.

In the mITT analysis set on-treatment period, a lower proportion of patients in the edoxaban 60 mg / 30 mg DR arm than the warfarin arm experienced the composite secondary efficacy endpoints of stroke, SEE and cardiovascular-related mortality (2.39%, and 2.84% per year, respectively), MACE (2.92% and 3.43% per year, respectively), or stroke, SEE and all-cause mortality (2.56% and 2.98% per year, respectively). There was a significantly lower rate in the edoxaban 60 mg / 30 mg DR arm versus the warfarin arm for all three outcomes ($p \leq 0.02$ for all comparisons) (Table 21).

Edoxaban was associated with a lower rate of cardiovascular-related mortality (HR: 0.89; [95% CI: 0.74–1.10]; $p \geq 0.1$) and all-cause mortality (HR: 0.91 [95% CI: 0.77–1.10]; $p \geq 0.1$) (Table 21). There was also no significant difference in the rate of myocardial infarction between the edoxaban 60 mg / 30 mg DR arm compared with warfarin (HR:0.84 [95% CI: 0.64–1.12]; $p \geq 0.1$), which indicated there was no signal for myocardial infarction with edoxaban treatment (Table 21).

Table 21: Secondary efficacy results from ENGAGE AF-TIMI 48 (mITT analysis set, on-treatment analysis).

Efficacy Outcome	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value
Stroke, SEE or death from CV cause	441 (2.84)	369 (2.39)	0.84 [0.73, 0.97]; p=0.01
MACE	530 (3.43)	449 (2.92)	0.85 [0.75, 0.97]; p=0.01
Stroke, SEE or death	463 (2.98)	395 (2.56)	0.86 [0.75, 0.98]; p=0.02
All-cause death	258 (1.65)	234 (1.51)	0.91 [0.77, 1.10]; p=0.32
Death from CV cause	236 (1.51)	208 (1.34)	0.89 [0.74, 1.10]; p=0.21
Myocardial infarction	105 (0.68)	88 (0.57)	0.84 [0.64, 1.12]; p=0.24

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event; SEE systemic embolic event

Similar trends were observed for the ITT analysis set overall study period (Table 22). The rates of all three pre-specified secondary composite outcomes were significantly lower with edoxaban 60 mg / 30 mg DR than with warfarin. Treatment with edoxaban was associated with lower annualised rates of death from cardiovascular causes than was warfarin: 3.17% with warfarin, as compared with 2.74% with edoxaban 60 mg / 30 mg DR (HR: 0.86; 95% CI, 0.77 - 0.97; p = 0.013)

Table 22: Secondary efficacy results from ENGAGE AF-TIMI 48 (ITT analysis set, overall study period).

Efficacy Outcome	Warfarin (N=7036), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7035), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value
Stroke, SEE or death from CV cause	831 (4.43)	728 (3.85)	0.87 [0.78–0.96]; p=0.005
MACE	926 (4.98)	827 (4.41)	0.88 [0.81–0.97]; p=0.01
Stroke, SEE or death	1046 (5.57)	949 (5.01)	0.90 [0.82–0.98]; p=0.02
All-cause death	839 (4.35)	773 (3.99)	0.92 [0.83–1.01]; p=0.08
Death from CV cause	611 (3.17)	530 (2.74)	0.86 [0.77–0.97]; p=0.013
Myocardial infarction	141 (0.75)	133 (0.70)	0.94 [0.74–1.19]; p=0.60

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event; SEE systemic embolic event

Similar trends were observed for the mITT analysis set overall study period (Table 23).

Table 23: Secondary efficacy results from ENGAGE AF-TIMI 48 (mITT analysis set, overall study period).

Efficacy Outcome	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value
Stroke, SEE or death from CV cause	828 (4.43)	723 (3.83)	0.86 [0.78–0.95]; p=0.004
MACE	923 (4.98)	821 (4.39)	0.88 [0.80–0.97]; p=0.01
Stroke, SEE or death	1043 (5.58)	943 (4.99)	0.89 [0.82–0.98]; p=0.01
All-cause death	836 (4.35)	769 (3.99)	0.91 [0.83–1.01]; p=0.07
Death from CV cause	608 (3.16)	527 (2.73)	0.86 [0.77–0.97]; p=0.013
Myocardial infarction	141 (0.75)	132 (0.70)	0.93 [0.74–1.18]; p=0.56

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event; SEE systemic embolic event

Quality of life results

Health-related quality of life data were collected from patients in the ENGAGE AF-TIMI 48 trial as part of a health economic substudy that ran alongside the trial. Data were collected using the self-administered EQ-5D questionnaire at baseline and every 3 months, until the end of the study. Approximately 60% of patients participated in quality of life data collection, though a sizable proportion of those did not enrol in this substudy until some time after baseline. In total, baseline utilities were calculated for 11,995 patients who participated in ENGAGE AF-TIMI 48. The country with the largest number of patients for whom baseline EQ5D data were available was the US, with 2,853 (approximately 24% of all respondents). Baseline EQ5D data were collected from a total of 164 patients from the UK. The baseline utility was calculated as 0.836 using this methodology.

Subgroup analyses

Subgroup analyses for the primary efficacy outcome are presented in Figure 7. These prespecified analyses were done on the mITT analysis set, overall study period.

These analyses demonstrate consistency across major subgroups; for most subgroups, the event rate of primary endpoint (composite stroke/SEE) was numerically lower in the edoxaban 60 mg / 30 mg DR group compared to the warfarin group, i.e., the hazard ratio was 1.0 or less.

The HR for the comparison of edoxaban 60 mg / 30mg DR vs warfarin was greater than 1.0 for several subgroups (subjects with CrCL ≥ 80 mL/min, subjects using verapamil or quinidine at randomisation, subjects with prior TIA, subject without prior hypertension, subjects with paroxysmal AF, subjects in the group defined as Western Europe, subjects in Japan and subjects in study centres with a TTR above 73.9%.). However, the associated CIs for those respective HRs crossed the line of unity and no significant interactions were found, except for the subgroups based on baseline CrCl levels. This result is discussed further in section 6.10.

Figure 7: Subgroup analysis of primary efficacy outcome (Stroke or SEE) of ENGAGE AF-TIMI 48 –edoxaban 60 mg / 30 mg DR vs. warfarin (mITT analysis set, overall study period)

Subgroup	High-dose Edoxaban (60/30 mg) n/M (%/yr)		Warfarin n/M (%/yr)		P-value for interaction
Age (years)					
<75	152/4174	(1.33)	169/4207	(1.48)	0.6127
≥75	140/2838	(1.89)	167/2805	(2.31)	
Gender					
Male	168/4353	(1.43)	195/4383	(1.68)	0.9510
Female	124/2659	(1.75)	141/2629	(2.01)	
Race					
Caucasian	231/5679	(1.51)	255/5679	(1.68)	
Black	6/96	(2.40)	3/88	(1.37)	-
Asian	47/956	(1.83)	63/963	(2.51)	
Other	8/265	(1.16)	14/265	(2.09)	
Dose adjusted at randomisation					
Yes	104/1776	(2.28)	119/1780	(2.67)	0.9700
No	188/5236	(1.32)	217/5232	(1.53)	
CrCl (mL/min)					
<30	4/70	(2.41)	3/51	(2.61)	
30-≤50	76/1302	(2.29)	87/1305	(2.68)	0.0042
>50-<80	121/3007	(1.49)	176/3048	(2.18)	
≥80	91/2633	(1.26)	70/2608	(0.97)	
Verapamil/quinidine use at randomisation					
Yes	15/241	(2.30)	9/222	(1.51)	0.1500
No	277/6771	(1.52)	327/6790	(1.81)	
Weight (kg)					
≤40	1/11	(4.09)	2/16	(5.64)	
>40	291/7001	(1.55)	334/6996	(1.80)	0.9438
≤60	44/681	(2.55)	50/698	(2.92)	
>60	248/6331	(1.45)	286/6314	(1.69)	
VKA use at randomisation					
Naive	112/2879	(1.47)	158/2888	(2.12)	0.0253
Experienced	180/4133	(1.60)	178/4124	(1.59)	
$CHADS_2$ score					
≤3	193/5406	(1.31)	216/5427	(1.47)	
>3	99/1606	(2.44)	120/1585	(3.02)	0.5769
=2	105/3223	(1.17)	110/3321	(1.20)	
≥3	187/3784	(1.90)	226/3686	(2.39)	
Prior stroke/TIA					
Yes	124/1968	(2.43)	145/1983	(2.86)	0.8801
No	168/5044	(1.23)	191/5029	(1.41)	
Prior stroke					
Yes	85/1291	(2.55)	112/1321	(3.37)	0.2999
No	207/5721	(1.34)	224/5691	(1.46)	
Prior TIA					
Yes	52/836	(2.39)	46/793	(2.21)	0.2386
No	240/6176	(1.44)	290/6219	(1.75)	
Prior CHF					
Yes	170/4086	(1.57)	193/4038	(1.82)	0.9851
No	122/2926	(1.52)	143/2974	(1.78)	
Prior hypertension					
Yes	263/6568	(1.49)	315/6566	(1.80)	0.0892
No	29/444	(2.49)	21/446	(1.80)	
Prior diabetes					
Yes	95/2550	(1.39)	102/2516	(1.52)	0.5992
No	197/4462	(1.64)	234/4496	(1.96)	
Type of AF					
Paroxysmal	73/1747	(1.55)	59/1774	(1.23)	
Persistent	69/1645	(1.57)	85/1624	(2.00)	0.0416
Permanent	150/3620	(1.55)	192/3612	(2.01)	
Region					
North America	54/1559	(1.24)	66/1556	(1.54)	
USA	46/1288	(1.27)	54/1297	(1.50)	
Latin America	34/884	(1.56)	53/885	(2.50)	
Western Europe	52/1075	(1.85)	43/1070	(1.54)	0.1853
Eastern Europe	97/2374	(1.50)	104/2378	(1.60)	
Asia/Pac and SA	36/784	(1.74)	53/786	(2.64)	
Japan	19/336	(2.04)	17/337	(1.81)	
Centres with TTR					
>66.4%	125	(1.40)	142	(1.54)	0.5159
≤66.4%	159	(1.70)	195	(2.07)	
≥60%	208	(1.55)	227	(1.62)	0.0361
<60%	76	(1.57)	110	(2.36)	
TTR quartile					
First (≤57.7%)	65	(1.74)	84	(2.32)	
Second (>57.7% to ≤66.4%)	94	(1.67)	111	(1.91)	0.5028
Third (>66.4% to ≤73.9%)	70	(1.36)	92	(1.68)	
Fourth (>73.9%)	55	(1.47)	50	(1.34)	

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CrCl, creatinine clearance; SEE, systemic embolic event; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist.

Efficacy results for subgroups specified in the NICE scope are discussed more in detail below:

Subgroup analyses by centre level TTR

The primary efficacy results were analysed by study centre level TTR values to assess if the level of INR control achieved in a particular centre influenced the primary efficacy results. For the analysis comparing centre TTR above and below 60%, the p value for interaction was significant. This indicates that in centres with a TTR ≥60%, edoxaban has a similar effect versus warfarin to that observed in the total study population, while there is a significant reduction in risk in the cTTR <60% subgroup.

When the TTR data were examined by quartiles in the edoxaban 60 mg / 30 mg DR arm compared with warfarin, the hazard ratios for the primary endpoint in the first, second and third quartiles were 0.74, 0.88 and 0.82, respectively, and 1.08 for the fourth quartile, but the p-value for interaction was not significant (p=0.50).

Table 24: Primary efficacy (Stroke or SEE) results by centre level TTR (mITT analysis set, overall study period)

Stroke or SEE	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. warfarin, HR [95% CI]	P-value for interaction
Centres with TTR >66.4%	142 (1.54)	125 (1.40)	0.91 (0.719–1.163)	0.5159
Centres with TTR ≤66.4%	195 (2.07)	159 (1.70)	0.82 (0.667–1.015)	
Centres with TTR ≥60%	227 (1.62)	208 (1.55)	0.96 (0.795–1.159)	0.0361
Centres with TTR <60%	110 (2.36)	76 (1.57)	0.66 (0.495–0.888)	
First TTR quartile (≤57.7%),	84 (2.32)	65 (1.74)	0.74 (0.537–1.028)	0.5028
Second TTR quartile (>57.7% to ≤66.4%)	111 (1.91)	94 (1.67)	0.88 (0.670–1.161)	
Third TTR quartile (>66.4% to ≤73.9%),	92 (1.68)	70 (1.36)	0.82 (0.600–1.118)	
Fourth TTR quartile (>73.9%)	50 (1.34)	55 (1.47)	1.08 (0.737–1.585)	

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

The hazard ratio for edoxaban 60 mg / 30 mg DR vs. warfarin was stable and non-inferior across $CHADS_2$ scores 2 to 6. (Table 25)

Table 25: Primary efficacy (Stroke or SEE) results by $CHADS_2$ score (mITT analysis set, overall study period)

$CHADS_2$ Score	**Warfarin (N=7012), n (%/y)**	**Edoxaban** 60 mg / 30 mg DR (N=7012), n (%/y)	**Edoxaban 60 mg / 30 mg DR vs. warfarin, HR [95% CI]**
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]
6	[redacted]	[redacted]	[redacted]

Post-hoc analysis for Western Europe region

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

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

Subgroup analyses by creatinine clearance

As one of numerous efficacy and safety subgroup analyses, an analysis by renal function across 3 categories of creatinine clearance (CrCL: normal renal function [≥ 80 mL/min]; mild renal impairment [> 50 to < 80 mL/min] and moderate renal impairment [30 to 50 mL/min) demonstrated a significant interaction for heterogeneity for the edoxaban 60 mg /30 mg DR regimen (P < 0.001). The HRs for the primary efficacy endpoint were 0.86 (95% CI 0.63 to 1.17) and 0.68 (95% CI 0.54 to 0.85) for high-dose edoxaban (60 mg / 30 mg DR) vs. warfarin for subgroups with CrCl of 30 to ≤50 mL/min and >50 to <80 mL/min, respectively. In contrast, the relative risk of stroke or SEE was observed to be higher with edoxaban than with warfarin in the subgroup of subjects with normal renal function (CrCL ≥ 80 mL/min; HR 1.31 (95% CI 0.96 to 1.79)).

Comparison of the annualised event rates for stroke or SEE in the subgroups with normal renal function and mild renal impairment demonstrated that the event rates in the edoxaban 60 mg /30 mg DR group were very similar (1.06%/year and 1.07%/year, respectively). In contrast, the event rates in the warfarin groups were

different (0.76%/year and 2.0%/year, respectively). This represents a 62% difference in the event rate between the mild renal impairment and the normal renal function subgroups treated with warfarin. This magnitude of difference has not been seen in other contemporary NOAC studies, whereas the edoxaban event rates were broadly consistent with those observed in other NOAC studies given the order of background stroke/SEE risk defined by $CHADS_2$. Moreover, the similar event rates in the two 60 mg /30 mg DR edoxaban groups (mild renal impairment vs normal renal function) was unexpected considering that these two groups differed with respect to their median $CHADS_2$ score at baseline (2.6 in the normal renal function subgroup and 2.9 in the mild renal impairment subgroup).

Finally, one cannot exclude random variability as an explanation for the observed differences between these subgroups. Due to the lack of stratification by renal function as analyzed using 3 categories of CrCL, there may have been some unidentifiable sources of bias across treatment groups within the renal subgroups in terms of baseline characteristics, demographics, concomitant medication, and geographic recruitment that could have contributed to differences in event rates for stroke or SEE. When data were analyzed by the CrCL categories used for dose modification as well as for stratification (≤ or > 50 mL/min), no significant interaction was observed.

In summary, a variety of factors, an unusually low event rate in the warfarin group and potential imbalances between treatment groups due to randomization not being performed within subgroups, could have contributed to the observed HR for stroke or SEE compared with warfarin in the subgroup of subjects with normal renal function. Because of that the HR should be interpreted in the context of (1) a low absolute event rate for stroke or SEE, and (2) the small absolute differences between treatment groups.

6.6 Meta-analysis

6.6.1 **The following steps should be used as a minimum when presenting a meta-analysis.**

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

No meta-analysis of the data obtained through the edoxaban clinical study programme has been conducted. However a network meta-analysis comparing all NOACs and warfarin was conducted and the results are presented in section 6.7.

6.6.2 **If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.**

N/A

6.6.3 **If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.**

N/A

6.7 Indirect and mixed treatment comparisons

6.7.1 **Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.**

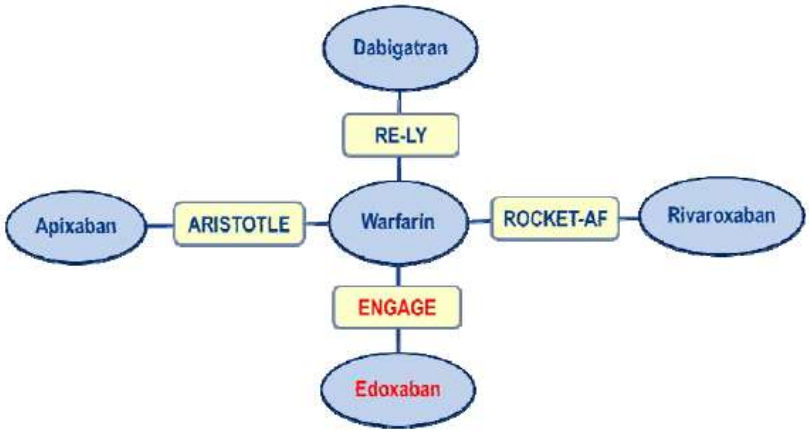
The methods used to identify studies for use in the network meta-analysis (NMA) are shown in section 6.1.

6.7.2 **Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5,**

appendix 5, a complete quality assessment for each comparator RCT identified.

Eligibility criteria and a flow diagram of included and excluded studies can be found in section 6.2. Of the 54 studies identified at i3 in the flow diagram in section 6.2.2, four large clinical trials that compared a non-VKA oral anticoagulant versus warfarin were included in the NMA. (Figure 8) These trials were chosen because they were the only phase 3 trials comparing a non-VKA oral anticoagulant with warfarin. A complete quality assessment for the 4 included trials is provided in Section**Error! Reference source not found.**.

Figure 8: Base case network diagram



6.7.3 **Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.**

A summary of the trials used to inform the NMA is provided in Table 26.

Table 26: Summary of the trials used to conduct the NMA

Study (primary ref)	Intervention	Trial design	Patient population	No randomised patients	Trial length (years)*
Edoxaban study					
ENGAGE AF-TIMI 48 ([68])	• Edoxaban 60 mg /30 mg DR • Edoxaban 30 mg/ 15 mg DR • Warfarin	Randomised double-blind, double-dummy	Adult patients ≥ 20 years old with NVAF and a $CHADS_2$ score of 2 or more	21,105	2.8
Comparator studies					
RE-LY[69]	• Dabigatran 150 mg • Dabigatran 110 mg • Warfarin	Randomised blinded dabigatran arms; open-label warfarin arm	Adult patients ≥ 18 years old with AF and a $CHADS_2$ score of 1 or more	18,113	2
ARISTOTLE [70]	• Apixaban 5 mg • Warfarin	Randomised double-blind, double-dummy	Patients with AF and a $CHADS_2$ score of 1 or more	18,201	1.8
ROCKET AF [71]	• Rivaroxaban 20 mg • Warfarin	Randomised double-blind, double-dummy	Adult patients ≥ 18 years old with NVAF and a $CHADS_2$ score of 2 or more	14,262	1.9

*: Median follow-up

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

Overall, 23 endpoints of interest (11 for efficacy and 12 for safety) were considered for meta-analysis, depending on data availability as shown in Table 27. Consistent with study endpoints in the pivotal trials, the composite endpoint of stroke and systemic embolism (SE) was defined as the primary efficacy endpoint and major bleeding as the primary safety endpoint in the network-meta-analyses, with all other endpoints considered secondary. Note that no hierarchical testing was performed for the meta-analyses.

Table 27: Overview of efficacy and safety outcomes by study

Study	ENGAGE AF-TIMI 48	ARISTOTLE	ROCKET – AF	RE-LY
Efficacy outcomes				
Composite of stroke and systemic embolism (SE)	✓	✓	✓	✓
SE	✓	✓	✓	✓
All-cause stroke	✓	✓	✓	✓
Ischaemic stroke	✓	✓	✓	✓
Haemorrhagic stroke	✓	✓	✓	✓
Disabling stroke	✓	✓	✓	
Fatal stroke	✓	✓	✓	
All-cause mortality	✓	✓	✓	✓
CV mortality	✓	✓	✓	✓
MI	✓	✓	✓	✓
Transient ischaemic attack (TIA)	✓			✓
Safety outcomes				
Composite of major bleeding and clinically relevant non-major bleeding	✓	✓	✓	
Any bleeding	✓	✓		✓
Major bleeding	✓	✓	✓	✓
Other major bleeding	✓	✓		
Major gastrointestinal bleeding	✓	✓	✓	✓

Study	ENGAGE AF-TIMI 48	ARISTOTLE	ROCKET – AF	RE-LY
Minor/minimal bleeding	✓		✓	✓
Clinically relevant non-major bleeding	✓		✓	
Fatal bleeding	✓		✓	
Intracranial bleeding	✓	✓	✓	✓
Life-threatening bleeding	✓			✓
Discontinuation	✓	✓	✓	✓
Dyspepsia	✓			✓

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

A network meta-analysis (NMA) was conducted to estimate the relative efficacy and safety of edoxaban compared with all treatments of interest. An advantage of this technique is that it allows for indirect comparisons to be made between pairs of treatments that have not been compared directly in clinical trials. Indeed, no RCTs comparing NOACs have been conducted.

The NMA included all treatments specified in the NICE scope; warfarin, edoxaban (60 mg once daily (OD), apixaban 5 mg twice daily (BD), dabigatran (150 mg BD, 110 mg BD) and rivaroxaban 20 mg OD.

ROCKET-AF and ENGAGE AF-TIMI 48 enrolled patients with $CHADS_2 \geq 2$, whereas RE-LY and ARISTOTLE enrolled patients with $CHADS_2 \geq 1$; thus, only data from patients with $CHADS_2 \geq 2$ in RE-LY and ARISTOTLE were used in the network meta-analyses to minimize potential biases resulting from differences in patient clinical characteristics among the trials.

[redacted]

Overview of statistical methods

A strength of the network meta-analysis approach is that the estimation of the relative effect between two treatments uses all the information available from the network of evidence, including direct comparisons (where available) and indirect comparisons.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Input data

In order to minimise potential biases resulting from differences in durations of study follow-up, annualised event rates were estimated.

[redacted]

[redacted]

[redacted]

Outputs

[redacted]

Assessment of model convergence

[redacted]

Assessment of inconsistency

[redacted]

Implementation of statistical analyses

Analyses were performed using SAS. SAS code used for the NMA analyses of the included outcomes are shown in Section **Error! Reference source not found.**.

6.7.6 Please present the results of the analysis.

6.7.6.1 Base case, Patients with baseline $CHADS_2 \geq 2$

Primary Efficacy Endpoint (Composite of Stroke and Systemic Embolism)

[redacted]

Table 28: NMA Risk Ratios on Composite of Stroke and Systemic Embolism, Baseline $CHADS_2$ ≥2

	Warfarin	Apixaban	Dabigatran 110 mg	Dabigatran 150 mg	Edoxaban 60mg/30mg DR	Rivaroxaban
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran 110 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban 60mg/30mg DR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 9: NMA Risk Ratios on Composite of Stroke and Systemic Embolism, Baseline $CHADS_2$ ≥2

[redacted]

Other efficacy outcomes

Subgroup data from patients with $CHADS_2$ ≥ 2 were not available for apixaban and dabigatran for many secondary endpoints. Table 29 summarises results for available data.

Among patients with $CHADS_2$ ≥ 2:

[redacted]

Table 29: NMA Risk Ratios on other efficacy outcomes, Baseline CHADS2 ≥2 (RR; 95% CrI)

	Edoxaban 60 mg / 30 mg DR vs. apixaban	Edoxaban 60 mg / 30 mg DR vs. dabigatran 110 mg	Edoxaban 60 mg / 30 mg DR vs. dabigatran 150 mg	Edoxaban 60 mg / 30 mg DR vs. rivaroxaban	Edoxaban 60 mg / 30 mg DR vs. warfarin
SEE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Edoxaban 60 mg / 30 mg DR vs. apixaban	Edoxaban 60 mg / 30 mg DR vs. dabigatran 110 mg	Edoxaban 60 mg / 30 mg DR vs. dabigatran 150 mg	Edoxaban 60 mg / 30 mg DR vs. rivaroxaban	Edoxaban 60 mg / 30 mg DR vs. warfarin
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transient ischaemic attack (TIA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA: Not available (No more than one trial had data, so analysis was not conducted), SEE: systemic embolism event

Principal Safety Endpoints: Major Bleeding; Composite of Major Bleeding, and Clinically Relevant Non-major Bleeding

[redacted]

[redacted]

Table 30: NMA Risk Ratios on major bleeding, Baseline $CHADS_2$ ≥2

	Warfarin	Apixaban	Dabigatran 110 mg	Dabigatran 150 mg	Edoxaban 60 mg / 30 mg DR	Rivaroxaban
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran 110 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban 60mg/30mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 10: NMA Risk Ratios on major bleeding, Baseline $CHADS_2$ ≥2

[redacted]

Figure 11: NMA Risk Ratios on composite of major bleeding and clinically relevant non-major bleeding, Baseline $CHADS_2$ ≥2

[redacted]

Other safety outcomes

Subgroup data from patients with $CHADS_2$ ≥ 2 were not available for apixaban and dabigatran for many secondary endpoints. Table 31 summarises results for available data.

[redacted]

[redacted]

[redacted]

Table 31: NMA Risk Ratios on other safety outcomes, Baseline $CHADS_2$ ≥2 (RR; 95% CrI)

	Edoxaban 60 mg / 30 mg DR vs. apixaban	Edoxaban 60 mg / 30 mg DR vs. dabigatran 110 mg	Edoxaban 60 mg / 30 mg DR vs. dabigatran 150 mg	Edoxaban 60 mg / 30 mg DR vs. rivaroxaban	Edoxaban 60 mg / 30 mg DR vs. warfarin
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major gastrointestinal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minor/minimal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinically relevant non-major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-threatening bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.7.6.2 Secondary analyses, patients with $CHADS_2$ score ≥ 3 at baseline

Figure 12 and Figure 13 below present the primary efficacy and safety analyses in the subgroup of patients with $CHADS_2$ score ≥ 3.

Figure 12: NMA Risk Ratios on composite of Stroke and Systemic Embolism, patients with CHADS2 score ≥ 3

[redacted]

Figure 13: NMA Risk Ratios on major bleeding, Baseline $CHADS_2$ ≥3

[redacted]

6.7.6.3 Secondary analyses, patients with time in therapeutic range (TTR) ≥ 66%

Figure 14 and Figure 15 below present the primary efficacy and safety analyses in the subgroup of patients with a cTTR ≥ 60%.

Figure 14: Risk Ratios on composite of Stroke and Systemic Embolism, patients with time in therapeutic range (TTR) ≥ 60%

[redacted]

Figure 15: Risk Ratios on major bleeding, patients with time in therapeutic range (TTR) ≥ 60%

[redacted]

6.7.6.4 Secondary analyses, patients unrestricted by $CHADS_2$ score (i.e., including $CHADS_2$ <2 where available)

Figure 16 and Figure 17 below present the primary efficacy and safety analyses in the subgroup of patients unrestricted by $CHADS_2$ score (i.e., including $CHADS_2$ <2 where available). In the figures below, and in section 7, this is referred to as the "all patients" dataset. These results were used to provide estimates for various parameters in the cost-effectiveness model when estimates for the population with $CHADS_2$ ≥2 or ≥3 were not available.

Figure 16: NMA Risk Ratios on Composite of Stroke and Systemic Embolism, all patients

[redacted]

Figure 17: NMA Risk Ratios on major bleeding, all patients

[redacted]

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

[redacted]

6.7.8 **If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.**

[redacted]

6.7.9 **Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.**

Based on qualitative assessment, the NMA results for each NOAC versus warfarin are in general consistent with the direct evidence from the original pivotal trials, supporting the validity of our analysis.

[redacted]

[redacted]

6.8 Non-RCT evidence

6.8.1 **If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.**

A systematic literature review was conducted to identify relevant non-RCTs on edoxaban from the published literature. The literature search is described in Sections 6.1, 6.2 and **Error! Reference source not found.**. No RCTs were identified, therefore non-RCT evidence is not considered.

6.9 Adverse events

The identification of clinical evidence is described in Sections 6.1 and 6.2. All studies relevant to this submission are listed in Table 6 in Section 6.2.4.

Additionally safety data on edoxaban from the Hokusai-VTE study is summarised in this section. Hokusai-VTE was a large study ever conducted in acute symptomatic VTE, with 8,292 patients randomized internationally and is reported in this section to provide additional evidence about the safety of edoxaban. The study was a phase III, event-driven, randomised, double-blind, double-dummy, parallel-group, multi-centre, multi-national non-inferiority study designed to evaluate the benefits and risks of edoxaban in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE.

6.9.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.**

6.9.2 **Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.**

All subjects in the safety analysis set were included in the safety analyses. The SAS includes all randomised subjects who received at least 1 dose of randomised study

drug, and is identical to the mITT analysis set, on treatment period. Disposition of subjects for the SAS population was summarised by treatment arm in Figure 4.

The measures used to assess the safety outcomes (and their respective definitions) investigated in ENGAGE AF-TIMI 48 are presented in Section 6.3.5, Table 9.

Adjudicated bleeding events

In the principal safety analysis, there was a significantly reduced rate of major bleeding in the edoxaban 60 mg / 30 mg DR arm compared to the warfarin arm (HR: 0.80; 95%CrI [0.71–0.91]; p<0.001) (Table 32, Figure 8).

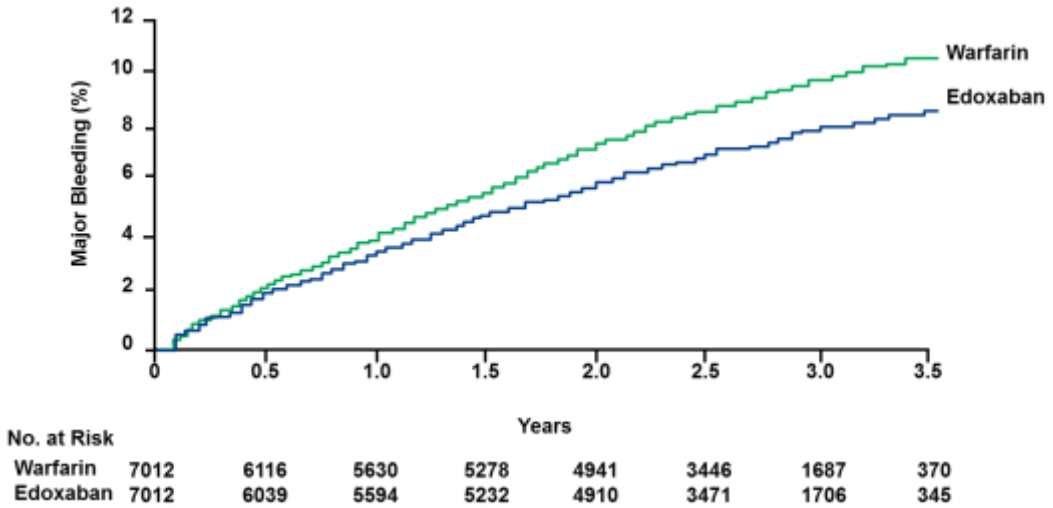
The edoxaban 60mg / 30mg DR arm had a significantly lower rate of several secondary bleeding endpoints, including intracranial, fatal, CRNM and life-threatening bleeds compared with the warfarin arm (p≤0.01 for all comparisons). (Table 32) With regard to gastrointestinal bleeding, a significantly higher rate was observed in the edoxaban arm compared to the warfarin arm (1.51% vs. 1.23%; p=0.03) (Table 32).

Table 32: Adjudicated bleeding events during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period).

Bleeding Outcome	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value
Major bleeding	524 (3.43)	418 (2.75)	0.80 [0.71–0.91]; p<0.001
Fatal bleeding	59 (0.38)	32 (0.21)	0.55 [0.36–0.84]; p=0.006
Any intracranial bleeding	132 (0.85)	61 (0.39)	0.47 [0.34–0.63]; p<0.001
Fatal intracranial bleeding	42 (0.27)	24 (0.15)	0.58 [0.35–0.95]; p=0.03
Gastrointestinal bleeding	190 (1.23)	232 (1.51)	1.23 [1.02–1.50]; p=0.03
Bleeding at a critical organ	211 (1.36)	108 (0.70)	0.51 [0.41–0.65]; p<0.001
Overt bleeding with blood loss of ≥2 g/dLdL	327 (2.13)	317 (2.08)	0.98 [0.84–1.14]; p=0.7878
Minor bleeding	714 (4.89)	604 (4.12)	0.84 [0.76–0.94]; p=0.002
Any overt bleeding	2114 (16.40)	1865 (14.15)	0.87 [0.82–0.92]; p<0.001
Major or clinically relevant non-major bleeding	1761 (13.02)	1528 (11.10)	0.86 [0.80–0.92]; p<0.001
Clinically relevant non-major bleeding	1396 (10.15)	1214 (8.67)	0.86 [0.79–0.93]; p<0.001

Figure 18 presents the Kaplan-Meier plot for major bleeding in the safety analysis set for the edoxaban 60 mg / 30 mg DR arm compared with the warfarin arm. As mentioned above, there was a significantly reduced rate of major bleeding in the edoxaban 60 mg / 30 mg DR arm compared to the warfarin arm (HR: 0.80; 95%CrI [0.71–0.91]; p<0.001)

Figure 18: Kaplan-Meier curve of major bleeding during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period).



Other adverse events

The five most frequent treatment-emergent adverse events (TEAEs) that were reported by patients in the edoxaban or warfarin arms were observed at similar rates (**Error! Not a valid bookmark self-reference.**); these were urinary tract infections (9.8% and 10.0%, respectively), nasopharyngitis (8.8% and 8.8%, respectively), bronchitis (8.1% and 8.2%, respectively), dizziness (7.3% and 8.4%, respectively) and peripheral oedema (8.2% and 9.6%, respectively). Treatment with edoxaban 60 mg / 30 mg DR therefore did not increase the risk of adverse events compared with well-controlled warfarin and was well tolerated.

Table 33: Adverse events during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period)

Outcome, n (%)	Warfarin (N=7012)	Edoxaban 60 mg / 30 mg DR (N=7012)
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)

Outcome, n (%)	Warfarin (N=7012)	Edoxaban 60 mg / 30 mg DR (N=7012)
Urinary Tract Infection	703 (10.0)	688 (9.8)
Nasopharyngitis	620 (8.8)	620 (8.8)
Oedema Peripheral	675 (9.6)	577 (8.2)
Bronchitis	572 (8.2)	567 (8.1)
Dizziness	592 (8.4)	514 (7.3)
Neoplasms	461 (6.6)	457 (6.5)
Bone Fractures	371 (5.3)	328 (4.7)
Deep venous thrombosis or pulmonary embolism	27 (0.4)	28 (0.4)

Abbreviations: AE, adverse event.

Analysis of patient samples and results of laboratory tests found that noteworthy changes were only seen for haemoglobin levels and CrCl levels. Minor decreases in haemoglobin were found across all treatment groups over the study (consistent with the occurrence of bleeding events). The mean haemoglobin change from baseline was -1.34 g/dL in the edoxaban arm and -1.09 g/dL in the warfarin arm.

With regard to renal function, the proportion of patients who experienced shifts from CrCl >50 mL/min and CrCl 30 to 50 mL/min at baseline to CrCl <30 mL/min at any point in the study, or at the end of treatment was balanced among the treatment groups. The mean CrCl change from baseline in the edoxaban 60 mg / 30 mg DR arm was also lower compared with warfarin (-13.80 mL/min vs. -12.52 mL/min, respectively). In addition, the analysis of vital signs between treatment arms found that similar changes in blood pressure recordings were observed between edoxaban 60 mg / 30 mg DR and warfarin arms. Electrocardiogram recordings made during the study showed that the shifts and changes observed were also comparable among the treatment arms.

The vital sign and laboratory tests from ENGAGE AF-TIMI 48 therefore found that once-daily edoxaban was well tolerated and was not associated with an increased risk of renal dysfunction or high blood pressure compared with well-controlled warfarin.

Hepatic events

Proportions of patients with an elevated level of liver enzymes or with hepatocellular injury were similar in the treatment arms (

Table **34**). This indicated that there was no clinically concerning signal for drug-induced hepatic injury with edoxaban 60 mg / 30 mg DR treatment compared with well-controlled warfarin.

Table 34: Adverse events during ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period)

Outcome, n (%)	Warfarin (N=7012)	Edoxaban 60 mg / 30 mg DR (N=7012)
Hepatic events AST or ALT ≥3x upper limit of normal Above with total bilirubin ≥2x upper limit of normal	 146 (2.1) 10 (0.1)	 150 (2.2) 15 (0.2)
Hepatic cases sent for adjudication Hepatocellular injury present Hepatocellular injury and cholestasis Cholestasis Other No liver injury present	155 (2.2) 86 (1.2) 23 (0.3) 7 (0.1) 43 (0.6) 1 (<0.1)	156 (2.2) 92 (1.3) 17 (0.2) 5 (0.1) 45 (0.6) 4 (0.1)
Hy's Law criteria satisfied	0	2 (<0.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Other outcome measures: Net clinical outcome

Edoxaban provides a favourable risk-benefit profile compared with well-controlled warfarin for net clinical outcome, a composite of efficacy and safety events, including stroke, disabling stroke or SEE, major and life-threatening bleeding outcomes, as well as mortality.

Edoxaban 60 mg / 30 mg DR was associated with significantly lower rates of all three composite outcomes than warfarin (p<0.01 for all comparisons) (Table 35). The very low rate of missing data in ENGAGE AF-TIMI 48 (0.5%) underscores the robustness of these observations

Table 35: Net clinical outcome results from ENGAGE AF-TIMI 48 (safety analysis set, on-treatment period)

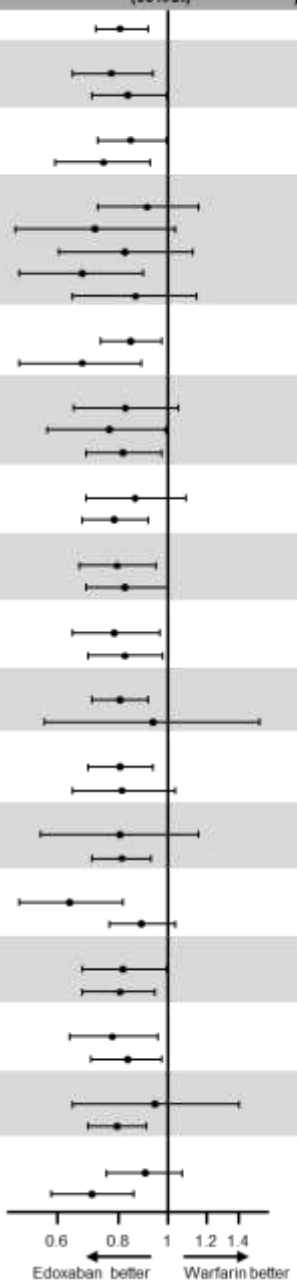
Outcome	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. Warfarin, HR [95% CI]; p-value
Primary (stroke, SEE, major bleeding or death)	1462 (8.11)	1323 (7.26)	0.89 [0.83–0.96]; p=0.003
Secondary (disabling stroke, life-threatening bleeding or death)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

Subgroup analysis

Analyses of major bleeding in a broad range of patient subgroups indicated that treatment with edoxaban was associated with a lower risk of bleeding than well-controlled warfarin in the majority of patient subgroups.

Figure 19: Subgroup analysis of primary safety outcome (Major bleeding) of ENGAGE AF-TIMI 48 –edoxaban 60 mg / 30 mg DR vs. warfarin (safety analysis set, on-treatment period).

Subgroup	Edoxaban Patients	Edoxaban High	Warfarin	Hazard ratio with Edoxaban 60/30 mg (95%CI)	Interaction p-value
All patients	21026	2.75	3.43		
Age group					0.57
<75 years	12594	2.02	2.62		
≥75 years	8432	4.01	4.83		
Sex					0.34
Male	13020	2.90	3.47		
Female	8006	2.48	3.35		
Region					0.50
North America	4665	4.07	4.47		
Latin America	2651	2.65	3.74		
Western Europe	3220	3.26	3.98		
Eastern Europe	7121	1.44	2.17		
Asia	3369	3.51	4.12		
Race					0.16
White	17008	2.72	3.23		
Non-white	4017	2.88	4.32		
AF Type					0.89
Paroxysmal	5348	3.06	3.69		
Persistent	4850	2.42	3.25		
Permanent	10825	2.75	3.38		
Prior Stroke or TIA					0.52
Yes	5950	3.11	3.65		
No	15076	2.61	3.35		
Congestive Heart Failure					0.76
Yes	12086	2.58	3.28		
No	8940	2.98	3.63		
Diabetes					0.70
Yes	7599	3.06	3.94		
No	13427	2.58	3.15		
Hypertension					0.68
Yes	19679	2.72	3.42		
No	1347	3.17	3.62		
$CHADS_2$ Score					0.94
≤3	16276	2.47	3.09		
>3	4750	3.79	4.68		
Prior MI					0.96
Yes	2423	3.09	3.89		
No	18600	2.71	3.37		
Dose adjusted					0.02
Yes	5330	3.05	4.85		
No	15696	2.66	3.02		
VKA Naive					0.88
Yes	8624	2.86	3.53		
No	12401	2.67	3.36		
Aspirin use at baseline					0.62
Yes	6152	3.62	4.71		
No	14872	2.41	2.92		
Amiodarone use at baseline					0.40
Yes	2484	2.79	2.98		
No	18542	2.74	3.49		
Centre Level TTR					0.06
>66.4%	9952	3.15	3.51		
≤66.4%	10628	2.33	3.35		



Abbreviations: AF, atrial fibrillation; MI, myocardial infarction; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist.

Safety results for subgroups specified in the NICE scope are discussed more in detail below:

Subgroup analysis by centre level TTR

Table 36 shows the effect of centre level TTR on the primary safety endpoint (major bleeding). As would be expected, edoxaban 60 mg / 30 mg DR performed better in centres with a lower TTR. For both subgroups with a TTR above or below the median, fewer patients in the edoxaban 60 mg / 30 mg DR arm experienced major bleeding than in the warfarin arm, and there was no significant interaction between the subgroups. The hazard ratio for the first, second and third quartiles were below 1.0 at 0.69, 0.70 and 0.80, respectively, and 1.05 for the fourth quartile compared with warfarin (p=0.11 for interaction; not significant).

Table 36: Major bleeding by centre level TTR (safety analysis set, on-treatment period)

Subgroup	Warfarin (N=7012)	Edoxaban 60 mg / 30 mg DR (N=7012)	Edoxaban 60 mg / 30 mg DR vs. warfarin, HR [95% CI]	p-value for interaction
Centres with TTR >66.4%, n (%/y)	273 (3.51)	225 (3.15)	0.90 [0.752–1.071]	0.0607
Centres with TTR ≤66.4%, n (%/y)	251 (3.35)	177 (2.33)	0.70 [0.576–0.847]	
Centres with TTR ≥60%, n (%/y)	[redacted]	[redacted]	[redacted]	[redacted]
Centres with TTR <60%, n (%/y)	[redacted]	[redacted]	[redacted]	
First quartile (≤57.7%), n (%/y)	[redacted]	[redacted]	[redacted]	[redacted]
Second quartile (>57.7% to ≤66.4%), n (%/y)	[redacted]	[redacted]	[redacted]	
Third quartile (>66.4% to ≤73.9%), n (%/y)	[redacted]	[redacted]	[redacted]	
Fourth quartile (>73.9%), n (%/y)	[redacted]	[redacted]	[redacted]	

Abbreviations: TTR, time in therapeutic range.

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

Overall there were similar hazard ratios for the comparion of edoxaban 60 mg / 30 mg DR vs warfarin for major bleeding, both for all patients irrespective of $CHADS_2$ score, and for scorespatients with $CHADS_2$ scores above 3.

Table 37: Major bleeding by $CHADS_2$ score (safety analysis set, on-treatment period)

$CHADS_2$ Score	Warfarin (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR (N=7012), n (%/y)	Edoxaban 60 mg / 30 mg DR vs. warfarin, HR [95% CI]
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]
6	[redacted]	[redacted]	[redacted]

Additional Safety Data

Post-marketing experience of the safety of edoxaban in Japan

As described in section 1.8, edoxaban is approved for the prevention of VTE after major orthopaedic surgery and was launched in July 2011. Analyses of post-marketing safety events have been published, as are described below.

A total of 67 AEs were reported in 56 patients (including 51 bleeding events in 42 patients), of which 15 serious adverse events (SAEs) in 14 patients were reported. All SAEs reported were bleeding events, and included cerebral (n=1), gastric (n=2), and surgical site (n=12) haemorrhages. Seven of the SAEs required transfusion, and all improved or resolved. The majority of bleeding events occurred in patients aged ≥75 years or who had a CrCl ≥50 mL/min. [72] These findings were consistent with the known safety profile of edoxaban and did not identify any unforeseen safety signals, further adding to the data on the safety of edoxaban.

Safety evidence of edoxaban from Hokusai-VTE

As described in section 1.8, edoxaban is separately being appraised by NICE for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults. Safety data from this indication are described below.

The safety population for Hokusai-VTE included 4118 patients treated with edoxaban 60 mg and 4122 who received warfarin. The on-treatment study period represented the primary period for all safety analyses, including bleeding. The treatment duration (the time from first to last dose) and treatment exposure to study drug are shown in Table 38.

Table 38: Study drug exposure, safety analysis set, HOKUSAI-VTE

	Edoxaban (n=4118)	Warfarin (n=4122)
Study Drug Exposure		
Mean (SD) (days)	250.3 (111.75)	248.4 (112.61)
Median (days)	265.0	261.0
Duration of treatment		
Mean (SD) (days)	251.9 (112.04)	250.3 (113.01)
Median (days)	267.0	266.0

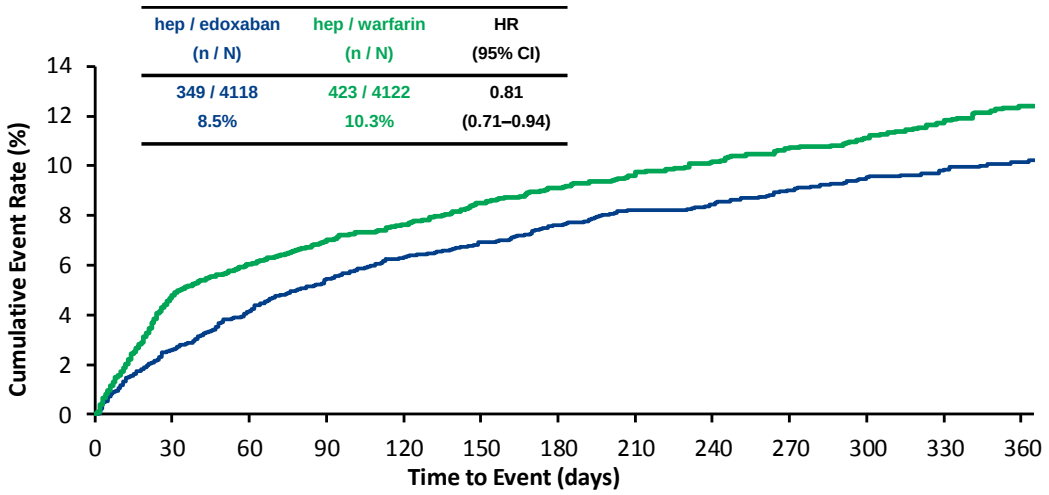
Patients in the edoxaban group experienced a significant reduction in the risk of major or CRNM bleeding (19%) compared with warfarin, which was driven primarily by a reduction in the risk of CRNM bleeding (Table 39). There were fewer major bleeding events with edoxaban compared with warfarin (not significant). There was a significant reduction in the risk of any bleeding event.

Table 39: Adjudicated bleeding events (safety analysis set, on-treatment study period) event, HOKUSAI-VTE

Bleeding Outcome	Warfarin (N=4122), n (%/y)	Edoxaban (N=4118), n (%/y)	Edoxaban vs. Warfarin, HR [95% CI]; p-value
Major bleeding	66 (1.6%)	56 (1.4%)	0.84 (0.592–1.205): p=0.004
Major or clinically relevant non-major bleeding	423 (10.3%)	349 (8.5%)	0.81 (0.705–0.936): p=0.3521
Clinically relevant non-major bleeding	368 (8.9%)	298 (7.2%)	0.80 (0.68–0.93) p=0.004
[redacted]	[redacted]	[redacted]	[redacted]
Any bleeding	1056 (25.6%)	895 (21.7%)	0.82 (0.75–0.90): p<0.001

The edoxaban group had a lower event rate estimate of clinically relevant (major/CRNM) bleeding than the warfarin group throughout the entire on-treatment study period, as shown by the cumulative Kaplan-Meier event rate estimates. (Figure 20)

Figure 20: Kaplan-Meier cumulative event rate estimates for the principal safety endpoint (major plus CRNM bleeding), edoxaban vs warfarin, safety analysis set (on-treatment period); HOKUSAI-VTE



Number of patients at risk

Warfarin	4122	3757	3627	3522	3313	3218	2979	2165	2007	1883	1754	1613	1212
Edoxaban	4118	3840	3695	3587	3382	3308	3038	2192	2043	1904	1764	1650	1241

The composite endpoint of MACE (non-fatal MI, non-fatal stroke, non-fatal SEE, and CV death) and its individual components were reported in similar percentages of patients across the treatment groups during the on-treatment period (Table 40). There were few additional events in the 30 day post-treatment period as shown by the broadly comparable percentages of patients in the edoxaban and warfarin groups in the treatment plus 30 days period. Incidence of all-cause mortality was comparable between the two groups, as were VTE-related and cardiovascular deaths.

Table 40: MACE and individual components (safety analysis set, on-treatment and treatment plus 30 days study periods); HOKUSAI-VTE

	Warfarin (N=4122), n (%/y)	Edoxaban (N=4118), n (%/y)	Edoxaban vs. Warfarin, HR [95% CI]
On-treatment period			
MACE	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
SEE	[redacted]	[redacted]	[redacted]
Cardiovascular death	[redacted]	[redacted]	[redacted]
Treatment plus 30 days period			
MACE	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
SEE	[redacted]	[redacted]	[redacted]
Cardiovascular death	[redacted]	[redacted]	[redacted]

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Bleeding

Compared with warfarin, edoxaban was associated with a consistent and dose-related reduction in all types of bleeding, including Major, and Clinically-Relevant Non-Major bleeding. The single exception was major GI bleeding, which occurred slightly more frequently in the edoxaban 60 mg /30 mg DR group compared to the warfarin group (annualised rate of 1.51% vs. 1.23%, respectively). However, it should be noted that the incidence of fatal bleeds was significantly lower for edoxaban 60 mg /30 mg DR compared with warfarin (HR=0.55; p=0.006), indicating it is likely that GI bleeds were well managed in clinical settings.

Other adverse events

The non-bleeding treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) were generally similar for both edoxaban and warfarin-treated subjects. Overall, non-bleeding TEAEs leading to study drug interruptions or discontinuations were also similar in both edoxaban and warfarin-treated subjects. The edoxaban arm had more reports of anaemia than the warfarin arm, which could possibly be due to a higher number of occult GI bleeding events in this group.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Primary evidence for the efficacy and safety of edoxaban in the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation comes from the study ENGAGE AF-TIMI 48.

ENGAGE AF-TIMI 48 was a randomised, double-blind, non-inferiority study that compared two regimens of edoxaban with well-controlled warfarin (median TTR 68.4%) for stroke or systemic embolism prevention in patients with NVAF (N=21,105).

Efficacy and safety of edoxaban

In the primary efficacy analysis of ENGAGE AF-TIMI 48, edoxaban 60 mg / 30 mg DR was non-inferior to well-controlled warfarin for the prevention of stroke or systemic embolism in patients with NVAF, with a numerical 21% reduction in risk (p<0.001 for non-inferiority) in the mITT on-treatment population. Moreover, edoxaban significantly reduced the risk of haemorrhagic stroke compared with well-controlled warfarin (46% risk reduction; p<0.001). Prespecified subgroup analyses demonstrate a consistent pattern across patient groups; the hazard ratios for the comparison of the high-dose edoxaban (60 mg / 30 mg DR) arm versus the warfarin arm on the primary efficacy endpoint was frequently 1.0 or less.

Edoxaban once-daily was associated with a significantly lower rate of the primary safety endpoint of major bleeding than well-controlled warfarin in the safety on-treatment population; risk reduction was 20% (p<0.001). Edoxaban also significantly reduced the risk of several bleeding outcomes compared with well-controlled warfarin, including fatal bleeding, life-threatening bleeding, the composite of major bleeding and clinically relevant non-major bleeding and minor bleeding. Analyses of major bleeding in a broad range of patient subgroups indicated that treatment with edoxaban was associated with a lower risk of bleeding than well-controlled warfarin in the majority of patient subgroups in ENGAGE AF-TIMI 48.

Analyses of major bleeding in a wide variety of patient subgroups in the safety on-treatment population found that there was a broadly consistent reduction in major bleeding across the majority of subgroups vs. well controlled warfarin.

Edoxaban demonstrated a favourable risk-benefit profile compared with well-controlled warfarin for net clinical outcome, a composite of efficacy and safety events, including stroke, systemic embolism, major bleeding, and death (HR 0.89; 95% CI 0.83–0.96; p=0.003). Furthermore, cardiovascular mortality was significantly reduced with edoxaban versus well-controlled warfarin (14% risk reduction; p=0.013).

In the absence of head-to-head data, a network meta-analysis (NMA) was conducted to estimate the relative efficacy and safety of edoxaban versus dabigatran, rivaroxaban, and apixaban. The NMA data should be interpreted with caution because of significant differences in patient characteristics and trial design that exist between the four pivotal phase III trials comparing individual non-VKA OACs with

warfarin. However, results from the NMA were generally consistent with the results of direct comparison of the NOACs versus warfarin in the individual pivotal studies.

Compared to other NOACs, results from the NMA suggest that, among patients with $CHADS_2$ score ≥2, edoxaban has similar efficacy in reducing the risk of the composite of stroke and systemic embolism as other OACs (including warfarin, rivaroxaban, apixaban, and dabigatran). [redacted] This indirect treatment comparison also confirmed the superior safety profile of edoxaban relative to warfarin, as seen in ENGAGE AF-TIMI 48.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

The ENGAGE AF – TIMI 48 study was a phase III, randomised, double-blind, double-dummy, non-inferiority study designed to evaluate the benefits and risks of two edoxaban regimens for stroke or systemic embolism in patients with non-valvular atrial fibrillation (21,105 patients were enrolled at 1393 centres in 46 countries, including 31 centres in the UK).

This study was the largest novel oral anticoagulant trial in AF to date, with a long median follow-up (2.8 years), and minimal missing data (< 1.3% withdrew consent and only 1 subject was lost to follow-up).

This trial was well-designed and adequately powered to detect differences in the treatment arms. Blinding was carried out appropriately using double-dummy concealment, and baseline patients' characteristics were well balanced between treatment groups.

In addition, the warfarin group had a higher median TTR, than the trials of the other NOACS (68.4%), indicating that edoxaban was compared with well-controlled warfarin therapy.

In both edoxaban treatment groups, the dose was halved for subjects with moderate renal impairment (CrCL ≥ 30 and ≤ 50 mL/min), low body weight (≤ 60 kg), or for subjects receiving concomitant P-gp inhibitors (verapamil, quinidine), allowing for optimisation of the dose, either at randomisation or at any point suring the study.

ENGAGE AF-TIMI 48 is the only trial where dose adjustment was also allowed throughout the trial in response to a change in a subject's condition, similar to real life clinical practice. Approximately 25% of subjects in the three treatment groups had a dose reduction at randomisation, and 7 to 8% had a dose adjustment during the study.

In addition, the implementation of a comprehensive transition plan to open-label anticoagulation therapy resulted in a low and evenly distributed number of events

after the discontinuation of study therapy. This finding makes it unlikely that there is a rebound activation of coagulation after the discontinuation of edoxaban. [9]

Limitations

ENGAGE AF-TIMI 48 enrolled moderate to high risk patients with a $CHADS_2$ ≥2, thus excluding low-risk patients (with a $CHADS_2$ ≥ 1) that were enrolled in other NOACs trials such as RE-LY or ARISTOTLE. Data on the benefits and risks of edoxaban in these patientspatients are by consequence not available. However, as both the primary efficacy and safety endpoints in the ENGAGE AF-TIMI 48 study showed a decrease in events with decreasing $CHADS_2$ score, it is reasonable to expect that this pattern would be observed among patientssubjects with a $CHADS_2$ score of 1.

The same pattern was observed for net clinical outcome (a measure that c, ombines efficacy and safety endpoints); higher event rates were reported with increasing $CHADS_2$ scores.

In addition, for both the primary efficacy and safety endpoints, the HRs for edoxaban vs warfarin are stable across the range of $CHADS_2$ scores, and therefore it is reasonable to expect that the overall HR for the study as a whole for subjects with $CHADS_2$ scores of 2 to 6 would also apply to subjects with a $CHADS_2$ score of 1.

Extrapolating the results for subjects with a $CHADS_2$ score of 2 and higher to those with a $CHADS_2$ score of 1 is appropriate because there is no fundamental difference in the pathophysiology of a subject's coagulation system by different levels of $CHADS_2$ score. The ESC has made similar extrapolations in the recommendations for other anticoagulants e.g. VKA and rivaroxaban for which studies included $CHADS_2$ scores greater than or equal to 2, as was done for edoxaban.

6.10.3 **Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.**

ENGAGE AF-TIMI 48 is relevant to the scope of this appraisal. This study compares edoxaban with the current standard of care, warfarin. The population evaluated in ENGAGE AF-TIMI 48 is representative of the population that would receive the product after marketing authorisation and similar to the population evaluated in other NOAC trials. ENGAGE AF-TIMI 48 included 398 patients from the UK, accounting for 1.9% of the study population.

The outcomes measured are standard objective endpoints used in the assessment of the response to treatment in AF patients at risk of stroke.

The evidence base demonstrates that the edoxaban 60 mg / 30 mg DR regimen is a safe and effective alternative to the current standard of care, warfarin, to prevent stroke and SEE in subjects with AF and supports the use of edoxaban 60 / 30 mg DR in different populations relevant to the decision problem.

Compared to other NOACs, results from the NMA suggest that, among patients with $CHADS_2$ score ≥2, edoxaban regimen has similar efficacy in reducing the risk of the

composite of stroke and SEE as other OACs (including warfarin, rivaroxaban, apixaban, and dabigatran), a similar safety profile to apixaban, but a superior safety profile compared with rivaroxaban and dabigatran. The indirect treatment comparison also confirmed the superior safety profile of edoxaban relative to warfarin, as seen in ENGAGE AF-TIMI 48.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Patients recruited into ENGAGE AF-TIMI 48 trial are representative of that likely to be seen in clinical practice. The PREFER in AF registry is a prospective observational study aiming to gain detailed insight on the characteristics and management of patients with AF. [24] 7243 patients were enrolled in France, Germany, Italy, Spain and the United Kingdom from January 2012 to January 2013. The population from ENGAGE AF-TIMI 48 and the UK subgroup population from PREFER-AF have similar clinical characteristics: Median age (72 years old and 70.7 years old, respectively), male proportion (61.9% and 64.5%, respectively, VKA experienced patients proportion (59% and 75 %, respectively). While ENGAGE-AF TIMI 48 did not recruit patients with $CHADS_2$ <2, it is important to note that for both the primary efficacy and safety endpoints, the HRs are stable across the range of $CHADS_2$ scores (as discussed in 6.10.2).. It is therefore reasonable to expect that the overall HR for the study as a whole for subjects with $CHADS_2$ scores of 2 to 6 would also apply to subjects with a $CHADS_2$ score of 1.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

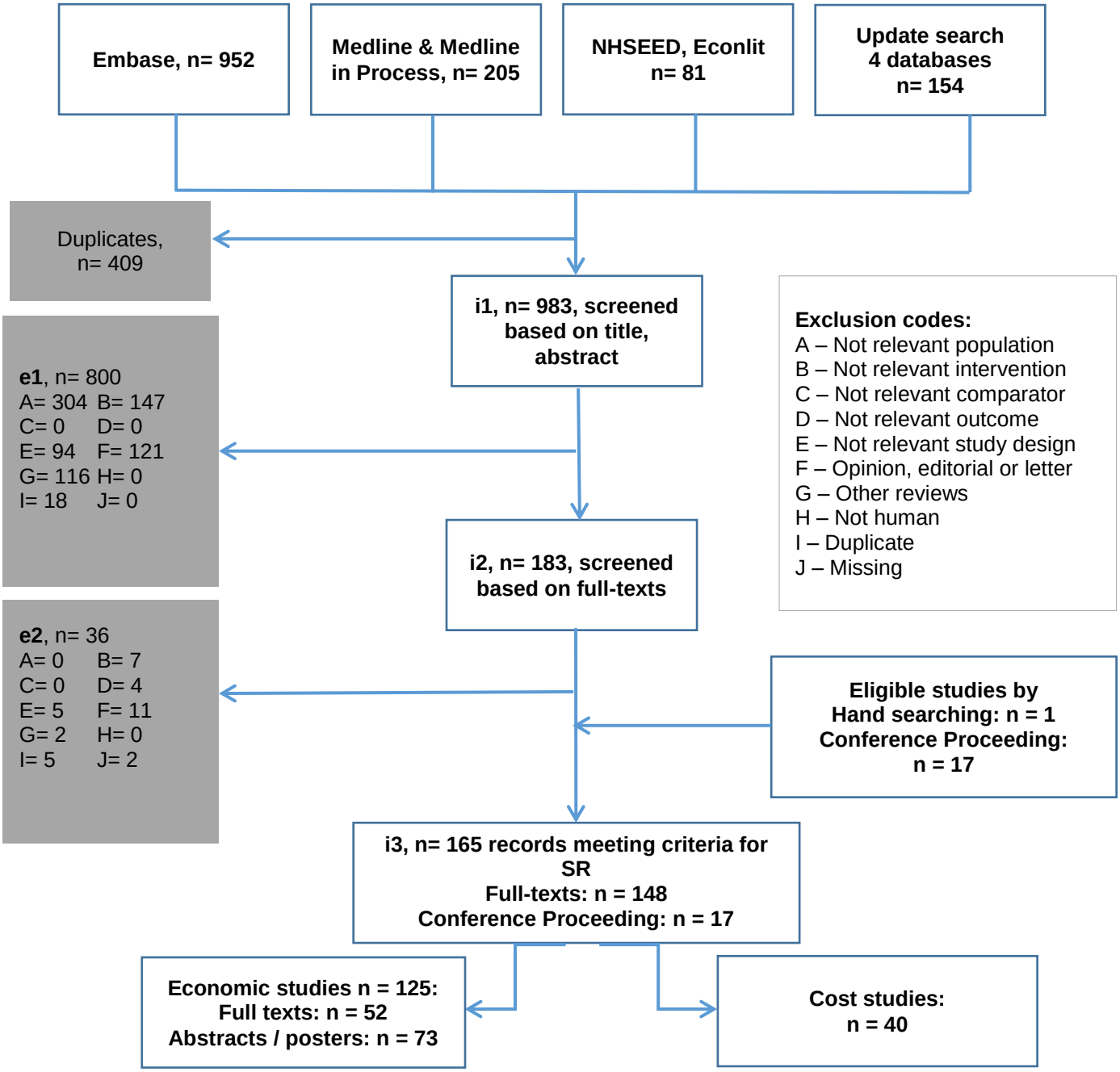
7.1.1 **Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.**

A systematic review has been conducted to identify cost-effectiveness and costing studies from the published literature of interventions (NOACS, warfarin) for the prevention of stroke and / or systemic embolism in adult patients with atrial fibrillation. The following electronic databases were examined: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), OvidSP Embase, NHSEED, Econlit. The search strategy and the inclusion / exclusion criteria are provided in Section **Error! Reference source not found.**. A flow diagram of included and excluded records is provided in Figure 21.

In total, 1,392 records were identified through the electronic searches. On removal of duplicates, 983 records were screened on title and abstract. Of these, 183 records were reviewed based on full texts, of which 36 were excluded. By hand searching 1 full text has been included, and 17 abstracts have been included from conference proceeding, resulting in 165 records for final inclusion (40 costing studies and 125 cost-effectiveness studies).

The costing studies are listed in Section 7.5.3, but only six have been included from further discussion as they were conducted in the UK and are therefore relevant to this submission.

Figure 21: Schematic for the systematic review of economic evidence



Abbreviations: SR, systematic review

Description of identified studies

7.1.2 **Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

A summary of the 52 full text papers is provided in Table 41. These studies evaluated currently available pharmacological interventions in an active comparator setting, and were deemed relevant to this submission. They are discussed further in this section.

Of the 52 full text papers identified, 6 were cost-utility analyses (CUA); 45 were cost-effectiveness analysis (CEA); one was a budget impact analysis (BIA). Most of the studies (90%) used a Markov modelling approach to evaluate the cost-effectiveness of NOACs or warfarin in the prevention of stroke and SE in AF patients. Out of the 52 studies, the majority were published in the last three years with two published before 2009, 18 from 2009 to 2013, and 32 in 2013 or 2014. Among the 52 studies, only 3 analysed outcomes over a time horizon of less than 10 years, the remaining used a greater time horizon, which is consistent with the NICE reference case (lifetime time horizon).

In subsequent search of conference proceedings, 17 abstracts have been included and 9 of them were cost-effectivness models (Table 41). Two recent abstracts (Magnusson 2014, Mearns 2014) assessed the cost-effectiveness of edoxaban vs. warfarin in NVAF from a US payer perspective. Both CEAs used a Markov modelling approach with a lifetime horizon.

Table 41: Summary list of other cost-effectiveness evaluations

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
Andrikopoulos 2013	Greece	Evaluate dabigatran etexilate in comparison to existing pharmaceutical therapeutic options available for the protection of moderate- to-high risk patients with non-valvular atrial fibrillation from cardio embolic risk.	CEA ,Markov Model ,Payer, Lifetime	Dabigatran (110 mg and 150 mg, both BID) Warfarin (up to 5mg, once daily) Acenocoumarol (up to 2.5 mg daily) Acetylsalicylic acid (162.5mg daily) Acetylsalicylic acid and clopidogrel (75 mg daily)	NVAF at moderate-to-high risk of stroke or embolism, eligible for anticoagulation treatment.	Dabigatran 110 mg 9.94 Dabigatran 150 mg 10.01 Acenocoumarol 9.64 Warfarin 9.64 Acetylsalicylic acid 9.43 Acetylsalicylic acid & clopidogrel 9.31	Dabigatran 110 mg €35 614 Dabigatran 150 mg €34 836 Acenocoumarol €30 683 Warfarin €30 618 Acetylsalicylic acid €28 014 Acetylsalicylic acid & clopidogrel €30 953	VS. Dabigatran 150 mg Acenocoumarol €11 224 Warfarin €11 400 Acetylsalicylic acid €11 762 Acetylsalicylic acid & clopidogrel €5 547 VS. Dabigatran 110 mg Acenocoumarol €16 437 Warfarin €16 653 Acetylsalicylic acid €14 902 Acetylsalicylic acid & clopidogrel €7 398
Bergh 2013	South Africa	To estimate cost-effectiveness and budget impact of dabigatran compared with warfarin for prevention of stroke in AF patients.	CEA ,Markov Model ,Payer, Lifetime	Dabigatran (150mg then switch to 110mg after 80y) Warfarin	AF	Dabigatran 7.19 Warfarin 6.98	Dabigatran: R320,286 Warfarin: R301,249	Dabigatran vs warfarin: R93,290
Bonet 2013	Spain	To estimate, in the context of a Health Department of the Valencia Health Agency, the budgetary impact of the widespread use of dabigatran at doses of 110 and 150 mg in patients with non-valvular atrial fibrillation (AF), regarding the current scenario with acenocoumarol therapy	BIA ,NR ,Healthcare provider, 1 year	Dabigatran 110mg Dabigatran 150mg Acenocumarol	NVAF	NR	Dabigatran 110: €1,338 Dabigatran 150: €1,337 Acenocoumarol: €300	NR
Canestaro 2013	USA	To evaluate the comparative cost-effectiveness of all the available oral agents for stroke prophylaxis in warfarin-eligible patients with AF	CEA ,Markov Model ,Societal, Lifetime	Dabigatran (110 and 150 mg) Rivaroxaban (20 mg) Apixaban (5 mg) Warfarin	Warfarin-eligible patients with AF, average CHADS score of 2	Warfarin 5.87 Rivaroxaban 6.18 Apixaban 6.28 Dabigatran 6.15	Discounted Warfarin $49 638 Rivaroxaban $84 192 Apixaban $87 794 Dabigatran $88 994	Cost-Effectiveness Ratio to Warfarin, Rivaroxaban $111 465 Apixaban $93 063 Dabigatran $140 557
Chang 2014	Taiwan	A CEA was performed with a Markov model to evaluate the value of dabigatran to prevent stroke and systematic embolism in patients with AF in Taiwan	CEA ,Markov ,Payer (Taiwan), Lifetime	Dabigatran (sequential dosing: patients < 80 150mg BID; patients over or equal 80 110mg BID) warfarin (real-world	Patients 18 years or older and have at least two records of AF diagnosis (ICD-9-CM codes 427.31)	Dabigatran: 8.40 Real-world adjusted dose warfarin: 7.96 Real-world prescribing behaviour warfarin: 7.20	USD Dabigatran: 39,135 Real-world adjusted dose warfarin: 34,500 Real-world prescribing behaviour warfarin:	USD per QALY of dabigatran Real-world adjusted dose warfarin: 10,551 Real-world prescribing behaviour warfarin: 280

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
				adjusted dose warfarin; real-world prescribing behaviour warfarin)	between January 1, 2001, and December 31 2006)		38,800	
Chevalier 2014	France	To estimate the cost-effectiveness from a French payer perspective, of dabigatran (150mg or 110 mg bid for patients < or >= 80 years, respectively) versus warfarin.	CEA ,Markov ,Payer (French) and All-payer (including dependency and out-of-pocket) , Lifetime	Dabigatran trial like warfarin real-world warfarin	The population matched RE-Ly trial. This analysis considers 10,000 patients with AF followed for their remaining lifetime to capture the lifelong consequences of stroke and haemorrhage.	Payer perspective: Dabigatran: 7.94 trial like warfarin: 7.70 real-world warfarin: 7.56 All Payer perspective: Dabigatran: 7.94 trial like warfarin: 7.70 real-world warfarin: 7.56	Payer perspective Dabigatran: 23,231 trial like warfarin: 19,397 real-world warfarin: 20,358 All Payer perspective Dabigatran: 24,263 trial like warfarin: 20,978 real-world warfarin: 3,285	Payer perspective: Dabigatran vs. 'trial like warfarin': 15,838 Dabigatran vs. 'real-world warfarin': 7,473 All Payer perspective: Dabigatran vs. 'trial like warfarin': 13,568 Dabigatran vs. 'real-world warfarin': 5,663
Clemens 2014	US	This study aims to estimate the cost-effectiveness of dabigatran 150 mg twice daily versus warfarin for stroke and systemic embolism risk reduction in patients with nonvalvular atrial fibrillation initiating treatment before age 7, at or after age 75, and the overall population (All) from a US Medicare payer perspective.	CEA ,Markov ,Payer (US), Lifetime	Dabigatran 150 mg twice daily Warfarin	Patients with AF in whom anticoagulation is appropriate, in cohorts initiating treatment before age 75, those initiating at or after age 75, and all RE-LY trial patients (All)	Age <75 Dabigatran 9.69 Warfarin 9.30 Age >/=75 Dabigatran 5.62 Warfarin 5.42 All Patients Dabigatran 8.07 Warfarin 7.75	Age <75 Dabigatran $46,444 Warfarin $25,485 Age >/=75 Dabigatran $28,645 Warfarin $15,178 All Patients Dabigatran $39,331 Warfarin $21,366	Incremental results—dabigatran vs. warfarin ($/QALY) Age < 75: 52,773 Age >/= 75: 65,946 All patients: 56,131
Coyle 2013	USA	To assess the cost-effectiveness of new oral anticoagulants compared with warfarin in patients with nonvalvular atrial fibrillation and to assess the cost-effectiveness of new oral anticoagulants stratified by center-specific time in therapeutic range, age and $CHADS_2$ scrore.	CEA ,Markov Model ,Payer, Lifetime (40years)	Dabigatran (110 and 150 mg) Rivaroxaban (20 mg) Apixaban (5 mg) Warfarin	NVAF with no previous stroke or myocardial infarction.	Warfarin: 6.480 Dabigatran 150: 6.617 Apixaban: 6.617 Rivaroxaban: 6.541 Dabigatran 110: 6.543	Warfarin: $18,620 Dabigatran 150mg: $21,486 Apixaban: $21,966 Rivaroxaban: $22,016 Dabigatran 110mg: $22,804	Drug vs warfarin: dabigatran 150mg: $20,797 apixaban: $24,312 Rivaroxaban: $55,757 dabigatran 110mg: $66,354

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
Davidson 2013	Sweden	Estimate the cost-effectiveness of dabigatran as preventive treatment of stroke and thromboembolic events compared with warfarin in 65-year-old patients with atrial fibrillation in Sweden.	CEA ,Decision analytic model ,Societal, 20 years	Dabigatran (150 mg and 110 mg) Warfarin	AF	Warfarin 8.31 Dabigatran 8.60	Warfarin €24 797 Dabigatran €27 009	Dabigatran vs warfarin €7 742
Dorian 2014	UK	To evaluate the potential cost-effectiveness of apixaban against warfarin and aspirin from the perspective of the UK payer perspective.	CEA ,Markov Model ,Payer, Lifetime	Apixaban Warfarin Aspirin	NVAF suitable for VKA based on ARISTOTLE, and unsuitable for VKA based on AVERROES	VKA suitable Apixaban: 6.26 Warfarin: 6.08 VKA unsuitable Apixaban: 6.22 Aspirin: 5.95	VKA suitable Apixaban: £9 078 Warfarin: £6 920 VKA unsuitable Apixaban: £8 925 Aspirin: £6 995	VKA suitable Apixaban vs Warfarin: £11 909 VKA unsuitable Apixaban vs Aspirin: £7 196
Eckman 2009	USA	To examine the cost-effectiveness of genotype-guided dosing versus standard induction of warfarin therapy for patients with nonvalvular atrial fibrillation.	NR ,Markov Model ,Societal, Lifetime	Genotype-guided warfarin (CYP2C9*2, CYP2C9*3, and/or VKORC1) Standard warfarin	NVAF	3% discounted: Standard warfarin: 7.5759 Genotype guided warfarin: 7.5780 No discount: Standard warfarin: 8.9873 Genotype guided warfarin: 8.9898	3% discounted: Standard warfarin: $19 315 Genotype guided warfarin: $19 684 No discount: Standard warfarin: $23 243 Genotype guided warfarin: $23 610	3% discounted: Genotype guided vs standard warfarin: $171 750 No discount: Genotype guided vs standard warfarin: $114 057
Freeman 2011	USA	To estimate the quality-adjusted survival, costs, and cost-effectiveness of dabigatran compared with adjusted-dose warfarin for preventing ischemic stroke in patients 65 years or older with nonvalvular AF.	CEA ,Markov Model ,Societal, Lifetime	Dabigatran (150 mg and 110 mg) Warfarin	NVAF and risk factors for stroke ($CHADS_2$ score 1 or equivalent) and no contraindications to anticoagulation.	Warfarin: 10.28 Dabigatran 110 mg: 10.70 Dabigatran 150 mg: 10.84	Warfarin: $143 193 Dabigatran 110mg: $164 576 Dabigatran 150mg: $168 398	VS. Warfarin Dabigatran 110mg: $51 229 per QALY Dabigatran 150mg: $45 372 per QALY
Gage 1995	USA	To examine the cost effectiveness of prescribing warfarin sodium in patients who have nonvalvular atrial fibrillation (NVAF) with or without additional stroke risk factors (a prior stroke or transient ischemic attack,	CEA ,Markov Model ,Societal, 10 years	Warfarin Aspirin (75 mg daily) No treatment	NVAF who were 65 years of age, and good candidates for warfarin therapy	High risk warfarin: 6.51 aspirin: 6.27 no therapy: 6.01 Medium risk	High risk warfarin: $12 500 aspirin: $13 200 no therapy: $15 300 Medium risk	High risk warfarin vs aspirin: warfarin dominant warfarin vs no therapy: warfarin dominant

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
		diabetes, hypertension, or heart disease)				warfarin: 6.60 aspirin: 6.46 no therapy: 6.23 Low risk warfarin: 6.70 aspirin: 6.69 no therapy: 6.51	warfarin: $10 900 aspirin: $9 700 no therapy: $11 400 Low risk warfarin: $9 000 aspirin: $5 400 no therapy: $6 300	Medium risk warfarin vs aspirin: $8 000 warfarin vs no therapy: warfarin dominant Low risk warfarin vs aspirin: $370 000 warfarin vs no therapy: $14 000
Gonzalez-Juanatey 2012	Spain	Assess the cost-effectiveness of dabigatran for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in Spain.	CEA ,Markov Model ,National Health System, Lifetime	Dabigatran (150 mg and 110 mg) Warfarin	Hypothetical cohort of 10 000 patients with NVAF that simulated the profile of the patients in the RE-LY trial	Scenario 1 Dabigatran: 8.73 Warfarin: 8.45 Scenario 2 Dabigatran: 8.73 Prescribing pattern: 8.32	Scenario 1 Dabigatran: €15 193 Warfarin: €10 343 Scenario 2 Dabigatran: €15 193 Prescribing pattern: €9 426	Scenario 1 Dabigatran vs Warfarin: €17 581 Scenario 2 Dabigatran vs prescribing pattern: €14 118
Harrington 2013	USA	Estimate the cost-effectiveness of stroke prevention in patients with nonvalvular atrial fibrillation by using novel oral anticoagulants apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg compared with warfarin	CEA ,Markov Model ,Societal, 30 years	Apixaban (5mg twice daily) dabigatran (150mg twice daily) rivaroxaban (20mg daily) warfarin	NVAF, an increased risk for stroke ($CHADS_2$ ≥1, or equivalent), a renal creatinine clearance of ≥50 mL/min, and no previous contraindications to anticoagulant therapy.	Base case warfarin 7.97 Rivaroxaban 8.26 Dabigatran 8.41 Apixaban 8.47	warfarin $77 813 Rivaroxaban $78 738 Dabigatran $82 719 Apixaban $85 326	Base case vs warfarin Rivaroxaban: $3 190 Dabigatran: $11 150 Apixaban: $15 026
Jarungsuccess 2014	Thailand	This study was performed to determine which NOACs yielded population-specified cost-effective results for SPAF compared with warfarin from both governmental and societal perspectives in Thailand	CUA ,Markov ,Thailand government and societal , Lifetime	Dabigatran 150 mg BID Dabigatran 110 mg BID Rivaroxaban 20 mg OD Apixaban 5 mg BID Dose-adjusted Warfarin	Patients older than 65 years of age with newly diagnosed NVAF, a moderate to high risk of stroke (CHADS2 score equal or over 2), and no history of stroke.	Government Perspective Base case: Dabigatran 150 mg BID: 2.34 Dabigatran 110 mg BID: 2.29 Rivaroxaban 20 mg OD: 2.31 Apixaban 5 mg BID:	Government perspective: Base case: Dabigatran 150 mg BID: 186,641.60 Dabigatran 110 mg BID: 187,653.46 Rivaroxaban 20 mg OD: 173,149.61 Apixaban 5 mg BID:	Vs. warfarin: Government Perspective: Base case: Dabigatran 150 mg BID: 2,268,738.48 Dabigatran 110 mg BID: 46,426,823.22 Rivaroxaban 20 mg OD: 5,050,231.84 Apixaban 5 mg BID:

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
						2.33 Dose-adjusted Warfarin: 2.29	299,536.42 Dose-adjusted Warfarin: 71,184.43	5,583,860.99
Jowett 2011	UK	The aim of this study was to determine the cost effectiveness of warfarin in this patient population.	CEA ,Markov Model ,National Health System, 4 years	Warfarin Aspirin (75 mg daily)	Primary care AF population of patients	Warfarin: 1.685 Aspirin: 1.665	Warfarin: £1 382 Aspirin: £1 548	Warfarin dominant
Kamel 2012	NR	Compare the cost-effectiveness of apixaban vs warfarin for secondary stroke prevention in patients with atrial fibrillation (AF).	CEA ,Markov Model ,Societal, 20 years	Apixaban (5 mg twice daily) warfarin	AF	Warfarin: 3.91 Apixaban: 4.19	Warfarin: $378 500 Apixaban: $381 700	Apixaban vs Warfarin: $11 400
Kamel 2012a	USA	Cost-effectiveness analysis of dabigatran compared with warfarin in patients with AF and a history of stroke or TIA.	CEA ,Markov Model ,Societal, 20 years	Dabigatran (150 mg) Warfarin	Hypothetical cohort of patients with NVAF, prior stroke or TIA, and no contraindications to anticoagulation.	Dabigatran: 4.27 Warfarin: 3.91	NR	Dabigatran vs Warfarin: $25 000
Kansal 2011	UK	To assess the cost-effectiveness of dabigatran etexilate, a new oral anticoagulant, versus warfarin and other alternatives for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation (AF).	CEA ,Markov Model ,NR, Lifetime	Dabigatran Warfarin Aspirin No treatment	AF	Dabigatran: 8.06 Warfarin: 7.82 Aspirin: 7.59 No treatment: 7.12	Dabigatran: £19 645 Warfarin: £18 474 Aspirin: £18 561 No treatment: £20 475	Under 80: Dabigatran versus warfarin: £4 831 Dabigatran versus aspirin: £3 457 Dabigatran versus no treatment: dominant 80 and above: Dabigatran vs warfarin: £7 090
Kansal 2012	Canada	To estimate the cost-effectiveness of dabigatran (twice daily dosing of 150 mg or 110 mg based on patient age) versus rivaroxaban from a Canadian payer perspective.	CEA ,Markov Model ,Payer, Lifetime	Dabigatran 110 mg Dabigatran 150 mg Rivaroxaban Warfarin	$CHADS_2$ score: 2 (13%), 3 (43%), 4 (29%), 5 (13%), 6 (2%)	Dabigatran: 6.167 Rivaroxaban: 6.015	Dabigatran: $59 613 Rivaroxaban: $59 766	Dabigatran dominant
Kleintjens 2013	USA	Evaluate, from a Belgian healthcare payer perspective, the cost-effectiveness of rivaroxaban versus use of warfarin for the treatment of	CEA ,Markov Model ,Payer, Lifetime	Rivaroxaban (15-20 mg once daily) Warfarin	NVAF, moderate ($CHADS_2$ score = 2) to high risk of stroke ($CHADS_2$	Rivaroxaban 8.213 Warfarin 8.119	Rivaroxaban €18 695 Warfarin €17 867	Rivaroxaban €8 809/QALY compared to warfarin

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
		patients with non-valvular AF at moderate to high risk.			score = 3 or higher)			
Kourlaba 2014	Greece	To assess cost-effectiveness of rivaroxaban relative vesus selected antithrombotic alternatives (VKAs)	CEA ,Markov Model ,Payer, Lifetime	Rivaroxaban Acenocoumarol	AF	Rivaroxaban: 6.50 VKA: 6.28	Rivaroxaban: €7868 VKA: €8107	Rivaroxaban dominant versus VKA
Krejczy 2013	Germany	The aim of this investigation was to examine cost-utility for current German drug market costs and compared to other countries	CUA ,Markov ,German public healthcare insurance, 20 years	Dose adjusted warfarin Dabigatran 110 mg and 150 mg Rivaroxaban 20 mg Apixaban 20 mg	Atrial fibrillation patients at medium or high risk of stroke in a Norwegian setting	• Dabigatran 110mg vs warfarin : Warfarin 7.64 QALY Dbigatran 7.68 QALY • Dabigatran 150mg vs warfarin : Warfarin 7.64 QALY Dabigatran 7.71 QALY • Rivaroxaban 20 mg vs warfarin : Warfarin 7.64 QALY Rivaroxaban 7.71 QALY • Apixaban vs warfarin warfarin 7.56 QALY Apixaban 7.75 QALY	• Dabigatran 110mg vs warfarin : Warfarin 7622 euro Dabigatran 110 mg 20048 Euro • Dabigatran 110mg vs warfarin : Warfarin 7622 euro Dabigatran 150 mg 19537 Euro • Rivaroxaban 20 mg vs warfarin : Warfarin 9069 euro Rivaroxaban 19874 euro • Apixaban vs warfarin warfarin 8915 euro Apixaban 19885 euro	• Dabigatran 110mg vs warfarin : 294349 euro/QALY • Dabigatran 150mg vs warfarin : 163184 euro/QALY • Rivaroxaban 20 mg vs warfarin: 133926 euro/QALY • Apixaban 5mg vs warfarin: 57245 euro/QALY
Langkilde 2012	Denmark	To estimate the economic implications of introducing dabigatran etexilate ('dabigatran') for anti-coagulation therapy in Danish patients with non-valvular atrial fibrillation based on results of the RE-LY trial.	CEA ,Markov Model ,Healthcare provider, Lifetime	Dabigatran (150 mg and 110 mg) Warfarin	Modelled cohort of 10,000 patients with a similar risk profile (described by CHADS2) to the patients aged 80 or below included in the RE-LY trial.	Dabigatran: 8.59 Warfarin: 8.32	Dabigatran: €18 752 Warfarin: €16 886	Dabigatran vs Warfarin: €6 950

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
Lanitis 2014	Sweden	The aim of this study was to assess the economic implications of apixaban against warfarin and aspirin in these patients from a Swedish societal perspective.	CEA ,Markov ,Societal, Lifetime	Apixaban Warfarin Aspirin	Patients with AF in Sweden	Warfarin suitable: Warfarin: 6.51 Apixaban: 6.71 Warfarin unsuitable: Aspirin: 6.41 Apixaban: 6.70	Warfarin suitable: Warfarin: 116,463 SEKs Apixaban: 123,361 SEKs Warfarin unsuitable: Aspirin: 113,216 SEKs Apixaban: 125,400 SEKs	Swedish kronor per quality-adjusted life year gained Warfarin suitable population vs. warfarin 33,458 Warfarin unsuitable population vs. aspirin 41,453
Lanitis 2014	France	To conduct an economic evaluation of the currently prescribed treatments for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) including warfarin, aspirin, and novel oral anticoagulants (NOACs) from a French payer perspective.	CEA ,Markov ,Payer, Lifetime	Dose adjusted warfarin Aspirin Apixaban 5mg BID Dabigatran 110 mg BID Dabigatran 150 mg BID and switch to 110 mg BID at the age of 80 years Dabigatran 150 mg BID Rivaroxaban 20 mg	Patients with NVAF eligible for stroke preventive treatment	Displayed vs warfarin dose adjusted warfarin Aspirin: 0.074 Apixaban 5mg BID: 0.190 Dabigatran 110 mg BID: 0.087 Dabigatran 150 mg BID and switch to 110 mg BID at the age of 80 years: 0.121 Dabigatran 150 mg BID: 0.122 Rivaroxaban 20 mg: 0.143	Displayed vs warfarin dose adjusted warfarin Aspirin: Euros 359 Apixaban 5mg BID: Euros 2,315 Dabigatran 110 mg BID: Euros 2,682 Dabigatran 150 mg BID and switch to 110 mg BID at the age of 80 years: Euros 2,324 Dabigatran 150 mg BID: Euros 2,315 Rivaroxaban 20 mg: Euros2,507	ICERs displayed were calculated using the efficiency frontier approach. Using dose adjusted warfarin as reference Aspirin: dominated Apixaban 5mg BID: Euros 12,227 Dabigatran 110 mg BID: dominated Dabigatran 150 mg BID and switch to 110 mg BID at the age of 80 years: dominated Dabigatran 150 mg BID: dominated Rivaroxaban 20 mg: dominated
Lee 2012	USA	Determine cost-effectiveness of apixaban vs aspirin	CEA ,Markov Model ,Medicare, 10 years	Apixaban 5 mg twice daily Aspirin 81-324 mg daily	AF, a $CHADS_2$ score of 2 and a low-risk of bleeding, who initiated pharmacological stroke prevention with either apixaban (5 mg twice daily) or aspirin (81-324	Trial length model Apixaban: 0.96 Aspirin: 0.96 10-years model Apixaban: 6.87 Aspirin: 6.51	Trial length model: Apixaban $3,454 Aspirin $1,805 10-years model: Apixaban $44,232 Aspirin $50,066	Apixaban is the inferior strategy (more costly but no more effective) in the trial-length model, but the dominant one (less costly and more effective) in the 10-year model.

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
					mg daily).			
Lee 2012	USA	Estimate the costs, quality-adjusted life years (QALYs), and cost–effectiveness of rivaroxaban compared to adjusted-dose warfarin for the prevention of stroke in patients with AF.	CEA ,Markov Model ,Payer, 35 years	Rivaroxaban (15-20 mg once daily) Warfarin	AF at high-risk for stroke (congestive heart failure, hypertension, age, diabetes, stroke [$CHADS_2$] score of 3) and no contraindications to anticoagulation.	Warfarin: 9.812 Rivaroxaban: 10.027	Warfarin: $88 544 Rivaroxaban: $94 456	Rivaroxaban vs Warfarin: $27 498
Lee 2012	USA	To estimate the costs, quality-adjusted life years (QALYs), life-years saved (LYS) and cost-effectiveness of apixaban compared to adjusted-dose warfarin for the prevention of stroke in patients with AF and at least one additional risk factor for stroke.	CEA ,Markov Model ,Payer, Lifetime	Apixaban (5 mg twice daily) warfarin	AF and at least one additional risk factor for stroke.	Warfarin: 10.89 Apixaban: 11.23	Warfarin: $90 225 Apixaban: $87 592	Apixaban dominant
Leey 2009	NR	To evaluate the potential clinical and economic outcomes of genotype-guided warfarin therapy in elderly patients newly diagnosed with AF and identify a threshold in bleeding risk at which genotype-guided warfarin therapy may be cost-effective	CEA ,Decision tree ,Payer, Lifetime	CYP2C9 and VKORC1 Genotyping with warfarin strategy warfarin therapy	Elderly patients with newly diagnosed AF.	NR	Cost of testing: $250 warfarin: $832 annually However, costs of testing will be immediately offset by reduction of major bleeding	NR
Lip 2014	UK	Evaluate the cost-effectiveness of apixaban against other NOACs from the perspective of the United Kingdom National Health Services	CEA ,Markov Model ,Payer, Lifetime	Apixaban5 mg BID dabigatran 110 mg BID dabigatran 150 mg rivaroxaban 20 mg once daily	AF suitable for VKA therapy (matched to participants in ARISTOTLE)	Apixaban: 6.26 Dabigatran 110 mg: 6.16 Dabigatran 150 mg: 6.19 Rivaroxaban: 6.21	Apixaban: £9 078 Dabigatran 110 mg: £8 614 Dabigatran 150 mg: £8 424 Rivaroxaban: £8 832	Apixaban vs: Dabigatran 110 mg: £4 497 Dabigatran 150 mg: £9 611 Rivaroxaban: £5 305
Miguel 2013	USA	Estimate the cost-effectiveness and cost-utility of dabigatran in the prevention of stroke and systemic	CEA ,Markov Model ,Societal, Lifetime	Dabigatran (150 mg and 110 mg) Warfarin	NVAF	Incremental QALY Dabigatran vs warfarin: 0.354	Incremental cost Dabigatran vs warfarin: €2 978	Dabigatran vs warfarin: €8 409

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
		embolism in patients with non-valvular atrial fibrillation in Portugal.						
Morais 2014	Portugal	To project the long-term cost-effectiveness of treating non-valvular atrial fibrillation (AF) patients for stroke prevention with rivaroxaban compared to warfarin in Portugal.	CEA ,Markov model ,Societal, Lifetime	Rivaroxaban (20 mg oral tablet, once daily) Warfarin (dose-adjusted, target INR of 2.0---3.0)	Matched with the ROCKET AF: patients suffering from non-valvular AF with a $CHADS_2$ score ≥2 (mean $CHADS_2$ score 3.5), of whom 62.5% had previously been treated with VKAs.	Rivaroxaban: 3.83 Warfarin: 3.81	Rivaroxaban: 6142 Euros Warfarin: 6061 Euros	VS. warfarin: 3895 Euros / QALY
Nshimyumukiza 2013	Canada	To compare the cost/utility (CU) of three main anticoagulation options: 1) standard warfarin dosing (SD-W) 2) warfarin dosage under the guidance of CYP2C9 and VKORC1 genotyping (GT-W) and 3) dabigatran 150 mg twice a day	CEA ,Markov Model ,National Health System, 5 years	Dabigatran (150 mg) Warfarin	Virtual population newly diagnosed with AF who never had a previous stroke and who didn't have a contraindication to anticoagulation therapy.	Standard Warfarin: 3.5368 Pharma warfarin: 3.5453 Dabigatran 150 mg: 3.7897	Standard Warfarin: CA$7 289 Pharma warfarin: CA$7 749 Dabigatran 150 mg: CA$8 494	Standard Warfarin: n/a Pharma warfarin: dominated Dabigatran 150 mg: CA$4 765
Patrick 2009	USA	To evaluate under what circumstances CYP2C9 and VKORC1 genotyping before warfarin initiation could be cost-effective in our population	CEA ,Markov Model ,Societal, Lifetime	Genotyping guided warfarin Standard warfarin	Newly diagnosed AF	Warfarin (discounted): 7.28	Warfarin: $22 541 lifetime	ICER is linked with model assumptions : If the therapies help to target the INR range during the first 3 months of 5 percentage point compared to usual care, the ICER is <$100 000 per QALY; if this increase to 9 percent point, the ICER is <$50 000 per QALY; genotype guided warfarin vs. standard warfarin

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
Pink 2011	USA	Determine the incremental net health benefits of dabigatran etexilate 110 mg and 150 mg twice daily and warfarin in patients with non-valvular atrial fibrillation and to estimate the cost effectiveness of dabigatran.	CEA ,Discrete event simulation model ,Payer, Lifetime	Dabigatran (150 mg and 110 mg) Warfarin	Population modelled reflected patients in the RE-LY study. Mean baseline $CHADS_2$ score was 2.1, and 32.4% of patients had a score of 3 or more; 50.4% of patients were naive to vitamin K antagonists.	Warfarin: 6.390 dabigatran 110mg: 6.484 dabigatran 150mg: 6.536	Cost (lifetime) warfarin £6480 Dabigatran 110 mg £10 529 Dabigatran 150 mg £9850	Low dose dabigatran versus warfarin: £43 074 per QALY gained High dose dabigatran versus warfarin: £23 082 per QALY gained Dabigatran 110 mg was dominated by dabigatran 150 mg worse outcomes (−0.052 QALYs) and higher cost (£679).
Pink 2014	UK	To estimate the cost-effectiveness of a variety of clinical and pharmacogenetic dosing algorithms and compare them with those for the newer anticoagulants.	CEA ,Discrete-event simulation ,Healthcare provider, Lifetime	Apixaban Dabigatran Rivaroxaban Warfarin (genotype guided) Warfarin (clinical)	AF	Apixaban: 5.851 Dabigatran: 5.827 Rivaroxaban: 5.817 Warfarin (genotype guided): 5.724 Warfarin (clinical): 5.721	Discounted Apixaban: £8437 Dabigatran: £8426 Rivaroxaban: £9112 Warfarin (genotype guided): £5921 Warfarin (clinical): £5880	Vs genotype guided warfarin Apixaban: £19858 Dabigatran: extendedly dominated by apixaban Rivaroxaban: dominated by dabigatran and apixaban Genotype vs clinical Warfarin: £13226
Pletscher 2013	Switzerland	Evaluate the cost-effectiveness of dabigatran versus vitamin K antagonists for stroke prevention in atrial fibrillation in Switzerland.	CEA ,Markov Model ,Payer, Lifetime	Dabigatran 110 mg dabigatran 150 mg Phenprocoumon	AF	Incremental QALY gain (10,000 patients) Dabigatran 110 mg: 1 848 Dabigatran 150mg: 2 433 Sequential dose dabigatran: 2 846	Incremental costs (10,000 patients) Dabigatran 110 mg CHF 46 388 675 Dabigatran 150mg CHF 23 606 493 Sequential dose dabigatran CHF 29 073 626	Dabigatran 110 mg: CHF 25 108 Dabigatran 150mg: CHF 9 702 Sequential dose dabigatran: CHF 10 215
Rognoni C 2013	USA	The aim of this study was to estimate the cost effectiveness of NOAs in an Italian setting.	CUA ,Decision tree + Markov ,National Health System, Lifetime	Dabigatran (110 and 150 mg) Rivaroxaban (20 mg) Apixaban (5 mg) Warfarin	NVAF	Discounted $CHADS_2$ ≤1 Warfarin 11.133 Apixaban 11.890 Dabigatran 12.223 $CHADS_2$ =2 Warfarin 8.764	Discounted $CHADS_2$ ≤1 Warfarin 14,138 Apixaban 21,434 Dabigatran 22,122 $CHADS_2$ =2 Warfarin 12,801	Discounted $CHADS_2$ ≤1 Warfarin – Apixaban 9,631 Dabigatran 7,320 $CHADS_2$ =2 Warfarin –

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
						Apixaban 9.402 Dabigatran 9.587 Rivaroxaban 9.122 $CHADS_2$ ≥3 Warfarin 7.127 Apixaban 7.997 Dabigatran 7.518 Rivaroxaban 7.581	Apixaban 18,960 Dabigatran 19,065 Rivaroxaban 19,993 $CHADS_2$ ≥3 Warfarin 14,115 Apixaban 18,224 Dabigatran 18,813 Rivaroxaban 20,041	Apixaban 9,660 Dabigatran 7,609 Rivaroxaban 20,089 $CHADS_2$ ≥3 Warfarin – Apixaban 4,723 Dabigatran 12,029 Rivaroxaban 13,063
Shah 2011	USA	To compare the cost and quality-adjusted survival of various antithrombotic therapies.	CEA ,Markov Model ,Payer, 20 years	Dabigatran (150 mg) Dabigatran (110 mg) Warfarin Aspirin & Clopidogrel Aspirin	AF who had a moderate risk of stroke and no contraindication to anticoagulant therapy.	Dabigatran 150mg: 8.65 Dabigatran 110mg: 8.54 Warfarin: 8.40 Aspirin & clopidogrel: 8.32 Aspirin: 8.17	Dabigatran 150mg: $43 700 Dabigatran 110mg: $44 300 Warfarin: $23 000 Aspirin & clopidogrel: $34 000 Aspirin: $20 000	Vs. Aspirin (per QALY) Dabigatran 150mg: $50 000 Dabigatran 110mg: $66 000 Warfarin: $12 500 Aspirin & clopidogrel: $99 000 Vs. Warfarin (per QALY) Dabigatran 150mg: $86 000 Dabigatran 110mg: $150 000 Aspirin & clopidogrel: dominated
Singh 2013	USA	Assess the projected quality-adjusted survival and costs associated with the strategies of stroke prevention with warfarin, dabigatran, or LAA occlusion in patients with NVAF	CEA ,Markov Model ,Payer, Lifetime	Warfarin Dabigatran PLAAO	NVAF at risk of stroke	Undiscounted Warfarin 6.06 Dabigatran 6.17 LAA occulusion 6.23 Discounted Warfarin 4.55 Dabigatran 4.64 LAA occulusion 4.68	Undiscounted Warfarin $25 877 Dabigatran $32 143 LAA occulusion $30 936 Discounted Warfarin $21 429 Dabigatran $25 760 LAA occulusion $27 003	Undiscounted ICER vs Warfarin Dabigatran dominated LAA occulusion $30 813 Discounted ICER vs Warfarin Dabigatran $46 560 LAA occulusion $30 256
Sorensen 2011	Canada	To assess the cost-effectiveness of dabigatran etexilate	CEA ,Markov Model ,Payer, Lifetime	Dabigatran (150 mg and 110 mg) Warfarin	AF plus at least one additional risk factor for stroke or embolism, or with impaired LVEF, all eligible for anticoagulation	Warfarin: 7.08 Dabigatran: 7.29	Warfarin: CA$42 946 Dabigatran: CA$45 124	Dabigatran vs warfarin: CA$10 440

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
					treatment (naïve or experienced), but assumed not to be on any concomitant anticoagulation medication.			
Stevanovic 2014	Netherlands	To estimate the cost-effectiveness of apixaban compared to VKAs in non-valvular AF patients in the Netherlands.	CEA ,Markov ,Payer, Lifetime	Apixaban VKAs	NVAF patients whose characteristics were comparable to those in the ARISTOTLE trial in the Netherlands. Patients were predominantly male, aged 70 years, with an average $CHADS_2$ score of 2.3 and a history of previous VKA use	VKA: 7.00 Apixaban: 7.18	VKA 18 353 Euros Apixaban 20 205 Euros	Apixaban compared to VKA: 10,529 Euros
Sullivan 2006	USA	To estimate the lifetime societal costs and health benefits of warfarin therapy to prevent strokes, specifically in elderly patients (mean age 70 years) with atrial fibrillation who are at high risk of stroke, when anticoagulation is managed through usual care versus anticoagulation management services.	CEA ,Semi-markov decision model ,Societal, 10 years	Warfarin Anticoagulation management service	Elderly AF	Anticoagulation monitoring service: 6.617 Usual Care: 6.559	Anticoagulation monitoring service: $8 661 Usual Care: $10 746	Anticoagulation monitoring service dominated Usual Care
Vallejos 2014	Chile	The main objective in this study is to assess the incremental cost-utility ratio of apixaban vs acenocoumarol in patients with a diagnosis of NVAF and moderate-to-severe risk of embolism.	CUA ,Markov ,Payer, Lifetime	Acenocoumarol Apixaban	Chilean adult patients with NVAF and moderate-to-high risk of embolism ($CHADS_2$ score ≥1), who were	Acenocoumarol 6.338 Apixaban 6.875	Acenocoumarol $1,684,820.6 Apixaban $3,634,279.5	Apixaban vs. Acenocoumarol 3,633,622

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
					treated in the public health system and had no contraindications for the use of oral anticoagulants.			
Wisloff 2014	Norway	The objective of this study was to evaluate the relative cost effectiveness of warfarin, dabigatran, rivaroxaban, and apixaban in a Norwegian setting.	CEA ,Markov ,The Norwegian publicly financed healthcare system, Lifetime	Apixaban Dabigatran 110mg BID Rivaroxaban Warfarin	Atrial fibrillation patients at medium or high risk of stroke in a Norwegian setting	Warfarin 5.706 Sequential dabigatran 5.852 Apixaban 5.859 Rivaroxaban 5.810 Dabigatran 110 mg 5.806	Warfarin 47,498 Sequential dabigatran 49,821 Apixaban 50,402 Rivaroxaban 50,611 Dabigatran 110 mg 54,104	Vs. warfarin (Euros / QALY) Sequential dabigatran 15,920 Apixaban 18,955 Rivaroxaban 29,990 Dabigatran 110 mg 66,121
Wouters 2013	Belgium	To assess the cost-effectiveness of dabigatran etexilate ('dabigatran') vs vitamin K antagonists (VKAs) in the Belgian healthcare setting for the prevention of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (AF).	CEA ,Markov Model ,Payer, NR	Dabigatran (150 mg and 110 mg) Warfarin	AF patients whose baseline characteristics match those of the patients aged below 80 included in the RE-LY trial ($CHADS_2$ scores: 0 (3.0%), 1 (32.6%), 2 (34.4%), 3 (19.5%), 4 (7.7%), 5 (2.4%) and 6 (0.4%)	Dabigatran: 9.51 Warfarin: 9.19	Dabigatran: €13 333 Warfarin: €12 454	Dabigatran vs Warfarin: €2 807/QALY
Wu 2013	China	To compare the lifetime cost and effectiveness of five alternative chronic atrial fibrillation (AF) management strategies: rivaroxaban, warfarin, aspirin plus clopidorgel, aspirin, and no prevention	CEA ,Microsimulation , Healthcare provider, Lifetime	Rivaroxaban Warfarin Aspirin Aspirin/Clopidogrel No treatment	ROCKET AF	$CHADS_2$ score 0 No treatment: 10.440 Aspirin: 10.08 Aspirin plus clopidogrel: 9.91 Warfarin: 9.8 Rivaroxaban: 10.34 $CHADS_2$ score 1 No treatment: 9.82 Aspirin: 9.68	$CHADS_2$ score 0 No treatment: $3 515 Aspirin: $5 813 Aspirin plus clopidogrel: $16 627 Warfarin: $7 532 Rivaroxaban: $109 940 $CHADS_2$ score 1 No treatment: $3 837	$CHADS_2$ score 0 No treatment: -$1 064 250 Aspirin: $400 488 Aspirin plus clopidogrel: $217 007 Warfarin: $189 644 Rivaroxaban: NA $CHADS_2$ score 1 No treatment: $492 352 Aspirin: $289 700

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
						Aspirin plus clopidogrel: 9.68 Warfarin: 9.5 Rivaroxaban: 10.03 $CHADS_2$ score 2 No treatment: 9.15 Aspirin: 9.19 Aspirin plus clopidogrel: 9.25 Warfarin: 9.22 Rivaroxaban: 9.75 $CHADS_2$ score 3 No treatment: 8.83 Aspirin: 9.05 Aspirin plus clopidogrel: 9.12 Warfarin: 9.24 Rivaroxaban: 9.69 $CHADS_2$ score 4 No treatment: 7.86 Aspirin: 8.2 Aspirin plus clopidogrel: 8.46 Warfarin: 8.63 Rivaroxaban: 9.13 $CHADS_2$ score 5 No treatment: 6.09 Aspirin: 6.56 Aspirin plus clopidogrel: 6.97 Warfarin: 7.35 Rivaroxaban: 7.66 $CHADS_2$ score 6	Aspirin: $5 836 Aspirin plus clopidogrel: $16 413 Warfarin: $7 427 Rivaroxaban: $107 231 $CHADS_2$ score 2 No treatment: $4 203 Aspirin: $6 095 Aspirin plus clopidogrel: $16 291 Warfarin: $7 439 Rivaroxaban: $105 034 $CHADS_2$ score 3 No treatment: $4 785 Aspirin: $6 871 Aspirin plus clopidogrel: $16 397 Warfarin: $7 982 Rivaroxaban: $105 305 $CHADS_2$ score 4 No treatment: $5 158 Aspirin: $6 668 Aspirin plus clopidogrel: $15 777 Warfarin: $7 737 Rivaroxaban: $99 835 CHADS2 score 5 No treatment: $5 097 Aspirin: $6 128 Aspirin plus clopidogrel: $13 350	Aspirin plus clopidogrel: $259 480 Warfarin: $188 309 Rivaroxaban: NA $CHADS_2$ score 2 No treatment: $168 052 Aspirin: $176 677 Aspirin plus clopidogrel: $177 486 Warfarin: $184 142 Rivaroxaban: NA $CHADS_2$ score 3 No treatment: $116 884 Aspirin: $153 944 Aspirin plus clopidogrel: $155 979 Warfarin: $216 273 Rivaroxaban: NA $CHADS_2$ score 4 No treatment: $74 549 Aspirin: $ 100 180 Aspirin plus clopidogrel: $125 460 Warfarin: $184 196 Rivaroxaban: NA CHADS2 score 5 No treatment: $50 467 Aspirin: $71 093 Aspirin plus clopidogrel: $102 870 Warfarin: $250 248 Rivaroxaban: NA CHADS2 score 6

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
						No treatment: 3.33 Aspirin: 3.6 Aspirin plus clopidogrel: 3.81 Warfarin: 3.93 Rivaroxaban: 4.08	Warfarin: $6 753 Rivaroxaban: $84 330 $CHADS_2$ score 6 No treatment: $2 945 Aspirin: $2 962 Aspirin plus clopidogrel: $6 645 Warfarin: $2 662 Rivaroxaban: $42 870	No treatment: $53 233 Aspirin: $83 142 Aspirin plus clopidogrel: $134 167 Warfarin: $268 053 Rivaroxaban: NA
You 2012	NR	The cost-effectiveness of dabigatran versus warfarin therapy with genotype-guided management in patients with atrial fibrillation (AF).	CEA ,Markov Model ,Payer, 25 years	Genotype guided Warfarin Dabigatran (110 mg and 150 mg)	High risk for stroke ($CHADS_2$ score of 2 or higher)	Genotype guided warfarin: 9.554 Usual warfarin: 9.444 Dabigatran 150 mg: 10.065 Dabigatran 110 mg: 10.026	Genotype guided warfarin: $85 627 Usual warfarin: $90 481 Dabigatran 150 mg: $92 684 Dabigatran 110 mg: $102 536	Genotype guided warfarin: n/a Usual warfarin: dominated by genotype guided warfarin Dabigatran 150 mg: $13 810 Dabigatran 110 mg: dominated by dabigatran 150 mg
You 2013	USA	Compare the clinical and economic outcomes of pharmacogenetic-guided selection of warfarin and NOACs vs usual AF patients from the US healthcare payer perspective	CUA ,Markov Model ,Payer, 25 years	Usual AC (warfarin) PG-CA patients (NOACs or warfarin)	65 year-old patients with newly diagnosed AF	Usual AC 9.721 PG-AC 9.912	Usual AC $93853 PG-AC $94396	Usual AC - PG-AC $2843
You 2014	NR	To evaluate the cost-effectiveness of NOACs compared to warfarin therapy at various levels of TTR in patients with atrial fibrillation from the healthcare provider perspective.	CUA ,Markov Model ,Healthcare provider, Lifetime	Dabigatran 150 mg twice daily NOACs(Apixaban 5 mg twice daily, Rivaroxaban 20 mg once daily, or Standard warfarin therapy)	Patients with AF with $CHADS_2$ >= 2	TTR=60%: 9572 TTR=70%: 9666 TTR=75%: 9713	TTR=60%: No increment cost: $84274 1.5 fold: $86046 2 fold: $87819 2.5fold: $89592 3fold $91365 TTR=70%: No increment: $80241 1.5fold: $82051 2fold: $83861 2.5fold: $85671 3fold: $87482	TTR=60%: No increment: $35804 1.5fold: $31352 2fold: $26897 2.5fold $22442 3fold: $17987 TTR=70% No increment: $60141 1.5fold: $54188 2fold: $48234 2.5fold: $42280 3fold: $36322 TTR=75%:

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
							TTR=75%: No Increment: $78152 1.5fold: $79981 2fold: $81810 2.5fold: $83639 3fold: $85469	No increment: $79268 1.5fold: $72152 2fold: $65035 2.5 fold: $57918 3fold: $50798
Conference proceedings								
Cowper 2014	USA	Assess the cost-effectiveness of apixaban versus Warfarin	CEA, US health care system, Lifetime	Apixaban (5 mg, twice daily) Warfarin (target international normalized ratio, 2.0 to 3.0)	ARISTOTLE	Not reported	Apixaban 5mg $29,447 warfarin $11,883	Not reported
Dorian 2012	UK	Evaluate the potential cost effectiveness of apixaban against warfarin and ASA from the perspective of the UK National Health Services (NHS).	CEA, Markov model , Payer, life-time	Apixaban (5 mg, bid) Warfarin (5mg, average) Aspirin (150 mg)	Patients with atrial fibrillation (AF)	Warfarin Suitable population VS. warfarin apixaban ΔQALY over lifetime 0.17 Warfarin unsuitable population VS. aspirin apixaban ΔQALY over lifetime 0.22	Warfarin Suitable population VS. warfarin apixaban ΔCosts over lifetime = £3,148 Warfarin unsuitable population VS. aspirin apixaban ΔCosts over lifetime = £2,622	Warfarin Suitable population VS. warfarin apixaban ΔICER over lifetime = £18,151/QALY Warfarin unsuitable population VS. aspirin apixaban £12,136/QALY
Lip 2014	USA	Evaluate the potential cost effectiveness of apixaban 5mg BID against dabigatran 150mg BID and rivaroxaban 20mg QD from the perspective of the US health care payer.	CEA, Markov Model, Third-party payer, Lifetime	Apixaban (5mg, BID) Dabigatran (150mg, BID) Rivaroxaban (20mg, QD)	ARISTOTLE and AVERROES	Incremental QALYs VS. dabigatran: Apixaban 0.082 VS. rivaroxaban Apixaban 0.053	Incremental costs VS. VS. dabigatran: Apixaban $2479 VS. rivaroxaban Apixaban -$861	VS. dabigatran: Apixaban -$861 VS. rivaroxaban Apixaban dominant
Magnuson 2014	USA	Evaluate the economic value of edoxaban versus Warfarin	CEA, Markov Model, Lifetime	High dose edoxaban (60 mg, once-daily) low dose edoxaban (30 mg, once-daily) Warfarin (target international normalized ratio, 2.0 to 3.0)	ENGAGE AF-TIMI 48	Edoxaban 60 mg 7.249 warfarin 6.910	Edoxaban 60 mg $42,846 warfarin $27,094	VS. Warfarin Edoxaban 60 mg $46,393 Edoxaban 30 mg $67,320

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
Mearns 2014	USA	Assess the cost-effectiveness of high-dose edoxaban compared to adjusted-dose warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF).	CEA, Markov Model, Payer, life-time	High dose edoxaban (60 mg, once-daily) low dose edoxaban (30 mg, once-daily) Warfarin (target international normalized ratio, 2.0 to 3.0)	Patients with non-valvular atrial fibrillation (NVAF)	Edoxaban 60 mg 10.32 Warfarin 10.12	Edoxaban 60 mg $100,223 Warfarin 111,719	Not reported
Salata 2014	USA	Assess the cost perspectives of each payer (Medicare and patient) in relation to administration, monitoring and adverse outcomes for each medication.	CEA, Markov Model, payer (Medicare and patient), 35 years or lifetime	Dabigatran (150 mg, twice daily) Warfarin (target international normalized ratio, 2.0 to 3.0)	Patients 65 years of age and older with atrial fibrillation	Patients with Medicare Part D coverage Dabigatran 150 mg 11.22 Warfarin 10.74	From Medicare's perspective: -with Part D coverage: Dabigatran 150 mg $76,237 Warfarin $59,684 -without Part D coverage: Dabigatran 150 mg $45,421 Warfarin $59,284 From the patient's perspective -with Part D coverage: Dabigatran 150 mg $28,876 Warfarin $33,466 -without Part D coverage: Dabigatran 150 mg $59,692 Warfarin $33,866	From Medicare's perspective: -with Part D coverage: VS. warfarin Dabigatran 150 mg $34,707 -without Part D coverage: VS. warfarin Dabigatran 150 mg -29,065 From the patient's perspective -with Part D coverage: VS. warfarin Dabigatran 150 mg -$9,624 -without Part D coverage: VS. warfarin Dabigatran 150 mg $54,147
Sorensen 2012	USA	Investigate the cost-effectiveness of dabigatran 150mg bid versus rivaroxaban.	CEA, Markov Model, Payer, Lifetime	Dabigatran (150mg, bid) Rivaroxaban (20 mg, once day)	Patients with non-valvular atrial fibrillation (NVAF)	Dabigatran 6.54 Rivaroxaban 6.38	Dabigatran $36,649 Rivaroxaban $37,184	Dabigatran economically dominant to rivaroxaban

Study	Country	Objective	Analysis method, model type perspective, time horizon	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
Soyon Lee 2012a	USA	Assess the cost-effectiveness of rivaroxaban.	CEA, Markov model, Payer (Medicare), lifetime	Rivaroxaban 20 mg Adjusted-dose warfarin	Patients with non-valvular atrial fibrillation (NVAF)	Raviroxaban 10.28 Warfarin 10.07	Raviroxaban $83,415 Warfarin $78,160	VS. Warfarin Raviroxaban 25,024 $/QALY
Soyon Lee 2012b	USA	Estimate the costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness of apixaban compared to aspirin in patients with atrial fibrillation (AF).	CEA, Markov model, Payer (Medicare), 35 years	Apixaban (5 mg, bid) Aspirin (between 81-324 mg)	Patients with non-valvular atrial fibrillation (NVAF)	Apixaban 9.94 Aspirin 8.86	Apixaban $92,087 Aspirin $109,654	Apixaban is a dominant economic strategy.

7.1.3 **Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)5 or Philips et al. (2004)6. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.**

A quality assessment for each cost-effectiveness study is provided in Section **Error! Reference source not found.**.

7.2 De novo analysis

Patients

7.2.1 **What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.**

The population included in the base case economic evaluation reflects the licensed population, i.e. adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. This also reflects the population from ENGAGE AF-TIMI 48, which included patients with a history of non-valvular atrial fibrillation (AF) within the prior 12 months and a moderate to high risk of stroke, as defined by a $CHADS_2$ index score of at least 2.

In the cost-effectiveness analysis, the base case considered patients with AF with a $CHADS_2$ score ≥ 2. The analysis is designed in this way because of the risk profile of patients entering the ENGAGE AF-TIMI 48 study and the other pivotal studies of NOACs; ROCKET-AF and ENGAGE enrolled patients with $CHADS_2$ ≥ 2, whereas RE-LY and ARISTOTLE enrolled patients with $CHADS_2$ ≥ 1. To minimise potential biases resulting from differences in patient clinical characteristics among the trials, only data from patients with $CHADS_2$ ≥ 2 in RE-LY and ARISTOTLE were used in the network meta-analyses that were used to estimate relative treatment effects of the four NOACs. The risk profile of the starting patient population in the cost-effectiveness model is identical to that of the ENGAGE study (i.e. no patients with $CHADS_2$ scores of 0 or 1).

---

[5] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[6] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

The distribution of patients in the ENGAGE AF-TIMI 48 trial with each $CHADS_2$ score at baseline can be compared with the characteristics of patients in the PREFER in AF registry, which includes patients from 7 European countries, including the UK.

Table 42: CHA_2-DS_2-VAS(c) score of patient population in PREFER In AF registry

CHA_2DS_2VASc score	**UK**		**All countries**	
	ENGAGE AF – TIMI 48, n (%)	**PREFER in AF, n (%)**	**ENGAGE AF – TIMI 48, n (%)**	**PREFER in AF, n (%)**
	N=400	N=1194	N=21005	N=7228
Score collected (n)	400	1116		6585
Score not collected or missing (n)		78		643
0	0 (0)	205 (18.4)	1 (<0.1)	811 (12.4)
1	0 (0)	302 (27.2)	15 (<0.1)	1779 (27.1)
2	209 (52.3)	303 (27.2)	9876 (46.8)	2026 (30.9)
3	128 (32.0)	188 (16.9)	6445 (30.5)	1148 (17.5)
4	45 (11.3)	83 (7.5)	3279 (15.5)	544 (8.3)
5	16 (4.0)	28 (2.5)	1230 (5.8)	195 (3.0)
6	2	(0.3)	259	(0.8)

The model uses the patient characteristics from the ENGAGE AF-TIMI 48 trial; the average age of patients in the model is 71 years old, and it is assumed that the proportion of male patients is 62.29%. The base case results include all patients with a $CHADS_2$ score greater than or equal to two.

In addition to the base case, the following patient populations are modelled in separate scenario analyses:

- Patients with $CHADS_2$ score ≥3;
- Patients with time in therapeutic range (cTTR) ≥ 60%;

TTR for warfarin-treated subjects measured in the ENGAGE AF-TIMI 48 trial was based on international normalised ratio (INR) ranges (2.0 to 3.0 inclusive). Subjects in the trial were stratified based on INR-TTR, including the percent of subjects above or below the median INR-TTR, and the percentage of subjects dichotomized by with various thresholds of cTTR boundaries such as quartile boundaries and means observed in the prior three NOAC vs warfarin trials. Centre-TTR was used to stratify patients in the subgroup analysis included in the model.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A Markov cohort model was developed in Excel®, consisting of 18 health states, with one-month cycles and 30-year (remaining lifetime) time horizon. The health states were defined by the clinical events experienced by the patient. All patients start in the "Stable AF" health state at Cycle 0.

Clinical outcomes were classified either as model health states or as events (See Figure 22). Health states were associated with the clinical outcomes that were considered to have a permanent impact on patients, and were assumed to be associated with an initial impact, as well a long-term impact on costs, quality of life and mortality. In contrast to the health states, clinical outcomes modelled as events were not associated with a long-term impact on costs or quality or life.

The model's health states were defined by the events considered to have a permanent impact on patients, and included haemorrhagic and ischaemic stroke (HS and IS), systemic embolism (SE) and myocardial infarction (MI) events. Since these events were assumed to be associated with both an initial impact and a long-term impact on outcomes, health states were further subdivided into an initial health state where costs and quality of life associated with the acute event and the case fatality rate were applied, and a long-term health state, where ongoing event costs, quality of life and mortality were applied per monthly cycle. The initial cycle refers to the first (one-month) cycle after the patient experienced the event. If the patient survived, they moved to the post-event health state, where they remained until they transitioned to another health state.

Events included other intracranial haemorrhage (ICH), non-ICH major bleeds, clinically relevant non-major bleeds (CRNMBs), and transient ischaemic attack (TIA). In the model, these events incurred costs and a disutility for the length of the event (described in Section 7.4.9). Patients were at risk of experiencing an event whilst in each (initial and post-event) health state of the model (except death), and the monthly probability of each event was applied in each cycle of the model to these patients. A patient entering an initial health state can also experience an event in the same model cycle (i.e. two events can be experienced in the same model cycle, one having a temporary impact, and the other having a more permanent impact on the patient). Events can be considered to be analogous to the concept of adverse events implemented in other economic models, in that all patients on-treatment are at risk of the event, they are associated with a short-term impact on outcomes, and are not

represented with a distinct health state since they can be experienced while in any other health state in the model.

In addition, patients in the model were able to experience any clinical outcome more than once (henceforth referred to as recurrent events), or more than one type of clinical outcome over the timeframe of the model. It was assumed that patients were only able to move to a health state considered to be more severe than their previous health state. Patients in the severe stroke health states may only transition to the initial severe stroke health state (in addition to death); patients in the moderate stroke health state can transition to the moderate or a severe stroke health states. Patients in the SE health state can transition to the SE, moderate or severe stroke initial health states; and patients in the MI health state can transition to the MI, a SE, moderate or severe stroke initial health states. Patients in the post-mild stroke health states faced a probability of transitioning to all other initial health states. The risk of recurrent haemorrhagic stroke (HS) and ischaemic stroke (IS) was assumed to be higher than the risk of the first stroke. The number of recurrent strokes was limited in previous technology appraisals (one recurrent stroke per patient, TA275 [51]); however based on the critique provided by the Evidence Review Group of that appraisal, it was decided that the model would be developed without a limit on the number of events that could be experienced. [73]

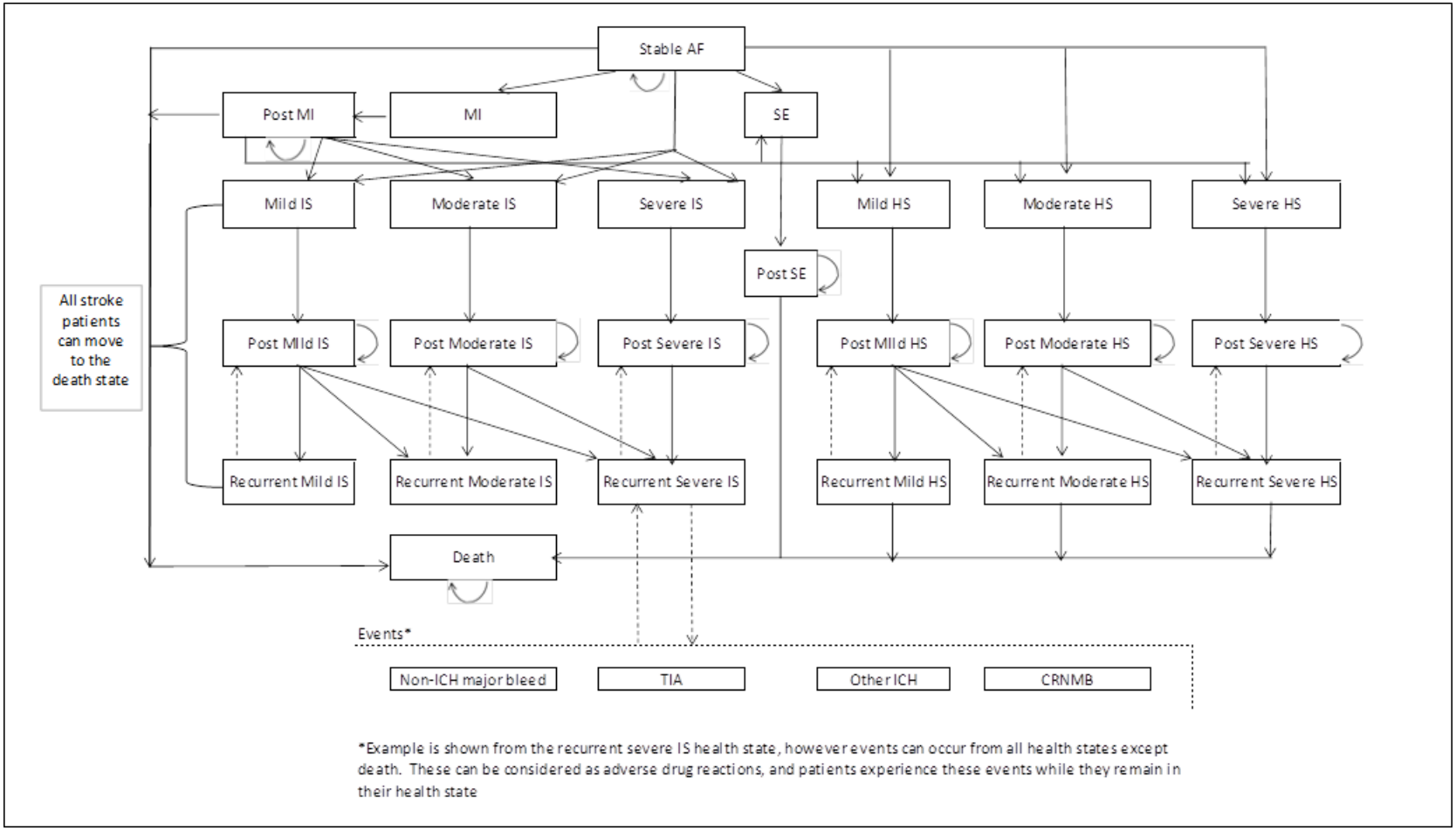
Patients were also able to discontinue treatment (permanently or temporarily) and switch to another treatment option. The type of discontinuation post-stroke was dependent upon the treatment. Warfarin patients experiencing an HS temporarily discontinued, with some patients switching to a different line of therapy, while 50% of NOAC patients permanently discontinue treatment. All warfarin patients experiencing an IS will temporarily discontinue with all patients restarting on a NOAC, and 50% of NOAC patients experiencing an IS will temporarily discontinue and resume treatment with a NOAC, with the remainder of patients permanently discontinuing treatment.

Patients entering the SE and MI health states were not at risk of treatment discontinuation, and similarly patients experiencing an event were also not at risk of treatment discontinuation.

Details of discontinuation assumptions are described in section 7.3.6.

The health states are described in more detail in section 7.2.3.

Figure 22: Economic model diagram



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The cost-effectiveness model was structured in order to capture the main thrombotic events associated with AF and the adverse events that can occur as a result of treatment, as well as the all-cause and event-related mortality risk for this patient group. The mortality risk is related to the patient age and background risk of mortality, as well as the health state that the patient is in; hazard ratios for stroke, SE and MI are applied to the background mortality to give an overall risk of death. Full details of how this is calculated are shown in Section 7.3.6. The costs and health consequences of each of these mutually exclusive health states were modelled using one-month cycles, i.e. patients can only be in one healh state in any given cycle, an assumption that is consistent with the most recent NICE technology appraisal for stroke prevention in AF. [51] It was also possible for patients in any health state except death to experience an event (bleeding or TIA) that was associated with an impact on costs and utilities for a period not exceeding the duration of one cycle. AF is a predominantly lifelong chronic condition. Therefore, a 30-year (remaining lifetime) time horizon was used in order to capture all relevant factors. Clinical outcomes in the model included thrombotic events and treatment-related adverse events, and were modelled as either health states or events. Associated costs and quality of life values were captured in order to calculate cost and utility estimates. Future costs and utilities were discounted to present values, in line with the NICE reference case.

7.2.4 Please define what the health states in the model are meant to capture.

Table 43 presents a description of the health states in the model.

Table 43: 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) Initial health state (patients stay in this health state for one cycle only before transitioning to the post-IS health state.
Post-IS	Patients who have experienced a mild, moderate or severe ischaemic stroke in a previous model cycle.
HS	Patients who are experiencing a haemorrhagic stroke. Separated into mild (Rankin score of 0-2), moderate (Rankin score of 3-4) and severe (Rankin score of 5-6). Initial health state (patients stay in this health state for one cycle only before transitioning to the post-HS health state.

Health State / Event	Description
Health states	
Post-HS	Patients who have experienced a mild, moderate or severe haemorrhagic stroke in the previous model cycle.
SE	Patients who are experiencing a systemic embolism. Initial health state (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 in a previous cycle of the model.
MI	Patients who are experiencing a myocardial infarction. Initial health state (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 in a previous cycle of the model.
Death	Terminal state; patients can die due to the events captured in the model and due to all-cause mortality.
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.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Anticoagulation treatment is associated with a reduction in the risk of thrombotic events and increased risk of bleeding. Relevant health states were included in the model to capture the benefits and risks of the treatment.

Disease progression was not explicitly modelled; the risk of AF does not increase purely as a function of time spent with AF (further details are provided in section 7.3.3). Rather, AF is a condition that increases the risk of a thrombotic event, and as such the risk progression was modelled over the course of the model. Risks of events were adjusted by elements of the $CHADS_2$ score, such as the cohort age, as the age of the patient is a risk factor for stroke.

Health states

Health states in the model are associated with the clinical outcomes considered to have a permanent impact on the patient, and are categorised as being eitheran initial health state of one cycle (the cycle in which the event occurs) where the immediate cost, mortality and QoL impact is incorporated, and a post-event health state where the long-term cost, mortality and QoL impacts are modelled. Patients remain in the post-event health state until they transition to either the death health state, or the initial health state of another clinical outcome (this is described fully in Section 7.2.2). Patients were assumed to be at risk of a recurrent event in each cycle of the model (i.e. a patient may experience two SE events, or a stroke followed by SE event in two consecutive cycles).

Stroke and SE are potential clinical outcomes for patients with AF, and were therefore components of the primary efficacy endpoint in the ENGAGE AF-TIMI 48 trial and considered in the model. Stroke and SE are considered separately within the model. Stroke events are separated into ischaemic and haemorrhagic strokes, and further divided into mild, moderate and severe categories. This was incorporated in order to more accurately estimate costs and utilities associated with the different classifications of strokes. Mild strokes were defined as those with a modified Rankin score of 0 to 2, moderate with a score of 3 to 4, and severe with a score of 5 to 6. The proportion of patients in each group at baseline was extracted from the full analysis dataset of the ENGAGE AF-TIMI 48 trial.

MI was an endpoint in the ENGAGE AF-TIMI 48 trial, and was included in the model as different interventions for stroke prevention in AF may also have an impact on the risk of MI.

Events

In the model, clinical outcomes that were not considered to be associated with long-term consequences (other ICH, non-ICH major bleed, TIA and CRNMB) were modelled as events that incurred costs and a disutility for the length of the event (presented in Section 7.4.9). Further details are provided in Section 7.2.2.

The primary safety endpoint in the ENGAGE AF-TIMI 48 trial was major bleeding (MB). Bleeding events were reported as MB or CRNMB. Anticoagulant therapy can heighten the risk that bleeding events, including ICH will occur.

An ICH is defined as bleeding that occurs when a blood vessel within the skull is ruptured or leaks blood. While a haemorrhagic stroke is technically an ICH, the model considers haemorrhagic strokes separately from other ICHs, owing to assumed differences in outcomes associated with each type of event. Haemorrhagic strokes were assumed to have a long-term impact on outcomes and were modelled as a distinct health state (HS), while ICH was only assumed to impact on short-term outcomes. This event is referred to other-ICH in the model.

A TIA is caused by a temporary disruption in the blood supply to part of the brain. The disruption in blood supply results in a lack of oxygen to the brain. This can cause symptoms similar to those of a stroke, such as speech and visual disturbance and

numbness or weakness in the arms and legs. However, a TIA does not result in permanent damage, either due to the blood flow re-establishing itself within the affected vessel or due to collateral circulation early enough to avoid damage. The effects may range from a few minutes to a few hours, and are usually fully resolved within 24 hours.

CRNMBs are defined as clinically overt bleeding that does not meet the criteria for MB, but requires medical attention or a change in therapy. By definition, CRNMBs are not fatal.

Non-ICH major bleeds refer to all extracranial MBs, such as major GI bleeds and intraocular bleeds.

7.2.6 **Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.**

Table 44: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime	To capture the lifetime clinical and cost outcomes of patients with AF	NICE reference case
Cycle length	1 month	To reflect the potential frequency of clinical outcomes represented in the model and to capture the associated costs and outcomes	Clinical expert opinion, consistent with previous SPAF technology appraisals
Half-cycle correction	Applied	In line with good practice in modelling	NICE reference case
Were health effects measured in QALYs; if not, what was used?	Yes	To capture the health outcomes of patients with AF	NICE reference case
Discount of 3.5% for utilities and costs	Yes	NICE reference case	NICE reference case
Perspective (NHS/PSS)	NHS Perspective	NICE reference case	NICE reference case

Abbreviations: NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years

7.2.7 **Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?**

Edoxaban is implemented as per its expected marketing authorization.

The comparators are implemented in the model according to their marketing authorisations and doses.

Table 45: Intervention and comparators

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

Abbreviations: BD: Twice daily; DR: Dose reduced; OD: once daily

The method for modelling the dabigatran 150mg regimen differs to those for modelling the other comparators, since it involves patients in that arm switching from one dose to another over time, with each associated with distinct event rates and drug costs. The proportion of patients under the age of 80 years is estimated in each cycle of the model, by using a cumulative normal distribution defined by the age of the cohort in the ENGAGE AF-TIMI 48 trial (further details in Section 7.3.6). Event rates and drug costs relating to each dabigatran dose are applied to the estimated proportion of patients in the cohort taking that dose. This method more accurately captures the events associated with each dose of dabigatran over the model timeline, as opposed to an alternate method where it is assumed that the starting age is fixed (at 71) and all patients receive the 150mg for 9 years and then all switch to 110mg.

7.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- **The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).**
- **The robustness and plausibility of the endpoint on which the rule is based.**
- **Whether the 'response' criteria defined in the rule can be reasonably achieved.**
- **The appropriateness and robustness of the time at which response is measured.**
- **Whether the rule can be incorporated into routine clinical practice.**

- **Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.**
- **Issues with respect to withdrawal of treatment from non-responders and other equity considerations.**

No explicit treatment continuation rule has been applied. The model considers treatment discontinuations following ischaemic and haemorrhagic strokes. The assumptions around treatment discontinuation are presented in Section 7.3.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Base case analysis

Edoxaban was used as the reference treatment in the model. Data were extracted from the ENGAGE AF-TIMI 48 trial, specifically the rates for edoxaban for the first clinical event. The number of patients and number of clinical events per month over the trial period (median follow-up, 33 months) was used to calculate the probability of each event type for each month (see Section 7.3.2 for a description of the method).

Rates for recurrent HS and IS and IS following an MI were extracted from a published study (see Section 7.3.6) and were applied to all treatment arms in the model, while the rate of recurrent events for the remaining health states were assumed equal to that of the first event and remain specific to each treatment arm [74].

In the absence of head-to-head data, a NMA was conducted to determine the relative efficacy and safety of edoxaban versus dabigatran, rivaroxaban, apixaban, and warfarin (see Section 6.7). The network was informed by the pivotal Phase III trial for each NOAC comparator, including ARISTOTLE (apixaban), ENGAGE AF-TIMI 48 (edoxaban), RE-LY (dabigatran) and ROCKET-AF (rivaroxaban). Data were also collected in the ENGAGE AF-TIMI 48 trial for warfarin; thus, there are two data sources available to provide a comparison against warfarin. Evidence from the NMA can provide an indirect comparison against warfarin, and evidence from ENGAGE AF-TIMI 48 can provide a direct comparison against warfarin. In the base case analysis, outcomes from the ENGAGE AF-TIMI 48 trial were used for a direct comparison of edoxaban with warfarin, since a direct comparison was preferable where possible, while edoxaban was compared to the other NOACs using data from the NMA, where direct evidence was not available.

In the NMA, annualised event rates for efficacy endpoints from the population assessed for the overall study period were used. Risk ratios for the following endpoints were derived:

- Stroke /SEE (composite endpoint);
- Ischaemic stroke;
- Haemorrhagic stroke;
- All stroke;

- Systemic embolic event.

For safety endpoints, annualised event rates from the safety population, assessed for the on-treatment period, were used, except for dabigatran, since safety data in the RE-LY study were reported for the ITT analysis set, Risk ratios for the following endpoints were derived:

- MB and CRNMB (composite endpoint);
- Intracranial haemorrhage;
- CRNMB;
- Any bleed;
- Major GI bleed;
- Minor bleed;
- Fatal bleeding;
- Myocardial infarction.

In addition, risk ratios for all-cause mortality, cardiovascular mortality, and discontinuations were determined in the NMA.

ROCKET-AF and ENGAGE AF-TIMI 48 enrolled patients with $CHADS_2 \geq 2$, whereas RE-LY and ARISTOTLE enrolled patients with $CHADS_2 \geq 1$; thus, only data from patients with $CHADS_2 \geq 2$ in RE-LY and ARISTOTLE were used in the base case NMA to minimise potential biases resulting from differences in patient clinical characteristics among the trials.

Hazard ratios were used in the economic model to represent the relative treatment effect of each comparator compared with edoxaban. Using a hazard ratio allows for all available data from the trial to be included in the estimation of treatment effect, including patients who do not experience an event. Alternative measures of relative treatment effect were not suitable for the analysis, such as odds ratios, since they cannot be directly applied to a probability of an event to estimate the probability for a comparator [75], or relative risks, since as they represent cumulative risk over the study period and do not account for time interval, i.e. differing trial periods.
When the NMA data were introduced to the cost-effectiveness model, it was only possible to provide a full economic analysis (i.e. containing evidence for all health states and events) for the warfarin vs edoxaban comparison.

Where HRs for the relative effects of NOACs were not available from the NMA, it was assumed that the hazard ratio was equivalent to the hazard ratio estimated in the “all patients” analysis, i.e. patients unrestricted by $CHADS_2$ score. Where there were also no available data in the “all patients” analysis, the hazard ratio was assumed to be 1. See section 6.7.5.

The base case economic analysis in the cost-effectiveness model reflects the most rigorous data set for comparative effectiveness comparisons between NOACs, as follows:

Table 46: Base case scenario

Factor	Data source/assumption
Treatment period	Lifelong
Time horizon	30 years (remaining lifetime)
Data source for edoxaban health state and event probabilities	ENGAGE AF-TIMI 48
Data source for warfarin (HRs)	Base case: ENGAGE AF-TIMI 48 Alternative scenario: NMA edoxaban vs warfarin; $CHADS_2 \geq 2$
Data source for NOACs (HRs)	NMA edoxaban vs NOAC; $CHADS_2 \geq 2$ Missing data: NMA edoxaban vs NOAC; all patients

Abbreviations: HR, Hazard ratio; NOAC, New oral anticoagulants; NMA, Network meta-analysis;

Patient subgroups

The model also included additional analyses in accordance with the NICE scope, for the following subgroups:

- Patients with $CHADS_2$ score ≥3 at baseline;
- Patients with time in therapeutic range (TTR) ≥ 60%.

Efficacy and safety data for edoxaban were sourced from the relevant subgroup of patients in the ENGAGE AF-TIMI 48 trial, with the NMA providing hazard ratios for each comparator arm. Evidence from the NMA for each population subgroup is limited, due to a lack of reported data in the relevant trials. Data availability is presented inTable 47.

Table 47: Availability of hazard ratios for subgroups from NMA

	Ischaemic stroke	Haemorrhagic stroke	Systemic embolism	Myocardial Infarction	Other ICH	TIA	Non-ICH major bleed	CRNMB
All patients								
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2$ score ≥ 2								
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2$ score ≥ 3								
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Ischaemic stroke	Haemorrhagic stroke	Systemic embolism	Myocardial Infarction	Other ICH	TIA	Non-ICH major bleed	CRNMB
cTTR > 60%								
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Baseline Risks

Baseline event probabilities for edoxaban were estimated from annual event rates observed in the ENGAGE AF-TIMI 48 trial. Annual event rates were converted to monthly probabilities. In the following equation, p refers to the monthly probability, and r refers to the annual event rate:

$$\mathrm{p} = 1 - \exp(-\mathrm{r}/12)$$

The economic model contains two methods for deriving the baseline probabilities of stroke. One option converted the annual event rates observed in the ENGAGE AF-TIMI 48 trial stroke rates each $CHADS_2$ subpopulation were estimated from ENGAGE AF-TIMI 48 trial data, and converted to a monthly probability. In the following equation, p refers to the monthly probability, and r refers to the annual event rate:

$$p = 1 - \exp(-r/12)$$

A $CHADS_2$ -adjusted monthly probability of stroke was then estimated by calculating a weighted average of the monthly probability of stroke in each $CHADS_2$ subpopulation and the proportion of patients in each $CHADS_2$ subgroup at baseline. Using a single $CHADS_2$ -adjusted rate, rather than modelling each subpopulation individually, enabled the model to use a more straightforward (but no less accurate) method to adjust the baseline event probability for age over the model time horizon.

Hazard Ratios

The impact of the comparator interventions compared with edoxaban (the reference treatment) was modelled using hazard ratios from the NMA. Hazard ratios calculated from the NMA were applied to the monthly probabilities to derive transition probabilities. In the following equation, pbaseline refers to the monthly probability for edoxaban, pcomparator refers to the monthly probability for the comparator, and HR refers to the hazard ratio for that comparator:

$$\mathrm{p_{comparator}} = 1 - (1 - \mathrm{p_{baseline}})^{\mathrm{HR}}$$

Variation of Transition Probabilities over Time

AF predisposes patients to stroke and other events in an age-dependent manner; this is reflected in the model and was confirmed by clinical expert opinion obtained at an advisory board (Section 7.3.5) and supported by published evidence, including a systematic review of risk factors for haemorrhages [76] and an analysis of risk factors for stroke of pooled data from five RCTs [77]. This has been incorporated into the economic model by way of a risk adjustment factor. To allow the risk of events to gradually increase with patients' increasing age, each factor was converted into a per cycle adjustment factor as follows:

$$Rc = Rd\hat{}(\frac{t}{10}.\frac{dy}{dw})$$

Where: R_C is the per cycle risk adjustment factor; R_d is the per decade risk adjustment factor; t is the cycle length in weeks; dy is the number of days in a year and dW is the number of days in a week. The risk factor is applied to the corresponding event probability multiplicatively.

The risk of stroke is increased after other AF-related events have been experienced. Ten-year cumulative event probabilities of stroke [74] were converted to monthly probabilities. In the following equation, pm refers to the monthly probability and pc refers to the ten-year cumulative event probability:

$$\mathrm{p_m} = 1 - \exp(\frac{1}{120}\ln(1 - \mathrm{p_m}))$$

Annual general mortality rates from UK Life Tables [78] were converted to monthly probabilities. In the following equation, p refers to the monthly probability, and r refers to the annual event rate:

$$p = 1 - \exp(-r/12)$$

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is no published evidence that event rates captured in the model should vary independently as a function of time spent with AF. Stroke risk equations that include AF as a regression coefficient have not included a term for the duration of AF. [27] A patient aged 75 with a one-year history of AF will not necessarily have a lower risk of stroke than a patient aged 75 with a ten-year history of AF. Risk of stroke is reflected in the $CHADS_2$ score, which acknowledges CHF, hypertension, age, diabetes and previous stroke as risk factors. A patient treated for AF with anticoagulation therapy does have a higher risk of bleeding events by virtue of longer treatment exposure. However, this consequence has not been included in the model as it was not possible to quantify the effect over time. Previous technology appraisals for SPAF have not included this effect.

However, the model does assume that the risk of events increases with patient age, as described in the section 7.3.2. Other-cause mortality (i.e. causes of death not due to the events captured in the model) also varied as a function of age, and was based on life table data for England and Wales. [78]

The risk of haemorrhagic and ischaemic strokes is also assumed to be higher following a previous stroke event. The risk of subsequent stroke was independent of treatment, but was adjusted for age. These data were taken from a study which considered the recurrence of stroke in patients for up to 10 years after their initial

stroke event. [74] This assumption was corroborated by clinical opinion (advisory board, Section7.3.5).

7.3.4 **Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?**

No intermediate outcome measures were included in the analysis. The end points of the clinical trials used to inform the effectiveness parameters were hard end points and not surrogate markers of disease progression or control.

7.3.5 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details**[7]:

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Expert opinion was utilised at an advisory board with the aims of validating a preliminary version of the model regarding the structure, decision problem, assumptions, parameters and outcomes.

The expert advice received was used to inform the further development of a robust economic analysis, and included:

---

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- The classification of TIA and extra cranial haemorrhage (non-ICH major bleed) as events that could occur while patients were in other health states, with no long-term impact on costs or outcomes beyond that cycle;
- Risk adjustment by age for event rates;
- Adjustment of stroke risk using $CHADS_2$ scores;
- Recurrence of events;
- Second-line treatment following discontinuation;
- The use of baseline EQ-5D utilities measured from the ENGAGE AF-TIMI 48 trial, with utilities outside the trial period taken from published literature.

Expert opinion was elicited using a qualitative technique. All opinions were collected and represented but not quantified. Clinical experts were selected by Daiichi Sankyo, and were recruited based on expertise and international reputation. Health economics (HE) experts were recommended by an external agency (Hayward Medical), given their extensive expertise within health economics and health technology appraisal experience. Three HE experts and two clinical experts were approached and recruited. There were no conflicts of interest recorded. Experts were provided with details of the pivotal trial, drafts of the model and model protocol, the NMA, key points for discussion, and a summary of past NOAC appraisals. The experts were posed the questions outlined above by a direct interview. Following discussion of the key issues by the experts, the health economists formulated an answer which was then agreed or discussed until consensus was agreed by the experts. Following a two week interlude the minutes of the meeting were circulated for clarification and approval. No discrepancies were identified and a further consensus meeting was not required.

A number of assumptions were also developed following the advice of clinical experts which was provided on an ad hoc basis. These include:

- The duration of discontinuation following a clinical event (assumptions presented in Section 7.3.6);
- Choice of anticoagulant post-stroke and post-SE (either a NOAC, warfarin or aspirin);
- Resource use associated with treatment discontinuation (i.e. anticoagulation clinic);
- Acute mortality associated with certain events (i.e. no mortality associated with CRNMB, TIA and non-ICH major bleed, Section 7.3.6).

Summary of selected values

7.3.6 **Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.**

Patient characteristics

Patient characteristics at baseline, including mean patient age, were extracted from the ENGAGE AF-TIMI 48 trial. The inputs were estimated from pooled warfarin and edoxaban 60mg arms in the ENGAGE AF-TIMI 48 trial.

Table 48: Patient characteristics

Variable	Value	95% CI	Distribution
Age (years)	70.6	52.1 to 89.1	Normal
Gender	62.29% male	NA	NA
$CHADS_2$ group	**Patients (%)**		**Distribution**
$CHADS_2$ = 0	0.0%	NA	Dirichlet a: 1, b = 14,023
$CHADS_2$ = 1	0.1%	NA	Dirichlet a: 9, b = 14,015
$CHADS_2$ = 2	46.7%	NA	Dirichlet a: 6544, b = 7480
$CHADS_2$ = 3	30.5%	NA	Dirichlet a: 4279, b = 9745
$CHADS_2$ = 4	15.7%	NA	Dirichlet a: 2195, b = 11,829
$CHADS_2$ = 5	5.9%	NA	Dirichlet a: 821, b = 13,203
$CHADS_2$ = 6	1.2%	NA	Dirichlet a: 175, b = 13,849

Table 49 to Table 57 summarise the clinical variables and values used in the model. The base or constant intervention in this model is edoxaban.

<u>Edoxaban base case event rates</u>

The monthly probability of each clinical outcome for edoxaban was estimated from event rates from the ENGAGE AF-TIMI 48 trial. These rates reflect the $CHADS_2 \geq 2$ patient population, the subgroup modelled in the base case analysis. The method of estimating the transition probabilities from the event rates is outlined in Section 7.3.2. The transition probabilities for the remaining interventions are obtained by applying the hazard ratio for the intervention to the baseline probability, as describing in Section 7.3.2, Table 51 for hazard ratios).

Stroke rates were adjusted by baseline $CHADS_2$ score. Annual rates of IS and HS for each $CHADS_2$ subgroup and the distribution of patients in each $CHADS_2$ subgroup at baseline were extracted from the ENGAGE AF-TIMI 48 trial (Section 6.3.4for patient characteristics) to estimate a weighted average stroke risk. The method is presented in Section 7.3.2. As with the other event rates, the transition probabilities for the remaining interventions are obtained by applying the hazard ratio for the intervention to the baseline probability.

The monthly probability of each event was assumed to be distributed according to a beta distribution. This distribution is a conjugate of the binomial, and is bounded by 0

and 1. The Dirichlet distribution was selected for $CHADS_2$ distribution since it is a multivariate generalisation of the beta distribution.

Table 49: Event rates for edoxaban ($CHADS_2 \geq 2$ population)

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

<u>Age-adjustment of event rates</u>

The risk of each clinical event was assumed to increase with age, and as such a per-decade risk-adjustment factor was included in the model. To allow for a continuously increasing risk in each cycle, the per-decade adjustment factor was converted to a monthly adjustment factor (described in Section 7.2.2) and applied to the baseline probability of the event (using the methodology described in section 7.3.2). An adjustment factor of 1.30 indicates that an AF patient's risk increases by 30% each decade. The risk adjustment factors are presented in Table 50, and were extracted from published literature identified in a review of previous STAs for SPAF.[51;76;77;79;80] The risk adjustment factors used in the model represent a ratio (of the risk of each event at two time points a decade apart), and the logarithm of the ratio can be assumed to be normally distributed. Therefore, the risk-adjustment factors were assumed to follow a lognormal distribution.

Table 50: Risk adjustment factor per decade

Event	Adjustment factor	95% CI (distribution)	Source
IS	1.40	1.1 – 1.8 (lognormal)	Risk Factors for Stroke, 1994 [77]
HS	1.97	1.79 – 2.16 (lognormal)	Ariesen *et al*. 2003 [76]
SE	1.29*	1.02 – 1.63 (lognormal)	Flegel *et al.* 1989 [79]
MI	1.30	NR	Freeman *et al*. 2011 [80]
Other ICH	1.97	1.79 – 2.16 (lognormal)	Ariesen *et al*. 2003 [76]
TIA	1.29*	1.02 – 1.63 (lognormal)	Flegel *et al.* 1989 [79]
Non-ICH major bleed	1.97	1.79 – 2.16 (lognormal)	Ariesen *et al*. 2003 [76]
CNRMB	1.97	1.79 – 2.16 (lognormal)	Ariesen *et al*. 2003 [76]

*5-year risk adjustment

Hazard ratios of events for comparator interventions

The hazard ratios in Table 51 are presented for the comparison of NOACS or warfarin versus edoxaban (i.e. a value greater than 1 favours edoxaban regarding that event); the hazard ratios for edoxaban in Section 6 are against warfarin.

The base case analysis used hazard ratios from the NMA analysis of patients with $CHADS_2 \geq 2$. Where there were no available data for a clinical outcome, it was assumed that the hazard ratio was equivalent to the hazard ratio estimated in the “all patients” analysis. Where there were also no available data in the “all patients” analysis, the hazard ratio was assumed to be 1.

Hazard ratios for warfarin were extracted from ENGAGE AF-TIMI 48 trial data, and hazard ratios for the other NOACs were obtained from the NMA. The hazard ratios presented in these tables were applied to the baseline event probabilities for edoxaban to generate transition probabilities for each comparator treatment, using the methodology outlined in Section 7.3.2. All hazard ratios were assumed to be distributed according to a lognormal distribution. Confidence intervals were estimated on the log-scale in the NMA, and the logarithm of the risk can, therefore, be assumed to be normally distributed.

Table 51: Clinical outcome hazard ratios for subgroups (comparators vs edoxaban)

Subgroup	IS	HS	SE	MI	Other ICH	TIA	Non-ICH major bleed	CRNMB
All patients								
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2$ score ≥ 2 (base case scenario)								
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2$ score ≥ 3								
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cTTR > 60%								
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	IS	HS	SE	MI	Other ICH	TIA	Non-ICH major bleed	CRNMB
Apixaban	[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]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Distribution of stroke severity

IS and HS were separated into mild, moderate and severe to ensure a more accurate view of the costs and health consequences of stroke events, given the wide variation in the severity of stroke.

The definitions of mild, moderate and severe stroke used in the model were based on the modified Rankin scale [81;82].

Table 52: Definitions of the severity levels of stroke based on the rankin score

Event	Rankin scale	Description
Mild stroke	0 to 2	Results in minimum residual sequelae, patients able to return to independent living
Moderate stroke	3 to 4	Requires some assistance with walking and bodily needs
Severe stroke	5 to 6	Requires inpatient rehabilitation after stabilisation and with residual sequelae that prevents patients from returning to independent living A Rankin Scale of 6 indicates a fatal stroke.

The distribution of mild, moderate and severe strokes for the model was obtained by pooling ischaemic and haemorrhagic stroke events for the high dose edoxaban (60 mg / 30 mg DR) and warfarin arms in the mITT analysis set overall study period in the ENGAGE AF-TIMI 48 trial. It was not possible to estimate the distribution of mild, moderate and severe strokes for ischaemic and haemorrhagic strokes separately, as the dataset presented the pooled data only. The proportion of patients experiencing strokes of each severity category was assumed to be constant for all interventions. The Dirichlet distribution was selected for this parameter, since it is a multivariate generalisation of the beta distribution, which creates a bound of 0 and 1 for each parameter, and it allows for a number of categories to be fit in a probabilistic manner.

Table 53: 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

Recurrent stroke

Patients in the post-HS and post-IS health states were assumed to be at increased risk of stroke. Recurrent stroke rates were based on a study of patients in the South

London Stroke Registry[74], which captured recurrence up to ten years after stroke. The study also reported increased risk of stroke in patients who have previously experienced an MI, which has also been incorporated into the economic model.

The risk of recurrent stroke was adjusted for age. The number of strokes that a patient can experience over the course of the model is limited to the number of cycles in the model (since the number of events a patient can experience per cycle is limited to one event). The distribution of stroke severity for edoxaban was then applied to all patients who had a recurrent stroke event. A beta distribution was chosen for these probabilities as it is a conjugate of the binomial and is bounded by 0 and 1.

Table 54: Risk of stroke following prior clinical events

Event	10-year cumulative risk	95% CI (distribution)	Monthly probability	Source
Stroke after MI	41.1%	29.1% to 55.8% (beta)	0.44%	Mohan *et al.* 2009 [74]
Recurrent IS	25.7%	21.9% to 29.9% (beta)	0.25%	Mohan *et al.* 2009 [74]
Recurrent HS	27.0%*	16.6% to 45.5% (beta)	0.26%	Mohan *et al.* 2009 [74]

*Includes primary intracerebral haemorrhage and subarachnoid haemorrhage

Mortality

Mortality in the model reflected both death due to clinical events and all-cause mortality. Table 55 presents the case-fatality rates associated with each health state in the economic analysis. A beta distribution was chosen for these probabilities as it is a conjugate of the binomial and is bounded by 0 and 1.

Patients experiencing an event are also at risk of death in the model. The number of patients dying is moved proportionally from the living permanent health states (e.g. Stable AF, new and post event states) to the death health state.

Table 55: Acute event-related mortality

Health state	Probability of death	95% CI (distribution)	Source
Health states			
Mild IS	0%	-	Clinical assumption from advisory board (Section 7.3.5)
Moderate IS	16.8%	13.9% to 20.1% (beta)	Janes *et al.* 2013 [83]
Severe IS	16.8%	13.9% to 20.1% (beta)	Janes *et al.* 2013 [83]
Mild HS	0%	-	Clinical assumption

Health state	Probability of death	95% CI (distribution)	Source
Moderate HS Severe HS	31.6% 31.6%	22.7% to 42.8% (beta) 22.7% to 42.8% (beta)	Janes *et al.* 2013 [83] Janes *et al.* 2013 [83]
SE	0%	-	ENGAGE AF-TIMI 48 trial
MI	13.2% (10.8 for males and 15.6% for females)	NR in source	Scarborough *et al.* 2010 [84]
Events			
Other ICH	31.6%	22.7% to 42.8% (beta)	Janes *et al.* 2013 [83]
TIA	0%	-	Clinical assumption from ad hoc advice (Section 7.3.5)
Non-ICH major bleed	0%	-	Clinical assumption from ad hoc advice (Section 7.3.5)
CRNMB	0%	-	Clinical assumption from ad hoc advice (Section 7.3.5)

Mortality rates for event survivors and for patients in the stable AF health state were estimated by applying a hazard ratio of death to general population rates. UK Life Tables provide annual mortality weights by age and gender [78], which were weighted by gender in the ENGAGE AF-TIMI 48 trial. The weighted annual mortality rate for each age was then converted to a monthly probability of death (see Section 7.3.2).

Other-cause mortality for patients with AF (who have not experienced a stroke or other events in the model) was estimated by using UK life tables as described above, and applying a hazard ratio of 1.34 to reflect the increased risk of mortality associated with AF compared to the general population. This hazard ratio was reported in a study of AF patients in Sweden by Friberg et al. [85], which was identified from a review of methods used to model background mortality in a previous STA for SPAF (TA275,[51;86]). The study was carried out in a Swedish population, and was deemed appropriate to the UK setting due to the similarities in annual mortality rates in the general population (reported as being 5% for the Swedish population). [51;86] Moreover, the Friberg et al. study had a number of features that allowed the hazard ratio to be estimated; there was a large patient population and lengthy follow-up

duration; furthermore, the number of deaths relating to both clinical events and all-cause death in the AF population and a matched general population were available. The study reported the all-cause mortality rate for each AF subtype and the total number of deaths due to stroke and MI. The all-cause mortality rates for each AF subtype were adjusted by the proportion of patients dying due to causes other than stroke and MI to generate an other-cause mortality rate. A weighted average of other-cause mortality rates were calculated, weighted by the proportion of patients in each AF subtype in the study. This was estimated to be 6.69%. The mean other-cause mortality rate for the AF population was then compared with the overall mortality rate in the general population, estimated to be 5%, resulting in a hazard ratio of 1.34 (6.69%/5% = 1.34).

For those patients who have previously experienced and survived a clinical event and are in the post-event health state, an event-specific hazard ratio was applied to background general mortality. Table 56 presents the hazard ratio applied to the background mortality rate for AF patients who have survived each clinical event. It was assumed that there is no long-term impact on mortality for bleeding and TIA.

Hazard ratios for mortality for the clinical outcomes were sourced from published literature. There were no published data on the long-term mortality following a SE, so this was estimated from ENGAGE AF-TIMI 48 trial data. The hazard ratio for mortality due to SE was estimated from mortality observed in the ENGAGE AF-TIMI 48 trial and general population mortality. In the trial, [redacted], resulting in a mortality rate of [redacted]. This was divided by the mean annual mortality rate for the population at age 71 (the mean age of patients in the trial). This approach assumes a constant hazard of death for SE survivors.

These parameters were assumed to follow a lognormal distribution, since the logarithm of the ratio can be assumed to be normally distributed.

Table 56: Long-term mortality for event survivors

Health states	Hazard ratio* (distribution)	Source
IS		
Mild	3.18 (lognormal)	Bronnum-Hansen *et al.* 2001 [87]
Moderate	5.84 (lognormal)	Henriksson *et al.* 2010 [88]
Severe	15.75 (lognormal)	Huybrechts *et al.* 2008 [89]
HS		
Mild	3.18 (lognormal)	Bronnum-Hansen *et al.* 2001 [87]
Moderate	5.84 (lognormal)	Henriksson *et al.* 2010 [88]
Severe	15.75 (lognormal)	Huybrechts *et al.* 2008 [89]
SE	[redacted] (lognormal)	Estimated from UK Life Tables and ENGAGE AF-TIMI 48 trial data

Health states	Hazard ratio* (distribution)	Source
MI	3.36 (lognormal)	Bronnum-Hansen *et al.* 2001 [87]

*Variation in estimate not reported in sources

Stroke-related discontinuation

Patients may permanently discontinue or switch treatment following an IS or an HS. Assumptions around stroke-related discontinuation are presented in Table 57. When patients discontinue in the model and switch to a new choice of therapy, transition probabilities for each health state and probabilities of each event do not change to reflect the new treatment since the probabilities were based on an ITT analysis of the ENGAGE AF-TIMI 48 trial data.

Other cause discontinuation

Other cause discontinuation was excluded from the model, as it is assumed that there would be no difference between treatment groups. The all-cause discontinuations would be primarily driven by death and event driven calculations which are captured elsewhere in the model.

Assumptions around event-related discontinuation are presented in Table 57.

Table 57: Event-related discontinuation

Event	Assumption	Source
IS	All warfarin patients discontinue treatment, and resume treatment with a NOAC (specifically, edoxaban). 50% of NOAC patients will permanently discontinue, and 50% will continue on the same therapy.	Clinical opinion (ad hoc advice) [90]
HS	Warfarin patients discontinue treatment, and resume treatment with: 20% restart on anti-platelet (aspirin); 20% restart on NOAC (edoxaban); 60% restart on warfarin. 50% of NOAC patients will permanently discontinue, and 50% will continue on the same therapy.	Clinical opinion (ad hoc advice) [90]

7.3.7 **Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the**

extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Given that AF is a chronic condition, patients are at risk of AF-related events and treatment-related adverse events over the course of a lifetime. As such, a state transition model was used to extrapolate from events occurring during the trial period to costs and outcomes that occur beyond the trial period.

In the absence of data indicating that efficacy and adverse events would differ beyond the trial period (median follow-up, 33 months), probabilities of clinical outcomes for edoxaban observed during the ENGAGE AF-TIMI 48 trial were assumed to continue but were modified as patients age. Risk adjustment factors were identified from a number of published studies [76;77;79;80], and were applied to the treatment specific event probabilities. Hazard ratios due to treatment were constant.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 58: Assumptions used in the model

Assumption	Justification
For temporary clinical events, the model assumes no impact on subsequent event risks.	Clinical opinion from Advisory Board. This assumption is in line with previous atrial fibrillation STAs (e.g. apixaban, dabigatran, rivaroxaban).
Health states (IS, HS, SE, MI) are mutually exclusive; i.e. a patient can only experience one of these per cycle.	Patients are unlikely to experience more than one of these clinical outcomes during any one-month period. This assumption is consistent with a previous submission for apixaban, where it was noted by the ERG that this was a reasonable cycle length.
Event-related mortality (incorporating acute and long-term probabilities) is equivalent for each treatment.	There is no evidence to support a reduction in the severity of consequences. This would confer an indirectly mortality benefit to a treatment.
Transitions between health states occur at the mid-point of a cycle (using half-cycle correction).	Events may occur at any point during the month so, on average, patients will transition to another state halfway through each cycle.
Recurrent strokes were assumed to be of the same type (IS or HS) as the initial event; however, the severity of a recurrent stroke was assumed to be equal or more severe than initial stroke severity.	Whilst a patient can experience a less severe recurrent stroke e.g. severe stroke followed by a mild stroke, it is not clinically appropriate to assume the patient would experience the long-term effects of a milder stroke if a severe stroke had previously been experienced.

Assumption	Justification
CRNMBs are assumed to have no impact on mortality.	By definition of CRNMB.
Event rates observed during the ENGAGE AF-TIMI 48 trial are applicable to periods beyond the follow-up.	AF is a chronic condition. Event rates observed during the ENGAGE AF-TIMI 48 trial were assumed to continue but to be modified as patients age (expert opinion from advisory board).

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Atrial fibrillation is a chronic condition characterised by a sustained cardiac arrhythmia.[7;84;87] It is caused by chaotic electrical impulses in the atria which result in rapid and irregular heartbeats. The most common symptoms of atrial fibrillation include palpitations, tiredness, shortness of breath, dizziness and chest pain. In addition to this, due to the way in which the heart beats in atrial fibrillation, patients can also experience low blood pressure and heart failure from a reduced efficiency and performance of the heart.

Patients with atrial fibrillation have an elevated risk of ischaemic stroke and of systemic embolism. The reduced efficiency of the heart can result in a lack of sufficient contractions. If the heart does not contract enough, then the blood in the atria becomes stagnant and can form clots. These clots can then get pumped around the body and travel to the brain, resulting in an ischaemic stroke.

Ischaemic strokes can have a major impact on the quality of life of a patient. Patients with AF that suffer an ischaemic stroke often experience a worse outcome (more disability, greater mortality) than those who have an ischaemic stroke in the absence of atrial fibrillation. $CHADS_2$ score, applicable to the AF population, gives a higher estimation than the regular cardiovascular risk scores applied to general populations. A stroke can have an impact on many areas of a person's wellbeing and can result in many problems including in communication, mobility and memory. [28]The health-related quality of life of a patient is also negatively impacted by systemic embolism. [91]

Previous studies have used various psychometric-based surveys and preference-based methods to estimate the quality of life of AF patients. The majority of studies utilised psychometric-based surveys such as the 36-item Short Form Health Survey (SF-36) and the European Quality of Life questionnaire (EQ-5D);[92;93] for example in Khan et al., a study of monitoring in warfarin patients. [94]The time trade-off method and standard gamble assessment was utilised by Gage et al. to estimate the impact of stroke on quality of life. [95]

7.4.2 **Please describe how a patient's HRQL is likely to change over the course of the condition.**

There is no decrease in HRQoL related to the time a patient spends with AF. The HRQL of a patient is likely to be permanently reduced if that patient suffers from an ischaemic stroke, myocardial infarction or systemic embolism. [95-97] If a patient suffers from a transient ischaemic attack, the patient is likely to experience a temporary reduction in HRQL, and therefore a disutility was applied, with the utility returning to the pre-event utility after the course of the event. In addition to disease-related quality of life, patients experience a gradual decline in quality of life as they age. [98]

HRQL data derived from clinical trials

7.4.3 **If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.**

- **Method of elicitation.**
- **Method of valuation.**
- **Point when measurements were made.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**

Health related quality of life data were collected from patients in the ENGAGE AF-TIMI 48 trial as part of a health economic substudy that ran alongside the trial.

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

For this analysis, US preference weights were applied to EQ-5D data from all patients, regardless of country of enrolment. The baseline utility was calculated as 0.836 using this methodology. The cost-effectiveness model uses this estimate as an alternative source of baseline utilities. The base case estimate is from a UK study by Khan et al. [94]

Mapping

7.4.4 **If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**

- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

No mapping techniques were performed for the derivation of health-state utility or quality of life values applied in the cost-effectiveness model described in this Single Technology Appraisal.

HRQL studies

7.4.5 **Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.**

A systematic literature review was conducted to identify relevant references for EQ-5D health state utility values in NVAF in order to populate health states utilities in the economic model.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) on the electronic databases Medline/Medline (R) In-Process, EMBASE, Econlit and NHSEED for NVAF and quality of life. Full details of the databases, search strategies employed and inclusion/exclusion criteria are presented in Section **Error! Reference source not found.**. This was supplemented by hand searching the bibliographies of relevant systematic review articles of the last five years, searching references of included studies, primary sources of utilities used in economic evaluations and relevant NICE technology appraisal data.

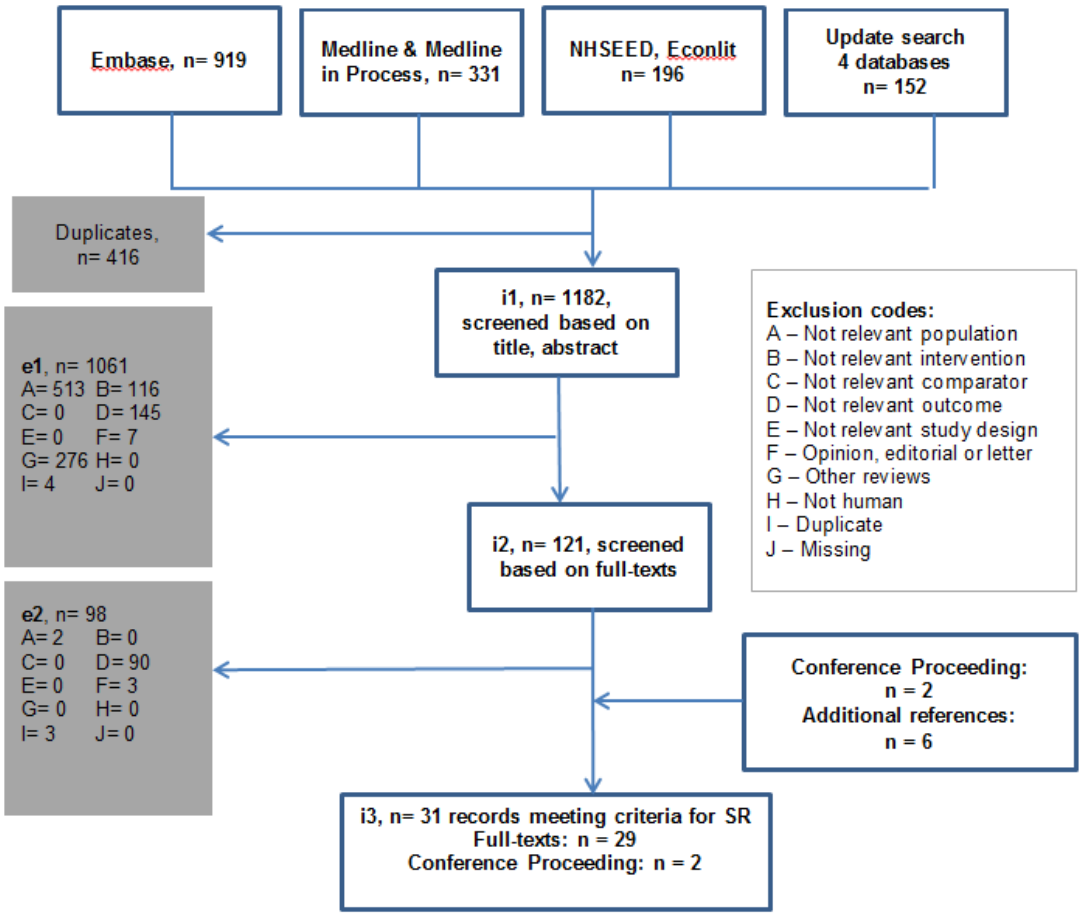
7.4.6 **Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.**

- **Population in which health effects were measured.**
- **Information on recruitment.**
- **Interventions and comparators.**
- **Sample size.**
- **Response rates.**
- **Description of health states.**
- **Adverse events.**
- **Appropriateness of health states given condition and treatment pathway.**
- **Method of elicitation.**
- **Method of valuation.**
- **Mapping.**
- **Uncertainty around values.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**

- **Appropriateness of the study for cost-effectiveness analysis.**

In total, 1,598 records were identified through the electronic searches. On removal of duplicates, 1,182 records were screened on title and abstract. Of these, 121 records were reviewed based on full texts, of which 98 were excluded. Two conference proceedings from ACC, AHA or ESC have been included and six additional references identified through hand-searching, resulting in 31 records for final inclusion (Figure 23), including 11 that presented HRQL (EQ-5D) data in an AF population. In total there are 29 full texts, plus 6 abstracts / conference proceedings (from ACC, AHA or ESC) included in this review (table 59).

Figure 23: Schematic for the systematic review of QoL evidence



Abbreviations: SR, systematic review

The utility sources of models identified in the literature review of cost-effectiveness evaluations and the references quoted in the apixaban, rivaroxaban and dabigatran HTA submissions were searched and three further publications considering utilities on AF patients were identified.[94;99;100]. (**Figure 23**)

Utility values needed in the economic evaluation of edoxaban for stroke prevention in atrial fibrillation, and that had not been identified, were searched by screening again references quoted in HTA submissions and sources of cost effectiveness models. A further three studies were included [96;97;101]:

- Lacey et al [96] provide utility value related to myocardial Infarction,
- Sullivan 2006 et al [101] provide disutility value related to TIA,
- Sullivan 2011 et al [97] provide utility value related to systemic embolism.

Table 59: Studies reporting utility values for health states used in the economic model

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
Berg, 2010[3]	35 European countries	AF	- Prospective study, - All types of AF, with episode in the previous 12 months	Baseline 5,050 1 year follow-up 3,045	EQ-5D	Baseline	0.751 (SD 0.269)
						Follow-up	0.779 (SD 0.253)
Doyle 2011[4]	UK	AF (all types)	Multinational euro heart survey	Paroxysmal N=493, Persistent N=233, permanent N=380, TTO interview: general pop N=127	EQ-5D	Paroxysmal AF (Baseline)	Mean: 0.79
						Persistent AF (Baseline)	Mean: 0.8
						Permanent AF (Baseline)	Mean: 0.73
						Paroxysmal/persistent (Baseline)	Mean: 0.93
						Permanent (Baseline)	Mean: 0.91
Gage 1995[5]	USA	AF	-	N=69 completed interviews	Standard gamble and TTO	Mild neurological event	0.75
						Moderate-to-severe neurological event	0.39
						Recurrent neurological event	0.12
Gage 1996[6]	US	Elderly population (>50 years old), who had AF	- Randomised control trial	N=70	TTO	Mild stroke (baseline)	Mean: 0.76
						Moderate stroke (baseline)	Mean: 0.39
						Major stroke (baseline)	Mean: 0.11
						Current health (baseline)	Mean: 0.82
						Warfarin therapy (baseline)	Mean: 0.987
						Aspirin therapy (baseline)	Mean: 0.998
					Standard Gamble	Moderate stroke (baseline)	0.26
Goren 2013[7]	US	AF	Internet-based 2009 US National Health and Wellness Survey	N=2,592	SF-6D	AF	Unadjusted mean: 0.697 (SD 0.14) Adjusted mean 0.711 (0.704-0.718)
HO 2012[8]	Hong Kong	Diagnosed with AF and prescribed dabigatran or warfarin for stroke prophylaxi	This quality-of life questionnaire, together with the drug compliance of patients, were assessed by a telephone interview conducted by the same student pharmacist.	N=244	EQ-5D-5L	Dabigatran (12 months)	0.77 ± 0.17
						Warfarin (12 months)	0.74 ± 0.16

Author year	Country	Patient populatio n	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
		s					
Monz 2013[9]	US, Canada, Central Europe, Western Europe, Latin America, Asia, Other	AF A sub-group of the overall RE-LY population (RE-LY was a phase III study)	RE-LY was designed as a prospective, randomised, open-label, blinded endpoint evaluation (PROBE) controlled parallel group trial, using open label warfarin while the two doses of dabigatran were assigned in a blinded manner	N=1435	EQ-5D	Dabigatran, 110 mg BD	Baseline: 0.788 (0.745-0.831) 3 months: 0.786 (0.742-0.829) Baseline: 0.775 (0.734-0.816) 12 months: 0.758 (0.717-0.799)
						Dabigatran, 150 mg BD	Baseline: 0.780 (0.744-0.816) 3 months: 0.766 (0.729-0.803) Baseline: 0.783 (0.750-0.816) 12 months: 0.758 (0.782-0.815)
						Dabigatran, Combined	Baseline: 0.784 (0.758-0.811) 3 months: 0.776 (0.749-0.803) Baseline: 0.781 (0.756-0.806) 12 months: 0.772 (0.747-0.797)
						Warfarin	Baseline: 0.791 (0.728-0.855) 3 months: 0.801 (0.738-0.865) Baseline: 0.777 (0.747-0.807) 12 months: 0.785 (0.755-0.815)
Morillo 2014[10]	International	AF	- Randomised control trial, - Patient with history of paroxysmal AF	N=127	EQ-5D	Radiofrequency Ablation (baseline)	0.86 (SD 0.14)
						Antiarrhythmic Drugs (baseline)	0.84 (SD 0.11)

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
						Radiofrequency Ablation (12 months)	1 (SD 0.11)
						Antiarrhythmic Drugs (12 months)	1 (SD 0.12)
Reynolds 2010[11]	North America	New-onset AF	Prospective study	N=933	SF-6D	No hospitalisation (first 12 months)	0.81 (SD 0.1)
						Any hospitalisation (First 12 months)	0.77 (SD 0.11)
						No CV hospitalisation (first12 months)	0.8 (SD 0.11)
						CV hospitalisation (first12 months)	0.78 (SD 0.11)
Roalfe 2011[12]	UK	Elderly (>75y) with AF (BAFTA study)	-RCT	N=1762	EQ-5D	Chronic AF (male)	0.76 (SD 0.25)
						Chronic AF (female)	0.71 (SD 0.29)
						Chronic AF (male)	0.77 (SD 0.22)
						Chronic AF (female)	0.68 (SD 0.26)
Robinson 2001[13]	UK		Standard gamble study	N=57 completed interviews	Standard gamble	GP-managed warfarin	0.948 (0.089)
						Hospital-managed warfarin	0.941 (0.101)
						Major bleed	0.841 (0.172)
						Mild stroke	0.641 (0.275)
						Severe stroke	0.189 (0.276)
Radholm 2011[14]	Sweden	Elderly (~85y) with AF, Sinus rhythm or pacemaker (ELSA-85 study)	Population-based survey	N=336	EQ-5D	AF patients	Baseline: median 0.73 (0.62-0.81)
						Sinus rhythm or pacemaker	Baseline: median 0.73 (0.66-0.85)
Steg 2012[15]	International	All types of AF, with	Cross-sectional observational study	N=10,523	EQ-5D	controlled AF	Baseline: median 0.78
						uncontrolled AF	Baseline: median 0.73

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
		episode in the previous 12 months				Sinus rhythm	Baseline: median 0.75
						AF with HR <80 bpm	Baseline: median 0.72
						AF not controlled	Baseline: median 0.67
Thomson 2000[16]	UK	AF	-	N=57 completed interviews	Standard gamble	GP-managed warfarin	0.948 (0.089)
						Hospital-managed warfarin	0.941 (0.101)
						Major bleed	0.941 (0.101)
						Mild stroke	0.641 (0.275)
						Severe stroke	0.189 (0.276)
Ozin 2014[17]	International	NVAF patients (>18y)	Observational study	N=213	EQ-5D	Warfarin	Baseline: 0.85 (0.12) 12 months: 0.67 (0.29)
						Antiplatelet agents (AA)	Baseline: 0.76 (0.13) 12 months: 0.62 (0.37)
Bruggenjurgen 2014[18]	International (7 EU contries)	AF patients	Prospective registry	N=6,390	Visual Analogue Scale (VAS)	Overall	Follow-up: 68.8 (18.1)
						NOAC	Follow-up: 68.3
						VKA	Follow-up: 68.9
						AP	Follow-up: 70.1
						VKA+AP	Follow-up: 71.7
					EuroQol EQ-5D-5L	Overall	Follow-up: 0.8 (0.21)
						NOAC	Follow-up: 0.79
						VKA	Follow-up: 0.8
						AP	Follow-up: 0.81
						VKA+AP	Follow-up: 0.8
Magnuson 2014[19]	International (46 countries)	AF patients from the ENGAGE AF-TIMI 48 Trial	RCT	N= 15,618	EQ-5D	Intracranial hemorrhage (ICH)	Decrement *Intercept estimate: -0.079 (-1.9 -0.032) *Linear effect of time (years): -0.017 (-0.111 – 0.077)
						Major GI	Decrement *Intercept estimate: -0.03 (-0.053 -0.007) *Linear effect of time (years): 0.031 (-0.008 - 0.07)
						Major non-GI	Decrement *Intercept estimate: -0.045 (-0.067 --0.022)

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
							*Linear effect of time (years): 0.037 (0.001 - 0.069)
						Clinically relevent non-major bleeding	Decrement *Intercept estimate: -0.009 (-0.018 --0.001) *Linear effect of time (years): -0.011 (-0.025 0.003)
						Minor bleeding	Decrement *Intercept estimate: -0.009 (-0.2 -0.002) *Linear effect of time (years): -0.008 (-0.026 0.009)
Sun 2014[20]	China	NVAF patients	Non-interventional, multicenter and cross-sectional study	N=3562	SF-36	SF-36 - physical functioning	Baseline: 65.55 (26.33)
						SF-36 - role physical	Baseline: 42.59 (45.37)
						SF-36 - bodily pain	Baseline: 77.36 (22.44)
						SF-36 - general health	Baseline: 46.41 (21.27)
						SF-36 - vitality	Baseline: 62.76 (19.21)
						SF-36 - social function	Baseline: 64.57 (22.07)
						SF-36 - role emotional	Baseline: 59.11 (45.56)
						SF-36 - mental health	Baseline: 66.72 (17.78)
Schron 2014[21]	US	AF Patients independent of heart failure	the NHLBI/NIH AFFIRM randomized clinical trail	N=693	SF-36	SF-36 – Physical component AFFIRM scores	Baseline: 38.4 (6.1)
						SF-36 - Mental component AFFIRM scores	Baseline: 40.8 (5.3)
						SF-36 - Physical component Normative scores	Baseline: 43.3 (11.12)
						SF-36 - Mental component Normative scores	Baseline: 52.7 (9.3)
					QLI-CV	QLI-CV - health and functioning AFFIRM scores	Baseline: 21.8 (5)
						QLI-CV - socio economic AFFIRM scores	Baseline: 24.5 (4.6)
						QLI-CV - psychological-spiritual AFFIRM scores	Baseline: 23.9 (5.2)
						QLI-CV – Family AFFIRM scores	Baseline: 23.9 (4.7)

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
						QLI-CV - health and functioning Normative scores	Baseline: 23.2 (4.5)
						QLI-CV - socio economic Normative scores	Baseline: 21.8 (4.1)
						QLI-CV - psychological-spiritual Normative scores	Baseline: 23 (5.2)
						QLI-CV – Family Normative scores	Baseline: 25.6 (4.5)
Poster/Conference abstract							
Selby 2014[22]	Canada	New-onset or chronic NVAF	48-week prospective study	N=497 (n=180 completed)	EQ-5D	Warfarin	Baseline: mean 0.85 [0.83; 0.88] At 48 week: mean change -0.01 [0; -0.02]
Wynn 2013[23]	UK	AF	Validation study for AFEQT score	N=362	EQ-5D (VAS)	EHRA: class 1	0.85 (0.21)
						EHRA: class 2	0.86 (0.18)
						EHRA: class 2a	0.81 (0.17)
						EHRA: class 2b	0.77 (0.15)
						EHRA: class 3	0.69 (0.27)
						EHRA: class 4	0.59 (0.29)
Gupta 2011[24]	International (5EU)	AF	Self-administered and Internet-based questionnaire	N=479	SF-6D	CHA2DS2-VASc = 0 (low risk of stroke)	0.703
						CHA2DS2-VASc = 1 (medium risk of stroke)	0.665
						CHA2DS2-VASc = 2 (high risk of stroke)	0.657
Aves 2010[25]	International	AF recently diagnosed	Longitudinal cohort study	N=4,501	EQ-5D	General	Baseline: 0.78 (0.22) 1 year: 0.821 (0.213)
						Rate control	Baseline: 0.78 (0.23) 1 year: 0.03 (0.21)
						Rhythm control	Baseline: 0.79 (0.22) 1 year: 0.04 (0.21)
						Control of AF	Baseline: 0.79 (0.22) 1 year: 0.04 (0.20)

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
						No control of AF	Baseline: 0.77 (0.23) 1 year: 0.02 (0.22)
						At least 1 clinical outcome: Stroke, TIA, MI, other..	Baseline: 0.74 (0.24) 1 year: 0.01 (0.24)
						No clinical outcome	Baseline: 0.79 (0.22) 1 year: 0.04 (0.2)
Jonathan 2012[1]	US	AF patients	Retrospective cohort	N=1 975	The Atrial Fibrillation Effect on QualiTy-of-life (AFEQT)	New onset AF	Baseline: 70 (24)
						Persistent AF	Baseline: 76 (21)
						Permanent AF	Baseline: 79 (18)
						<65 years	Baseline: 74 (22)
						65-79 years	Baseline: 77 (19)
						≥80 years	Baseline: 80 (19)
						EHRA score= No symptoms	Baseline: 85.6874
						EHRA score= Mild	Baseline: 77.2128
						EHRA score=Severe stroke	Baseline: 63.2768
						EHRA score= Disabling	Baseline: 59.1337
Piccini 2012[2]	US	AF patients	prospective registery	N=2005	AFEQT	Women	Baseline: 75 (21)
						Men	Baseline: 79 (19)
Identified via search of apixaban, rivaroxaban and dabigatran STA submissions and CE model sources							
Dagres 2007[26]	35 countries	AF: first detected, paroxysmal, persistent and permanent	Ambulant or hospitalised patients who had an electrocardiogram or Holter recording of AF during the qualifying admission or within the preceding 12 months.	N=5,333 (Women=2249, Men=3084)	EQ-5D	baseline	F=0.73 IQR (0.59–0.85) M=0.85 IQR (0.69–1.00)
						12months	Reported as change from baseline: F=0.00 [−0.10 to 0.15] M=0.00 [−0.07 to 0.11]
Khan 2004[27]	UK	Patients with AF with target INR range of 2-3, taking warfarin for at least 12 months, INR SD ≥ 0.5 over the	Retrospective database study	N=125	EQ-5D	Education:	Baseline: 0.74 (SD 0.27) AF – Week 24: 0.70 (SD 0.29)
						Education and self-monitoring	Baseline: 0.82 (SD 0.02) AF – Week 24: 0.75 (SD 0.27)

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
		previous 6 months and aged ≥ 65 years					
Meinertz 2011[28]	Germany	patients with AF seen by 730 physicians representing a random sample of all primary care physicians in Germany	ATRIUM (Outpatient Registry Upon Morbidity of Atrial Fibrillation) is a prospective, multicenter, epidemiological, non-interventional cohort study.	- Overall N=3,667 - EQ-5D completed by 3,460 patients,	EQ-5D	Baseline - AF	0.86 (SD 0.19)
Additional references retrieved for the economic evaluation of edoxaban							
Sullivan 2006[29]	US	CEA	CEA		EQ-5D	AF	0.81
						Decrement for age	0.00029
						Decrement for haemorrhagic stroke	0.1385
						Decrement for ischaemic stroke	0.1385
						Decrement for MI	0.1247
						Decrement for MBs	0.1814
						Decrement for system embolic event	0.1199
						Decrement for subdural haematoma	0.1814
						Decrement for TIA	0.10322
Sullivan 2011[30]	UK				EQ-5D	Acute MI	Acute MI
						Old MI	Old MI
						Arterial embolism	Arterial embolism
						Transient cerebral ischaemia	Transient cerebral ischaemia
						Other aneurysm	Other aneurysm

Author year	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD
Lacey 2003[31]	UK	Patients discharged from hospital following acute MI	-	N=229	EQ-5D	MI (at 6 weeks)	0683 (SD 0.23)

7.4.7 **Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.**

Not applicable

Adverse events

7.4.8 **Please describe how adverse events have an impact on HRQL.**

The adverse events that were considered in this model were the clinical outcomes modelled as events, namely non-ICH major bleed, CRNMBs, other ICH, and TIA. These were assumed to reduce a patient's HRQL for a limited time period and not permanently. This is based on expert clinical advice from the advisory board (Section 7.2.5), and consistent with assumptions in previous STAs (TA249 dabigatran, TA275 apixaban, TA287 rivaroxaban [49-51]) for SPAF. In the economic model, each of these four adverse events were associated with a temporary disutiliy. A disutility was subtracted from the health state utility of the patient experiencing the event, and applied for the duration of the event. For example, a patient experiencing the CRNMB event had a reduction of 0.06 applied to their utility for a period of two days. All disutilities applied in this model and their respective durations can be found in Table 60 in section 7.4.9 below.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.**

The utility values used in the economic analysis are summarised in Table 60.

Table 60: Summary of quality-of-life values for cost-effectiveness analysis

Health state / event	Utility value / decrement	CI (distribution)	Reference in submission	Justification
Stable AF	0.780 (Base case) 0.74 education group 0.82 education and self-monitoring group	SE 0.0427	Khan *et al.* 2004 [94]	The only EQ-5D utility from UK based study
	0.836		ENGAGE AF-TIMI 48	Based on US patients
Age-adjustment disutility per year	-0.00029	-0.00059 to 0.0000129 (beta)	Sullivan *et al.* 2011 [97]	Most recent and relevant source identified
Health states				
Mild IS Moderate IS Severe IS	0.68 0.31 0.03	0.14 to 1.0 0.0 to 0.99 0.0 to 0.51 (90% CI, beta)	Gage *et al.* 1996 [95]	It is the only study reporting stroke severity for mild, moderate and severe

Health state / event	Utility value / decrement	CI (distribution)	Reference in submission	Justification
Mild HS Moderate HS Severe HS	0.68 0.31 0.03	0.14 to 1.0 0.0 to 0.99 0.0 to 0.51 (90% CI, beta)	Gage *et al*. 1996 [95]	It is the only study reporting stroke severity for mild, moderate and severe
SE	0.680	NA**	Sullivan *et al*. 2011 [97]	Only source identified
MI	0.683	SD: 0.233 (beta)	Lacey *et al*. 2003 [96]	It is the only UK-based study using EQ 5D identified via the systematic review
Events				
Other ICH disutility	-0.107	NR	Thomson *et al*. 2000 [114]	Only source identified
	6 weeks	-	Apixaban STA [51]	
TIA disutility	-0.103**	-0.088 to -0.119 (beta)	Sullivan *et al*. 2006 [98]	Only source identified
	NA	-	-	
Non-ICH major bleed disutility	-0.107	NR	Thomson *et al*. 2000 [114]	Only source identified
	2 weeks	-	Apixaban STA [51]	
CRNMB disutility	-0.0582	NR	Sullivan *et al*. 2011 [97]	Only source identified
	2 days	-	Apixaban STA [51]	

7.4.10 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details8:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**

[8] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

No clinical experts were consulted to assess the utilities included in the analysis.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The utilities and disutilities associated with each health state or event in the model are presented in Section 7.4.9, and any time periods for which these disutilities were applied.

The utility estimates associated with each health state or event are assumed to be constant for a patient of a given age (with an adjustment for age being included in the model) in the base case analysis, with the between-subject variance accounted for in the probabilistic sensitivity analysis (PSA).

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Yes, the disutilities associated with treatment with NOACs and with warfarin were excluded from the base case analysis.

A previous STA of apixaban for SPAF [51] assumed a disutility of 0.013 for warfarin and a disutility of 0.002 for NOACs. [95] Warfarin was assumed to have the highest decrement due to the requirement for routine INR monitoring and the multiple food and drug interactions. By excluding these assumptions, this model provides a conservative estimate of the QALY gains associated with each treatment arm.

Trial based baseline utilities were also excluded from the base case analysis.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Baseline quality of life in the model refers to the health state of stable AF, where patients on treatment have not yet experienced a clinical event.

The baseline quality of life assumed in this analysis was 0.78, which was estimated from the baseline utility as reported in Khan (2004), a study of AF patients receiving warfarin in the UK. [94] Quality of life events were taken from this baseline.

Quality of life was measured at baseline using the SF-36 health survey and Euroqol questionnaire. [92;93] One arm of 39 patients had a mean baseline utility of 0.74 (SD 0.27) and, the other arm of 40 patients had a mean baseline utility of 0.82 (SD 0.02), resulting in an overall mean baseline utility of 0.78.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Health related quality of life is not assumed to be constant over time as adjustments were made for cohort aging. A disutility of -0.00029 per year was applied to the patients' utility. [97] Sullivan (2011) is a regression analysis of a large sample of the general population in the US (using data from 2000-2003 MEPS surveys), using UK-specific community preferences for health states in the EQ-5D. [119;120] The application of an age-related disutility reflects that a patient's quality of life would be affected by both events experienced and by increasing age.

7.4.15 **Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

Gage (1996) provided utility estimates for mild, moderate and severe stroke (0.76, 0.39, and 0.11 respectively). [95] In order to reflect that patients' quality of life is lower following a stroke, the stroke utility values were adjusted by the baseline patient utility in the Gage study (mean utility 0.82, 90% CI 0.5 to 1.0). The difference between the Gage baseline utility and stroke utility (0.06, 0.43, and 0.71 for mild, moderate and severe stroke respectively) was applied to the baseline Stable AF utility.

Many utility inputs have been extracted from the STA for apixaban, since this provides a recent and well-critiqued source of data. [51] In the apixaban submission, utility estimates were amended using the methodology described in this section. In the current submission, the calculations have been updated to use the utility values from the literature and from Khan (2004) where appropriate. [94]

In order to produce a utility associated with SE, a decrement of -0.1005 [97] was assumed from the baseline utility used in the model (0.78, from Khan (2004)[94]). This resulted in a utility of 0.680 for patients in the SE or post-SE health states.

To provide a utility decrement for other ICH and non-ICH major bleed, a utility decrement of 0.107 was applied, based on the difference between major bleed (mean utility 0.841, SD 0.172) and baseline AF (mean utility 0.948, SD 0.089) utilities reported in Thomson et al. 2000. [114]

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 **Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

Table 64 to Table 72 present the unit costs that were applied to each clinical event, and how the costs were estimated. Where possible the HRG codes were selected based on those employed in the NICE CG180 AF costing report. [7] Where HRG codes did not correspond to the resource use considered in the model, unit costs were obtained from the published literature, for example type of stroke and stroke severity, and for systemic embolism.

7.5.2 **Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.**

In the base case analysis, 2013/14 NHS reference costs are used where possible. Where procedures do not have HRG codes or the codes are not sufficiently disaggregated, such as for long term care and type and severity of stroke, unit costs have been identified from the published literature.

Resource identification, measurement and valuation studies

7.5.3 **Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:**

- **country of study**
- **date of study**
- **applicability to UK clinical practice**
- **cost valuations used in study**
- **costs for use in economic analysis**
- **technology costs.**

Forty costing studies were identified through the systematic review detailed in Section 7.1. Six of these studies were conducted in the UK and are summarised in Table 61.

Table 61: UK Costing studies identified through economic systematic review

Study and the type	Objective	Interventions	Population, sample size, time frame, cost reference year	Direct costs, indirect costs	Key results
Abdelhafiz 2003, Full publication	To investigate the use of resources and cost implications of stroke prophylaxis with warfarin in NVAF patients in clinical practice.	Warfarin	Newly referred NVAF patients to a single anticoagulation clinic for warfarin therapy, 402, 1 year, 1999/2000	Drug costs Bleeding costs (Physician visit, Hospital visit); Monitoring costs: (INR, travel, time off Work, postage)	Drug: £2.90 - Total: £19.80 Monitoring: (INR: £7.40; Travel: £3.50; Work missed: £0.12; Nurse visit: £0.65; Postage: £0.39) Bleeding: (Physician visit: £0.18; Hospital admissions: £6.13)
Ali 2012	To investigate cost of anticoagulation with dabigatran in comparison with warfarin in clinical practice.	Dabigatran (110 mg) Dabigatran (150 mg) Warfarin	NVAF, All patients with NVAF newly referred to anticoagulation clinic, NR, 40231 months, 2011	Drug cost Complications: Physician visits Hospital admissions, Monitoring: INR Travel Time off Work Postage	Warfarin - Total: £207.30 Drug: £28.20 Monitoring: (INR: £72.30; Travel: £33.90; Time off work: £1.20; Nurse visit: £6.40; Postage: £3.80) Complications: (Physician visit: £1.70; Hospital admissions: £59.80) Dabigatran 110 mg - Total: £968.50 Drug: £907 Monitoring: NA Complications: (Physician visit: £1.70; Hospital admissions: £59.80) Dabigatran 150 mg - Total: £968.50 Drug: £907 Monitoring: NA Complications: (Physician visit: £1.70; Hospital admissions: £59.80)
Ali 2012, Full publication	To investigate cost of anticoagulation with dabigatran in comparison with warfarin in clinical practice.	Dabigatran (110 mg) Dabigatran (150 mg) Warfarin	NVAF, All patients with NVAF newly referred to anticoagulation clinic, NR, 40231 months, 2011	Drug costs Complications: (Physician visits; Hospital admissions) Monitoring: (INR, travel, time off work; postage)	Warfarin - Total: £207.30 Drug: £28.20 Monitoring: (INR: £72.30; Travel: £33.90; Time off work: £1.20; Nurse visit: £6.40; Postage: £3.80) Complications: (Physician visit: £1.70; Hospital admissions: £59.80) Dabigatran 110 mg - Total: £968.50

Study and the type	Objective	Interventions	Population, sample size, time frame, cost reference year	Direct costs, indirect costs	Key results
					Drug: £907 Complications: (Physician visit: £1.70; Hospital admissions: £59.80) Dabigatran 150 mg - Total: £968.50 Drug: £907 Complications: (Physician visit: £1.70; Hospital admissions: £59.80)
Kachroo 2014, Abstract	To assess impact of apixaban on resource utilization in patients with non-valvular atrial fibrillation (NVAF) to the NHS in the United Kingdom	Apixaban Dabigatran Rivaroxaban VKA Aspirin	(NVAF), 384 400, 5 years, 2012	• Direct costs: medical cost reported • Indirect costs not reported	Addition of apixaban has a minimal increase of 1.2% (up to £25.6 million) in the healthcare budget over a 5-year period Medical cost savings of up to £11.1 million from the NHS perspective. Net increase of £13.33 per treated patient per year from the NHS perspective. 322 strokes, 417 major bleeds, 515 CRNM bleeds, 94 myocardial infarctions and 406 CV hospitalizations were avoided
Luengo-Fernandez 2013, Full publication	To determine the acute and longer term health-care costs of stroke in patients with a history of AF, including the costs of long-term institutionalization, using data from a population-based study (Oxford Vascular Study, OXVASC)	Not specified	Patients with suspected stroke Only stroke patients recruited in the first five-years of the study (1 April 2002 to 31 March 2007) Patients with history of AF, 153, 5 years, 2008/2009	Nurse visits General practitioner visits Emergency care Outpatient visits Day cases Hospitalizations Ischemic stroke Hemorrhage Unknown stroke Indirect costs not reported	Mean acute health-care costs by severity and subtype for 191 strokes: All strokes: Nurse visits £22; General practitioner visits £100; Emergency care £211; Outpatient visits £191 Day cases £48; Hospitalizations £9841; Total costs £10 413 Ischemic stroke £10 844 Hemorrhage £10 683 Unknown stroke £4206 Non disabling: Nurse visits £40; General practitioner visits £115; Emergency care £142; Outpatient visits £338; Day cases £76;

Study and the type	Objective	Interventions	Population, sample size, time frame, cost reference year	Direct costs, indirect costs	Key results
					Hospitalizations £3,234; Total costs £3,945 Ischemic stroke £3,401; Hemorrhage £9,903 Unknown stroke £5,117 Moderately disabling: Nurse visits £19; General practitioner visits £133; Emergency care £242; Outpatient visits £185; Day cases £38; Hospitalizations £16,791; Total costs £17,406 Ischemic stroke £17,743 Haemorrhage £25,442 Unknown stroke £6,326 Totally disabling patients: Nurse visits £2; General practitioner visits £48; Emergency care £272; Outpatient visits £93; Day cases £93; Hospitalizations £24,771; Total costs £25,279 Ischemic stroke £24,234 Hemorrhage £43,036 Unknown stroke n/a Case fatal: Nurse visits £8; General practitioner visits £43; Emergency care £244; Outpatient visits £2;Day cases £0; Hospitalizations £2,382; Total costs £2,680 Ischemic stroke £3,059 Hemorrhage £1,592 Unknown stroke £2,489

Study and the type	Objective	Interventions	Population, sample size, time frame, cost reference year	Direct costs, indirect costs	Key results
					Annual health-care costs for 136 strokes surviving past the acute period: 1> Baseline Nurse visits £90; General practitioner visits £231; Emergency care £35; Outpatient visits £256; Day cases £187; Hospitalizations £1767; Total costs £2566 Non disabling (n = 66) £1753 Moderately disabling (n = 58) £3339 Totally disabling (n = 12) £3304 2> Post-acute costs Nurse visits £110; General practitioner visits £330; Emergency care £133; Outpatient visits £264; Day cases £229; Hospitalizations £2,305; Total costs £3,370 Non disabling (n= 66) £2,135 Moderately disabling (n=58) £4,165 Totally disabling (n=12) £6,324
Sunderland 2013, Abstract	To estimate the number of clinical events and costs of these events for dabigatran etexilate (dabigatran) versus a combination of warfarin, aspirin, and no treatment in an England, UK, setting over 5 years.	Dabigatran Warfarin Aspirin No treatment	AF, 822 527, 5 years, reference year not reported	Direct costs reported: total costs of clinical events for each treatment and drug costs per day; Indirect costs not reported	Drug budget increase of £268 167 861 Overall cost saving of £11 240 201. Total cost per day for : Dabigatran £2.20 Warfarin £1.18; Aspirin £0.09 No treatment £0.00

7.5.4 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details9:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

No clinical experts were consulted to assess the resource use included in the analysis.

Intervention and comparators' costs

7.5.5 **Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Drug unit costs and dosing assumptions were extracted from BNF68 [121], and are presented in Table 62. Monitoring costs were applied to all patients on warfarin treatment, and a half-cycle correction was applied. Half-cycle correction was not applied to treatment costs since it was assumed that these costs would be incurred in full as part of a prescription charge at the beginning of the cycle.

[9] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 62: Unit costs associated with the technology in the economic model

Items	Edoxaban	Warfarin	Apixaban	Rivaroxaban	Dabigatran 150mg	Dabigatran 110mg
Technology cost	£63.92	£3.26	£66.85	£63.92	£66.86	£66.86
Dose	TBC	Average daily dose: 4.5mg	5mg twice daily.	20mg once daily.	150mg twice daily.	150mg twice daily. Switch to 110mg twice daily when patient is aged 80.
Unit cost	TBC	500mcg 28-tab pack: £1.29 1mg 28-tab pack: £0.83 3mg 28-tab pack: £0.88	5mg 56-tab pack = £61.50	20mg 100-tab pack = £210	150mg 60-cap pack = £65.90	150mg 60-cap pack = £65.90 110mg 60-cap pack = £65.90
Source	TBC	British National Formulary July 2014	British National Formulary July 2014	British National Formulary July 2014	British National Formulary July 2014	British National Formulary July 2014
Monitoring cost	£0	£22.09*	£0	£0	£0	£0
Total	£63.92	£25.35	£66.85	£63.92	£66.86	£66.86

*Source: NHS Costing Template for dabigatran

The monitoring costs for warfarin patients were adapted from the unit cost of anticoagulation monitoring, of £241.54, used in the NHS Costing Template for dabigatran. This was calculated from figures used by the Evidence Review Group (ERG) in their critique of dabigatran. [122] The ERG disaggregated the unit cost to derive costs for primary care and secondary care. The 2009/10 cost of £241.54 was weighted such that 75% of patients were monitored in primary care and 25% in secondary care, this assumes that patients have 18 visits per year. This was accepted in the Apixaban STA as being appropriate. The cost was disaggregated giving a unit cost in primary care of £188.92 (2004/05 price) and a unit cost in secondary care of £298.40 (2008/09 cost). These costs were inflated to 2013 costs using the PSSRU Hospital and Community Services Health Index (HCHS).

The model assumes that 34% of patients will be seen in a secondary care setting with the remaining 66% seen in primary care. These estimates were obtained from a review of the Rivaroxaban STA. [50] The manufacturers were unable to find suitable data on monitoring practices through a systematic review; therefore they carried out their own survey. The proportion in primary, secondary and hybrid care is reported, and it was assumed that hybrid services are split 50/50 between primary and

secondary care. The outcome of the survey subsequently results in an overall split of 66.45/33.55 between primary and secondary care.

Table 63: Warfarin monitoring cost

	Proportion	Cost per year
Primary care	66%	£235.11
Secondary care	34%	£323.10
Total		£265.03

The model assumes that 34% of patients will be seen in a secondary care setting with the remaining 66% seen in primary care. These estimates were obtained from a review of the Rivaroxaban STA. [50] The manufacturers were unable to find suitable data on monitoring practices through a systematic review; therefore they carried out their own survey. The proportion in primary, secondary and hybrid care is reported, and it was assumed that hybrid services are split 50/50 between primary and secondary care. The outcome of the survey subsequently results in an overall split of 66.45/33.55 between primary and secondary care.

Health-state costs

7.5.6 **Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.**

The costs applied to the health states in the economic model are shown in Table 64. The methods used to derive each of these estimates are described subsequently. Costs associated with events, i.e. other ICH, TIA, Non-ICH major bleed, and CRNMB, are discussed in Section 7.5.7.

Table 64: List of health states and associated costs in the economic model

Health states	Value (Standard error)	Duration	Reference
Mild IS	£3,683 (£1,080)	Acute, one off cost	Luengo-Fernandez et al. 2013 [123]
Post Mild IS	£193 (£41)	Monthly	Luengo-Fernandez et al. 2013 [123]
Moderate IS	£19,212 (£2,654)	Acute, one off cost	Luengo-Fernandez et al. 2013 [123]
Post Moderate IS	£376 (£91)	Monthly	Luengo-Fernandez et al. 2013 [123]
Severe IS	£26,240 (£4,273)	Acute, one	Luengo-Fernandez et al.

Health states	Value (Standard error)	Duration	Reference
		off cost	2013 [123]
Post Severe IS	£571 (£388)	Monthly	Luengo-Fernandez et al. 2013 [123]
Mild HS	£10,723 (£2,184)	Acute, one off cost	Luengo-Fernandez et al. 2013 [123]
Post Mild HS	£193 (£41)	Monthly	Luengo-Fernandez et al. 2013 [123]
Moderate HS	£27,548 (£6,023)	Acute, one off cost	Luengo-Fernandez et al. 2013 [123]
Post Moderate HS	£376 (£91)	Monthly	Luengo-Fernandez et al. 2013 [123]
Severe HS	£46,598 (Not reported)	Acute, one off cost	Luengo-Fernandez et al. 2013 [123]
Post Severe HS	£571 (£388)	Monthly	Luengo-Fernandez et al. 2013 [123]
SE	£4,285 (Not reported)	Acute, one off cost	Luengo-Fernandez et al. 2013 [123]
Post SE	£193 (£41)	Monthly	Luengo-Fernandez et al. 2013 [123]
MI	£2,446 (Not reported)	Acute, one off cost	NHS reference costs [124]
Post MI	£3.86 (Not reported)	Monthly	Electronic Drug Tariff [125], BNF68 [121]
Death	£2,902 (Not reported)	One off cost	Luengo-Fernandez et al. 2013 [123]

Health state costs

IS and HS were stratified by severity (mild, moderate or severe) and were modelled for both acute episodes and post-event costs. SE and MI health states were modelled for both acute episodes and long term effects. Long term cost outcomes were analysed by background cost per month.

All costs for IS, HS, and SE were based on by Luengo-Fernandez et al. (2012). [123] The study prices resource use using unit costs valued in 2008/2009 UK pounds sterling. These 2008/9 costs were inflated to 2013 costs using the PSSRU Hospital and Community Services Health Index (HCHS), using an increase factor of 1.0828. [126]

The Luengo-Fernadez study reports the acute health-care costs for non-disabling, moderately disabling and totally disabling ischaemic strokes and haemorrhagic strokes (interpreted as mild, moderate and severe respectively). [123] The costs include nurse visits, General Practitioner visits, Accident and Emergency, outpatient, visits, day case and hospitalisations. The paper also reports the annual post-acute costs of the three classifications of ischaemic stroke and haemorrhagic stroke; these were divided by 12 to obtain the monthly long term cost of events. The acute cost of an SE was assumed to be equivalent to mild stroke; this was a calculated weighted average cost of all non-disabling strokes (ischaemic, haemorrhagic, unknown). Post-event SE costs were assumed to be the same as a mild stroke.

The costs are outlined in Table 65 below, including inflation-adjusted final costs

Table 65: Stroke health state costs (One off acute costs and subsequent monthly cost)

	Acute cost (2008)	Acute cost (inflated to 2013)	Post-acute annual cost (2008)	Post-acute monthly cost (2008)	Post-acute monthly cost (inflated to 2013)
Mild IS	£3,401	£3,683	£2,135	£178	£193
Moderate IS	£17,743	£19,212	£4,165	£347	£376
Severe IS	£24,234	£26,240	£6,324	£527	£571
Mild HS	£9,903	£10,723	£2,135	£178	£193
Moderate HS	£25,442	£27,548	£4,165	£347	£376
Severe HS	£43,036	£46,598	£6,324	£527	£571
SE	£4,078	£4,285	£2,135	£178	£193

Source: Luengo-Fernandez et al. 2013 [123]

Acute MI costs include the cost of an MI event, cardiac rehabilitation and a coronary revascularisation assessment. NHS reference costs [124] were used to calculate the cost of an acute or suspected MI, using the weighted average of HRG codes EB10A to EB10E. The cost of cardiac rehabilitation is taken from Beswick et al. (2004) [127]; these 2001 costs were inflated to 2013 costs using the PSSRU HCHS. [126] NHS reference costs were used to calculate the cost of a coronary revascularisation assessment; this was assumed to be the cost of a cardiology outpatient appointment. Patients also received an antiplatelet (clopidogrel 75mg once daily) for one year.

Table 66: Acute MI costs

Description	Code	Activity	Cost
Actual or Suspected Myocardial Infarction with CC Score 13+	EB10A	3625	£3,277
Actual or Suspected Myocardial Infarction with CC Score 10-12	EB10B	10739	£2,469
Actual or Suspected Myocardial	EB10C	20775	£1,793

Description	Code	Activity	Cost
Infarction with CC Score 7-9			
Actual or Suspected Myocardial Infarction with CC Score 4-6	EB10D	32968	£1,414
Actual or Suspected Myocardial Infarction with CC Score 0-3	EB10E	29230	£1,074
Weighted MI cost			£1,578
Cardiac rehabilitation	N/A	N/A	£486
Coronary revascularisation assessment	320	N/A	£131
Clopidogrel 75mg for one year	N/A	N/A	£21.96 (unit cost £1.83 per 30-tab pack)
Total Weighted Cost			**£2,446**

Abbreviations: CC, complication and co-morbidity ; Reference: NHS Reference Costs 2013/14

Post MI costs comprises of the weighted average of the monthly cost of treatment with beta-blocker (bisoprolol), ACE inhibitor (ramipril) and statin (atorvastatin). These costs were sourced from prescription cost analysis 2013 and are summarised in Table 67.

Table 67: Monthly post MI costs

	Cost per 28-tab pack	Scripts PM	Weighted cost
Bisoprolol 5mg tablets	£0.91	199	
Bisoprolol 10mg tablets	£0.99	105	
			£0.94
Ramipril 1.25mg capsules	£1.00	188	
Ramipril 1.25mg tablets	£1.10	5	
Ramipril 10mg capsules	£1.21	811	
Ramipril 10mg tablets	£1.31	19	
Ramipril 2.5mg capsules	£1.07	480	
Ramipril 2.5mg tablets	£1.10	10	
Ramipril 5mg capsules	£1.14	550	
Ramipril 5mg tablets	£1.14	11	
			£1.14
Atorvastatin 10mg tablets	£1.09	119	
Atorvastatin 20mg tablets	£1.31	145	
Atorvastatin 40mg tablets	£1.53	167	
Atorvastatin 80mg tablets	£2.50	268	
			£1.78
Total monthly cost			**£3.86**

Cost of death

The cost of death was based on a published study (Luengo-Fernandez et al. 2012 [123]). The cost of fatal stroke is the calculated weighted average cost of all fatal strokes (ischaemic, haemorrhage, unknown) for 2008/9 subsequently inflated to 2013 costs using the PSSRU HCHS [126] -this gives a cost of death of £2,902. This cost is applied to all deaths that occur in the model.

Adverse-event costs

7.5.7 **Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Costs of each event are presented in Table 68.

Table 68: List of adverse events and summary of costs included in the economic model

Adverse events	Value	Duration	Reference
Other ICH	£2,589	Acute, one off cost	NHS Reference Costs 2013
Transient ischaemic attack	£938	Acute, one off cost	NHS Reference Costs 2013
Non-ICH major bleed	£1,803	Acute, one off cost	NHS Reference Costs 2013
CRNMB	£883	Acute, one off cost	NHS Reference Costs 2013

Other ICH

The cost of an other intracerebral haemorrhage is based on a one off, acute, cost. There are no long term monthly costs associated with this event.

The acute cost of an other ICH was taken from NHS reference costs 2013 [124] and is the weighted average of HRG codes AA23C to AA23G: Haemorrhagic Cerebrovascular Disorders. Table 69 shows a summary of these costs.

Table 69: ICH (excluding stroke) costs

	Code	Activity	Cost
Haemorrhagic Cerebrovascular Disorders with CC Score 14+	AA23C	344	£7,848
Haemorrhagic Cerebrovascular Disorders with CC Score 10-13	AA23D	1302	£4,623
Haemorrhagic Cerebrovascular Disorders with CC Score 6-9	AA23E	3324	£2,860
Haemorrhagic Cerebrovascular Disorders with CC Score 3-5	AA23F	4107	£2,159
Haemorrhagic Cerebrovascular Disorders with CC Score 0-2	AA23G	3456	£1,548
Total weighted cost			**£2,589**

Abbreviations: CC, complication and co-morbidity

TIA

The cost of a transient ischaemic attack is based on a one off, acute, cost. There are no long term monthly costs associated with this event.

The acute cost of a TIA was taken from NHS reference costs 2013 [124] and is the weighted average of HRG codes AA29C to AA29F: Transient Ischaemic Attack with CC.

Table **70** shows a summary of these costs.

Table 70: Transient Ischaemic Attack costs

	Code	Activity	Cost
Transient Ischaemic Attack with CC Score 11+	AA29C	1021	£2,384
Transient Ischaemic Attack with CC Score 8-10	AA29D	2988	£1,490
Transient Ischaemic Attack with CC Score 5-7	AA29E	8475	£999
Transient Ischaemic Attack with CC Score 0-4	AA29F	18496	£741
Total weighted cost			**£938**

Abbreviations: CC, complication and co-morbidity

Non- ICH major bleed

The cost of a non- Intracerebral haemorrhage major bleed is based on a one off, acute, cost. There are no long term monthly costs associated with this event.

The acute cost of a non-ICH major bleed was taken from NHS reference costs 2013 [124] and is the weighted average of the HRG codes shown in Table 71.

Table 71: Non- Intracerebral haemorrhage major bleed cost

	Code	Activity	Cost
Spinal Cord Conditions with CC Score 7+	HC28D	609	£8,360
Spinal Cord Conditions with CC Score 5-6	HC28E	696	£4,965
Spinal Cord Conditions with CC Score 3-4	HC28F	1168	£3,894
Spinal Cord Conditions with CC Score 0-2	HC28G	2275	£2,349
Non-Inflammatory Bone or Joint Disorders, with CC Score 12+	HD24D	933	£4,116
Non-Inflammatory Bone or Joint Disorders, with CC Score 8-11	HD24E	3048	£2,832
Non-Surgical Ophthalmology, with Interventions	BZ24D	1111	£3,337
Cardiac Conditions with CC Score 1+	PA23A	9145	£2,860
Major General Abdominal Procedures, 19 years and over with CC Score 10+	FZ12L	503	£9,662
Major General Abdominal Procedures, 19 years and over with CC Score 6-9	FZ12M	1491	£6,860
Major General Abdominal Procedures, 19 years and over with CC Score 3-5	FZ12N	3274	£4,989

	Code	Activity	Cost
Major General Abdominal Procedures, 19 years and over with CC Score 1-2	FZ12P	6572	£3,310
Major General Abdominal Procedures, 19 years and over with CC Score 0	FZ12Q	7641	£2,573
Gastrointestinal Bleed, with Multiple Interventions, with CC Score 5+	FZ38G	774	£4,993
Gastrointestinal Bleed, with Multiple Interventions, with CC Score 0-4	FZ38H	1217	£3,097
Gastrointestinal Bleed, with Single Intervention, with CC Score 8+	FZ38J	661	£3,591
Gastrointestinal Bleed, with Single Intervention, with CC Score 5-7	FZ38K	1721	£2,693
Gastrointestinal Bleed, with Single Intervention, with CC Score 0-4	FZ38L	7265	£1,872
Gastrointestinal Bleed, without Interventions, with CC Score 9+	FZ38M	1619	£2,121
Gastrointestinal Bleed, without Interventions, with CC Score 5-8	FZ38N	10300	£1,373
Gastrointestinal Bleed, without Interventions, with CC Score 0-4	FZ38P	66817	£791
Total weighted cost			**£1,803**

Abbreviations: CC, complication and co-morbidity

CRNMB

The cost of a CRNMB is based on a one off, acute, cost. There are no long term monthly costs associated with this event.

The acute cost of a CRNMB was taken from NHS reference costs 2013 [124] and is the weighted average of the HRG codes shown in Table 72.

Table 72: CRNMB cost

	Code	Activity	Cost
Gastrointestinal Bleed, without Interventions, with CC Score 5-8	FZ38N	10300	£1,373
Gastrointestinal Bleed, without Interventions, with CC Score 0-4	FZ38P	66817	£791
Intermediate Nose Procedures, 19 years and over without CC	CZ13Y	26929	£782
Unspecified Haematuria with Interventions, with CC Score 3-6	LB38D	1710	£2,286
Unspecified Haematuria with Interventions, with CC Score 0-2	LB38E	2269	£1,708
Unspecified Haematuria without Interventions, with CC Score 8+	LB38F	659	£2,061
Unspecified Haematuria without Interventions, with CC Score 4-7	LB38G	3130	£1,117
Unspecified Haematuria without Interventions, with CC Score 0-3	LB38H	12035	£719
Total weighted cost			**£883**

Abbreviations: CC, complication and co-morbidity

Miscellaneous costs

7.5.8 **Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

No additional costs were included in the model.

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The model was developed with reference to the recent model designed to support the apixaban technology appraisal [128], which was considered to have an acceptable structure when evaluated by the ERG [73]. The critique of the apixaban model by the ERG was used to further develop the model described in this section, for example, by incorporating no limitations on the number of recurrent events that a patient can experience. The ERG also noted that a discrete event simulation rather than a Markov modelling approach may be more appropriate for this disease area, due to the influence of individual patient characteristics on outcomes. However, the ERG acknowledged that a well-constructed Markov model may be sufficient to capture the mean differences in costs and consequences associated with prophylactic treatments in AF. As such, no scenario analyses investigating the uncertainty around structural assumptions have been undertaken.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Univariate sensitivity analyses were performed to examine the effect of changes in key model parameters. Deterministic sensitivity analysis was performed where each parameter was varied according to the measure of dispersion (95% confidence intervals and standard deviations where applicable). Where confidence intervals were unavailable, the standard deviation was assumed to be 25% of the mean. The variables included in the sensitivity analysis are presented in section **Error! Reference source not found.**, Appendix 16.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A PSA was conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. Key parameters were varied by sampling from probability distributions.

The model was run for 1,000 simulations to generate total costs and QALYs for each treatment arm by varying event rates, costs, risks and utilities and population characteristics simultaneously. Time horizon and model settings were kept constant.

A number of probability distributions were employed including the beta, lognormal, gamma, and Dirichlet distributions. The PSA parameters are provided in Section **Error! Reference source not found.** Appendix 17.

Probabilities, such as acute mortality rate and edoxaban event rates, were sampled from a beta distribution. This distribution is a conjugate of the binomial and is bounded by 0 and 1. The parameterisation consists of denoting the shape parameter (i.e. alpha) as the number of events and the scale parameter (i.e. beta) as the number of non-events. Patient numbers obtained from the trials or from published estimates were used to represent this source of variation. For baseline event rates for edoxaban, alpha and beta was estimated by calculating the mean alpha (number of events per cycle), and the mean beta (number of non-events per cycle) over the trial period.

The Dirichlet distribution was used to sample inputs pertaining to the distribution of patients amongst a number of different occurrences, such as stroke severity and $CHADS_2$ score at baseline. The Dirichlet distribution is a multivariate generalization of the beta distribution, and a series of conditional beta distributions was utilised [129], which involves the decomposition of a multi-branch node into a series of conditional dichotomous nodes.

Hazard ratios were assumed to be distributed according to a lognormal distribution. Confidence intervals around the HRs estimated in the NMA for relative treatment effect were estimated on the log-scale, and the logarithm of the risk was assumed to be normally distributed. The standard error around the HRs obtained from the NMA was estimated from the reported 95% confidence intervals , by taking the natural logarithms of the upper and lower limit, and dividing the width of the adjusted interval by 1.96*2. [129]

For utilities, a beta distribution was used due to the bounds of the distribution (i.e. 0 to 1). Standard deviations around the point estimate were taken from the published literature. The values of alpha (α) and beta (β) used to parameterize the distribution were calculated from the mean (μ) and standard error of the utility value, using the following equations:

$$\alpha = \frac{1-\mu}{\left(\frac{s}{\mu}\right)2} - \mu \qquad \beta = \frac{\alpha}{\mu} - \alpha$$

Costs were sampled from a gamma distribution, since this distribution has a lower bound of 0 and therefore avoids the generation of any negative costs. The distribution can be highly skewed to reflect the natural skew in costs. Standard deviations were used along with the mean to obtain the shape and scale parameters of the gamma distribution. Standard deviations around the point estimate were taken from the published literature, and where data wasn't reported, a 25% standard deviation of the mean was assumed. The values of alpha (α) and beta (β) used to parameterize the distribution were calculated from the mean (μ) and standard error (s) of the utility value, using the following equations:

$$\alpha = \mu^2 - s^2 \qquad \beta = \frac{s^2}{\mu}$$

7.7 Results

Clinical outcomes from the model

7.7.1 **For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

Clinical trial results are compared against model outcomes in Table 73. The median follow-up of the ENGAGE AF-TIMI 48 trial is 33 months, so the model outcomes have been evaluated at this time point, by calculating the total number of clinical outcomes represented by health states in the first 33 cycles of the model. It is important to note that the incidence of these outcomes (IS, HS, SE and MI) as captured in the ENGAGE AF-TIMI 48 study represent the number of first events. However due to the structure of this cost-effectiveness model, it was not possible to estimate the number of first events; instead, the estimates in the model refer to the total number of events experienced.

The model appears to provide a good approximation of the clinical trial for the majority of clinical outcomes. The number of predicted events is higher for IS, MI, non-ICH major bleed and CRNMB, while the model provides a good approximation of the number of HS, SE, other ICH and TIA.

Table 73: Summary of model results compared with clinical data

Outcome	ENGAGE AF-TIMI 48 events		Model events	
	Edoxaban (N=7,012)	Warfarin (N=7,012)	Edoxaban (N=7,012)	Warfarin (N=7,012)
Ischaemic stroke	147	149	244	236
Haemorrhagic stroke	41	76	52	93
Systemic embolism	11	14	16	23
Myocardial infarction	99	111	134	138
Other ICH	21	55	91	179
TIA	92	80	114	99
Non-ICH major bleed	419	457	546	592
CRNMB	1,653	1,904	1,847	2,067

7.7.2 **Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.**

Markov traces displaying the proportion of patients in each health state for each comparator are presented in Section **Error! Reference source not found.** Appendix 18.

7.7.3 **Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.**

Markov traces displaying the QALYs accrued in each health state for each comparator are presented in Section **Error! Reference source not found.** Appendix 20.

7.7.4 **Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:**

The tables below present the total costs and QALYs accrued for each health state and event in the model, for each comparator.

Table 74: Model outputs by clinical outcomes: total discounted costs per patient

Clinical outcome	Edoxaban	Apixaban	Rivaroxaban	Dabigatran 110mg	Dabigatran 150 mg	Warfarin
Intervention	£6,600	£6,980	£6,519	£6,911	£7,012	£599
Monitoring	£0	£0	£0	£0	£0	£2,14
Ischaemic stroke	£3,641	£3,360	£3,745	£4,056	£3,375	£3,515
Haemorrhagic stroke	£1,360	£1,275	£1,532	£625	£573	£2,394
Systemic embolism	£118	£147	£204	£153	£140	£174
Myocardial infarction	£185	£163	£182	£229	£236	£190
Other ICH	£163	£156	£212	£100	£135	£318
TIA	£66	£67	£65	£47	£52	£57
Non-ICH major bleed	£680	£641	£875	£816	£894	£730
CRNMB	£1,125	£1,141	£1,382	£1,126	£1,136	£1,249
Cost of death	£2,019	£2,011	£2,029	£2,011	£2,010	£2,044
Total costs	**£15,957**	**£15,940**	**£16,744**	**£16,074**	**£15,563**	**£13,413**

Table 75: Model outputs by clinical outcomes: total discounted QALYs per patient

Clinical outcome	Edoxaban	Apixaban	Rivaroxaban	Dabigatran 110mg	Dabigatran 150 mg	Warfarin
Stable AF	6.30	6.41	6.20	6.26	6.39	6.06
Ischaemic stroke	0.19	0.17	0.19	0.21	0.16	0.18
Haemorrhagic stroke	0.04	0.04	0.05	0.02	0.02	0.08
Systemic embolism	0.02	0.03	0.04	0.03	0.03	0.04
Myocardial infarction	0.16	0.14	0.16	0.20	0.20	0.16
Other ICH	0.00	0.00	0.00	0.00	0.00	0.00
TIA	0.00	0.00	0.00	0.00	0.00	0.00
Non-ICH major bleed	0.00	0.00	0.00	0.00	0.00	0.00
CRNMB	0.00	0.00	0.00	0.00	0.00	0.00
Disutility due to age	-0.20	-0.20	-0.19	-0.20	-0.20	-0.19
Total QALYs	**6.52**	**6.59**	**6.44**	**6.51**	**6.60**	**6.32**

7.7.5 **Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.**

Table 76: Summary of QALY gain by health state

Health state	Total QALYs						Increment: Edoxaban vs. comparator					Absolute increment: Edoxaban vs. comparator					% Absolute increment				
	Edoxaban	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin
Stable AF	6.30	6.41	6.20	6.26	6.39	6.06	-0.11	0.1	0.04	-0.09	0.24	0.11	0.1	0.04	0.24	0.24	61%	67%	29%	43%	67%
New IS																					
Mild	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%

Health state	Total QALYs						Increment: Edoxaban vs. comparator					Absolute increment: Edoxaban vs. comparator					% Absolute increment				
	Edoxaban	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin
Moderate	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Severe	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Post IS																					
Mild	0.16	0.14	0.16	0.17	0.14	0.15	0.02	0.00	-0.01	0.02	0.01	0.02	0.00	0.01	0.02	0.01	11%	0%	7%	10%	3%
Moderate	0.00	0.02	0.02	0.02	0.02	0.02	-0.02	-0.02	-0.02	-0.02	-0.02	0.02	0.02	0.02	0.02	0.02	11%	13%	14%	10%	6%
Severe	0.01	0.00	0.01	0.01	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.01	0.00	0.00	0.01	0.01	6%	0%	0%	5%	3%
New HS																					
Mild	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Moderate	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Severe	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Post HS																					
Mild	0.04	0.04	0.04	0.02	0.02	0.07	0.00	0.00	0.02	0.02	-0.03	0.00	0.00	0.02	0.02	0.03	2%	5%	14%	10%	8%
Moderate	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.01	0%	0%	0%	0%	3%
Severe	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
SE																					
New	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Post	0.02	0.03	0.04	0.03	0.02	0.04	-0.01	-0.02	-0.01	0	-0.02	0.01	0.02	0.01	0	0.02	6%	13%	7%	0%	6%
MI																					
New	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1%	0%	1%	1%	0%
Post	0.15	0.14	0.15	0.19	0.20	0.16	0.01	0	-0.04	-0.05	-0.1	0.01	0	0.04	0.05	0.01	6%	0%	29%	24%	3%
Other Events																					
Other ICH	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%

Health state	Total QALYs						Increment: Edoxaban vs. comparator					Absolute increment: Edoxaban vs. comparator					% Absolute increment				
	Edoxaban	**Apixaban**	**Rivaroxaban**	**Dab-110mg**	**Dab-150mg**	**Warfarin**	**Apixaban**	**Rivaroxaban**	**Dab-110mg**	**Dab-150mg**	**Warfarin**	**Apixaban**	**Rivaroxaban**	**Dab-110mg**	**Dab-150mg**	**Warfarin**	**Apixaban**	**Rivaroxaban**	**Dab-110mg**	**Dab-150mg**	**Warfarin**
TIA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Non-ICH major bleed	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
CRNMB	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0%	0%	0%	0%	0%
Disutility due to age	-0.20	-0.20	-0.19	-0.20	-0.20	-0.19	0.00	-0.01	0.00	0.00	-0.01	0.00	0.01	0.00	0.00	0.01	0%	7%	0%	0%	3%
Total QALYs	**6.52**	**6.59**	**6.44**	**6.51**	**6.60**	**6.23**	**-0.1**	**0.05**	**-0.02**	**-0.11**	**0.17**	**0.18**	**0.15**	**0.14**	**0.21**	**0.36**	**100%**	**100%**	**100%**	**100%**	**100%**

Abbreviations: Edox, edoxaban; Apix, apixaban; Riva, rivaroxaban; Dab-150, dabigatran 150mg; Dab-110, dabigatran 110mg; Warf, warfarin

Table 77: Summary of costs by health state

Health state	Costs						Increment: Edoxaban vs. comparator					Absolute increment: Edoxaban vs. comparator					% Absolute increment				
	Edoxaban	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin
Drug costs	£6,600	£6,980	£6,519	£6,911	£7,012	£599	-£380	£81	-£311	-£412	£6,001	£380	£81	£311	£412	£6,001	44%	8%	18%	23%	61%
Monitoring costs	£0	£0	£0	£0	£0	£2,143	£0	£0	£0	£0	-£2,143	£0	£0	£0	£0	£2,143	0%	0%	0%	0%	21%
New IS																					
Mild	£214	£199	£220	£236	£194	£205	£15	-£6	-£22	£20	£9	£15	£6	£22	£20	£9	2%	1%	1%	1%	0%
Moderate	£489	£451	£502	£546	£462	£471	£38	-£13	-£57	£27	£18	£38	£13	£57	£27	£18	4%	1%	3%	1%	0%
Severe	£1,673	£1,544	£1,718	£1,870	£1,582	£1,614	£129	-£45	-£197	£91	£59	£129	£45	£197	£91	£59	15%	5%	11%	5%	0%
Post IS																					
Mild	£501	£464	£516	£551	£440	£480	£37	-£15	-£50	£61	£21	£37	£15	£50	£61	£21	4%	2%	3%	3%	0%
Moderate	£266	£245	£274	£298	£243	£258	£21	-£8	-£32	£23	£8	£21	£8	£32	£23	£8	2%	1%	2%	1%	0%
Severe	£498	£457	£514	£557	£453	£486	£41	-£16	-£59	£45	£12	£41	£16	£59	£45	£12	5%	2%	3%	2%	0%
New HS																					
Mild	£170	£165	£190	£77	£71	£297	£5	-£20	£93	£99	-£127	£5	£20	£93	£99	£127	1%	2%	5%	5%	2%
Moderate	£176	£167	£198	£81	£75	£310	£9	-£22	£95	£101	-£134	£9	£22	£95	£101	£134	1%	2%	5%	6%	2%
Severe	£748	£701	£842	£344	£317	£1,315	£47	-£94	£404	£431	-£567	£47	£94	£404	£431	£567	5%	10%	23%	24%	7%
Post HS																					
Mild	£121	£113	£136	£55	£50	£213	£8	-£15	£66	£71	-£92	£8	£15	£66	£71	£92	1%	2%	4%	4%	1%
Moderate	£50	£47	£57	£23	£21	£90	£3	-£7	£27	£29	-£40	£3	£7	£27	£29	£40	0%	1%	2%	2%	0%
Severe	£95	£89	£108	£44	£39	£170	£6	-£13	£51	£56	-£75	£6	£13	£51	£56	£75	1%	1%	3%	3%	1%
SE																					
New	£41	£52	£72	£53	£49	£61	-£11	-£31	-£12	-£8	-£20	£11	£31	£12	£8	£20	1%	3%	1%	0%	0%
Post	£77	£95	£132	£99	£91	£113	-£18	-£55	-£22	-£14	-£36	£18	£55	£22	£14	£36	2%	6%	1%	1%	0%
MI																					
New	£175	£154	£172	£217	£223	£179	£21	£3	-£42	-£48	-£4	£21	£3	£42	£48	£4	2%	0%	2%	3%	0%
Post	£10	£9	£10	£13	£13	£11	£1	£0	-£3	-£3	-£1	£1	£0	£3	£3	£1	0%	0%	0%	0%	0%

Health state	Costs						Increment: Edoxaban vs. comparator					Absolute increment: Edoxaban vs. comparator					% Absolute increment				
	Edoxaban	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin	Apixaban	Rivaroxaban	Dab-110mg	Dab-150mg	Warfarin
Other Events																					
Other ICH	£163	£156	£212	£100	£135	£318	£7	-£49	£63	£28	-£155	£7	£49	£63	£28	£155	1%	5%	4%	2%	2%
TIA	£66	£67	£65	£47	£52	£57	-£1	£1	£19	£14	£9	£1	£1	£19	£14	£9	0%	0%	1%	1%	0%
Non-ICH major bleed	£680	£641	£875	£816	£894	£730	£39	-£195	-£136	-£214	-£50	£39	£195	£136	£214	£50	5%	20%	8%	12%	0%
CRNMB	£1,125	£1,141	£1,382	£1,126	£1,136	£1,249	-£16	-£257	-£1	-£11	-£124	£16	£257	£1	£11	£124	2%	27%	0%	1%	1%
Cost of death	£2,019	£2,011	£2,029	£2,011	£2,010	£2,044	£8	-£10	£8	£9	-£25	£8	£10	£8	£9	£25	1%	1%	0%	0%	0%
Total costs	**£15,957**	**£15,940**	**£16,744**	**£16,074**	**£15,563**	**£13,413**	£9	-£786	-£118	£395	£2,200	£861	£956	£1,770	£1,815	£9,828	**100%**	**100%**	**100%**	**100%**	**100%**

Table 78: Number of Events (per 1,000 patients)

Health state	Number of events					
	Edoxaban	Apixaban	Rivaroxaban	Dabigatran-110mg	Dabigatran-150mg	Warfarin
Ischaemic Stroke						
Mild	76	71	78	84	62	67
Moderate	34	31	34	38	70	26
Severe	84	78	86	94	32	64
Haemorrhagic Stroke						
Mild	22	20	24	10	9	34
Moderate	9	8	10	4	4	13
Severe	22	21	25	10	9	32
Other Events						

SE	13	16	22	17	16	17
MI	93	82	91	115	118	88
ICH	86	82	111	52	70	165
TIA	94	95	92	67	74	80
Other major bleed	513	485	658	616	672	546
CRNMB	1,734	1,764	2,121	1,735	1,756	1,907
Deaths	999	998	999	999	998	999

Base-case analysis

7.7.6 **Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

The base case results for each comparator option are presented below. These results reflect the $CHADS_2 \geq 2$ patient subpopulation. The base case data sources and assumptions are presented in Table 46.

In Table 79, ICERs are presented for each NOAC versus warfarin. Incremental results for edoxaban versus each NOAC are presented in Table 80.

Table 79: Base-case results.

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,412.98	8.55	6.32	-	-	-	-	-
Dabigatran 150mg	£15,563	8.88	6.60	£2,150	0.34	0.28	£7,645.43	£7,645.43
Apixaban	£15,940	8.87	6.59	£377	-0.01	-0.01	£9,382.94	Strictly dominated
Edoxaban	£15,957	8.79	6.52	£17	-0.08	-0.07	£12,880.91	Strictly dominated
Dabigatran 110mg	£16,074	8.80	6.51	£117	0.01	0.00	£13,565.23	Strictly dominated
Rivaroxaban	£16,744	8.69	6.44	£670	-0.10	-0.08	£28,180.18	Strictly dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 80: Incremental base-case results for edoxaban versus NOACs

Technologies	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Dabigatran 150mg	£394	-0.09	-0.08	Dominated
Apixaban	£17	-0.08	-0.07	Dominated
Dabigatran 110mg	-£117	-0.01	0.00	Less effective
Rivaroxaban	-£787	0.10	0.08	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years				

Sensitivity analyses

7.7.7 **Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

Figure **24** to

Figure **53** show the results of the deterministic sensitivity analysis for edoxaban compared with each comparator in the model. The graphs present the effect of uncertainty around estimates for various parameters on the net monetary benefit (NMB). For each comparison, tornado diagrams show the impact of the variables with the greatest effect on NMB, and subsequently, the relationship between variation in the top 5 parameters and NMB is also shown graphically. The comparisons versus edoxaban are presented in the following order: apixaban, rivaroxaban, dabigatran 110 mg, dabigatran 150 mg, warfarin.

The model also provides the option to present the impact of uncertainty around the same variables on the ICER, however in many of the scenarios in the analysis the incremental result for edoxaban versus the other NOACs fell in the three quadrants of the cost-effectiveness plane that are not associated with a numerical ICER (i.e. edoxaban was dominant to, dominated by, or less effective than the comparator). As such, the ICERs presented in the sensitivity analysis were expressed as the ratio of the incremental costs versus the incremental QALYs, regardless of the quadrant the estimate falls in. This results in a negative ICER for both dominant and dominated scenarios. The results of the PSA should be consulted to interpret these results, where the proportion of cost-effectiveness estimates in each quadrant of the cost-effectiveness plane are presented.

Figure 24: Tornado diagram; Edoxaban vs apixaban

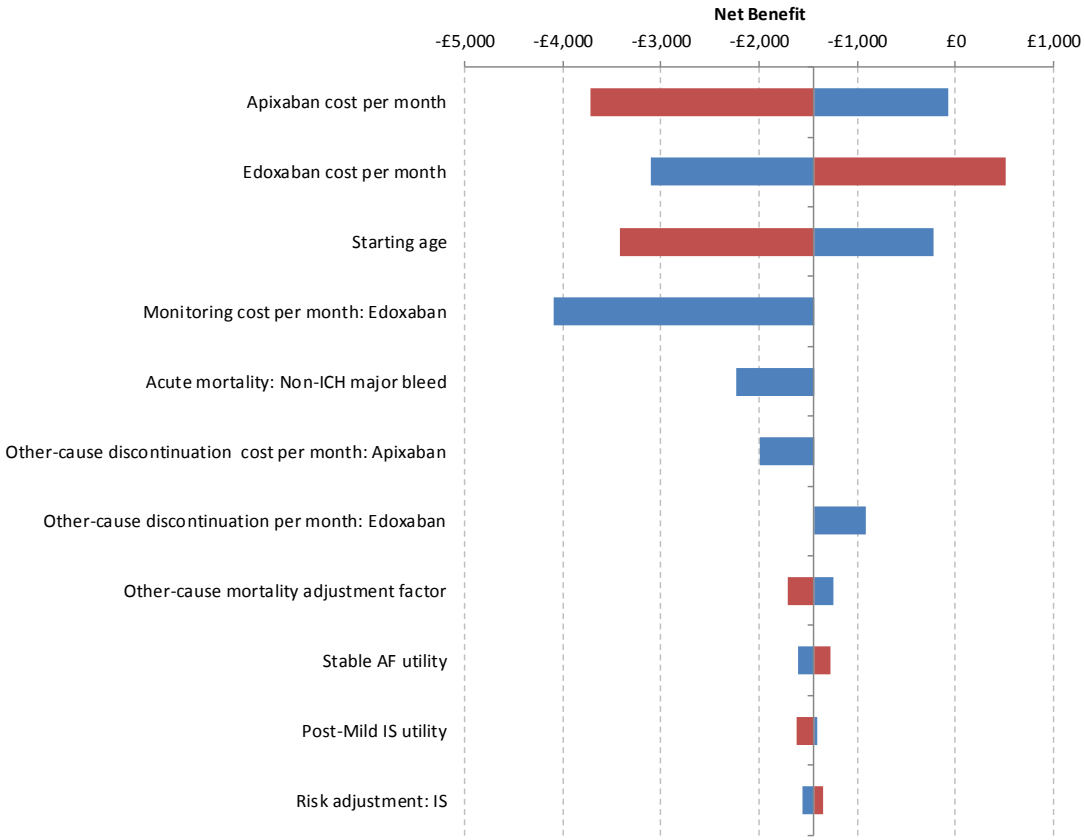
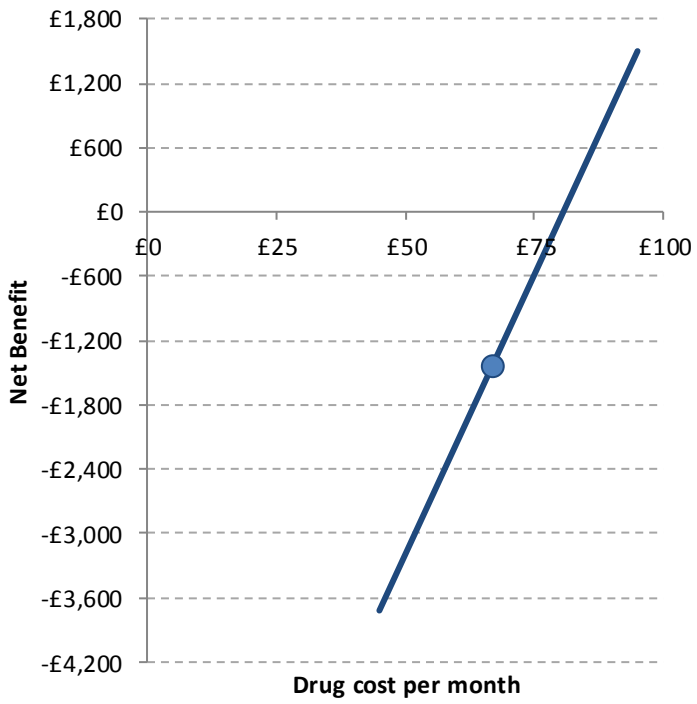
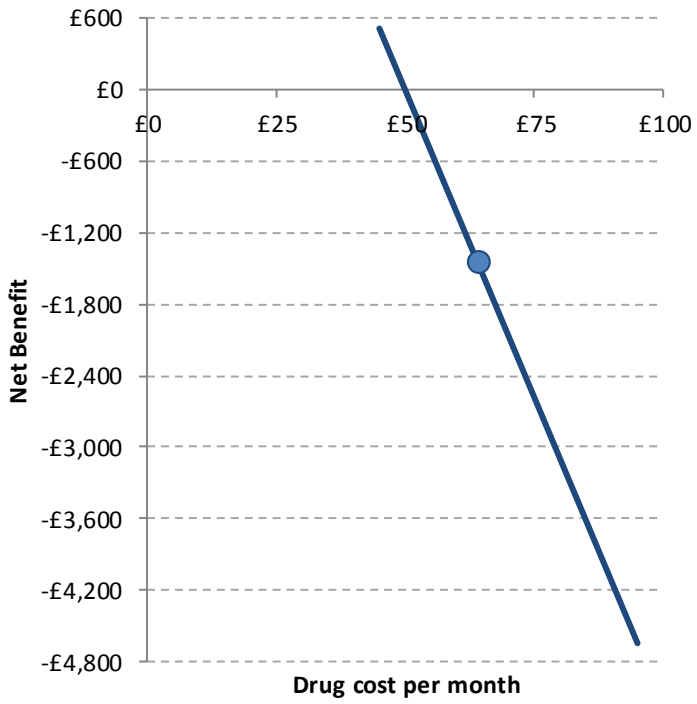


Figure 25: Sensitivity analysis; Apixaban total drug cost per month (Edoxaban vs apixaban)



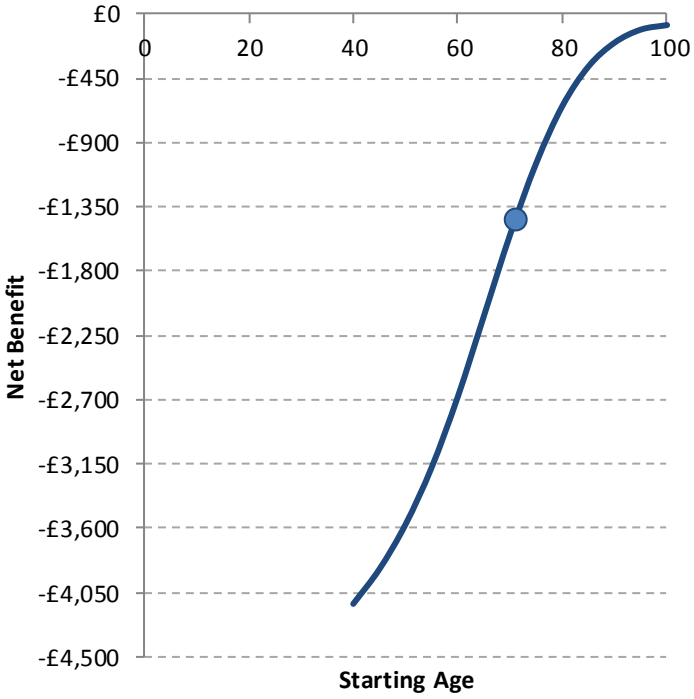
The chart shows the effect on net benefit as the monthly cost of apixaban changes. At a monthly cost of £95 the net benefit is £1,501, compared to -£3,715 when the cost is £45.

Figure 26: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs apixaban)



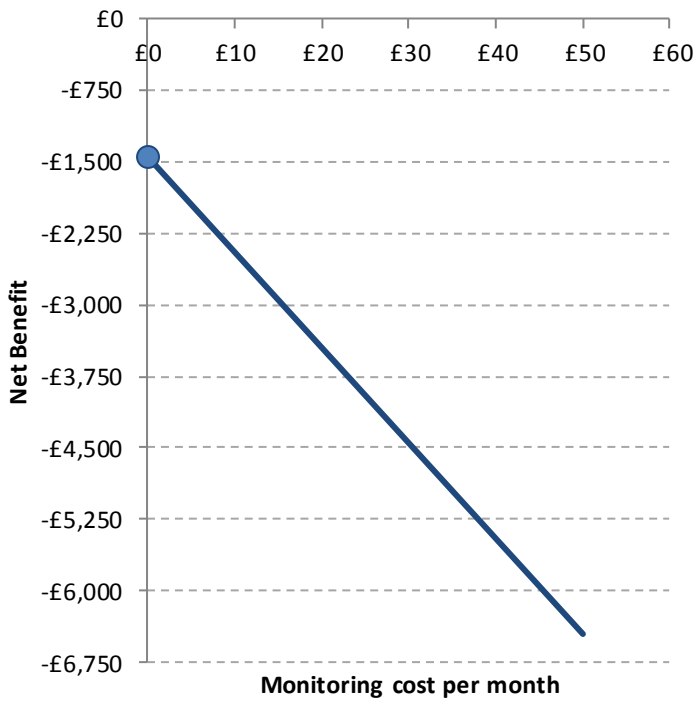
The chart shows the effect on net benefit as the monthly cost of edoxaban changes. At a monthly cost of £95 the net benefit is £-4,646, compared to -£516 when the cost is £45.

Figure 27: Sensitivity analysis; Starting age (Edoxaban vs apixaban)



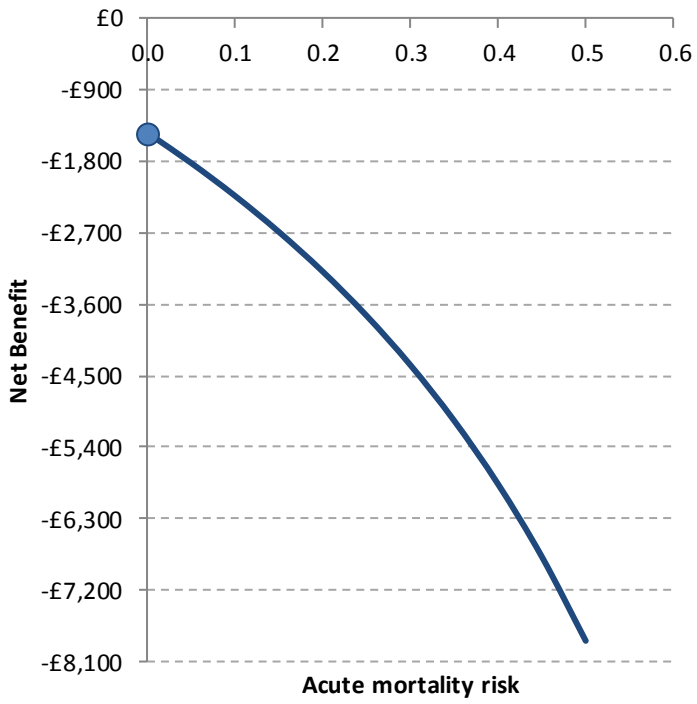
The chart shows the effect on net benefit as the starting age increases. If the starting age is 45 the net benefit is £-3,868, compared to -£643 when the starting age is 80.

Figure 28: Sensitivity analysis; Monitoring cost per month: Edoxaban (Edoxaban vs apixaban)



The chart shows the effect on net benefit as the monthly monitoring cost of edoxaban increases. At a monthly cost of £0, the net benefit is -£1,500 compared to -£6,400 when the cost is £50.

Figure 29: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs apixaban)



The chart shows the effect on net benefit as the acute mortality risk of non-ICH major bleed increases. At a risk of 0% the net benefit is £-1,600, compared to -£7,600 when the risk is 50%.

Figure 30: Tornado diagram; Edoxaban vs rivaroxaban

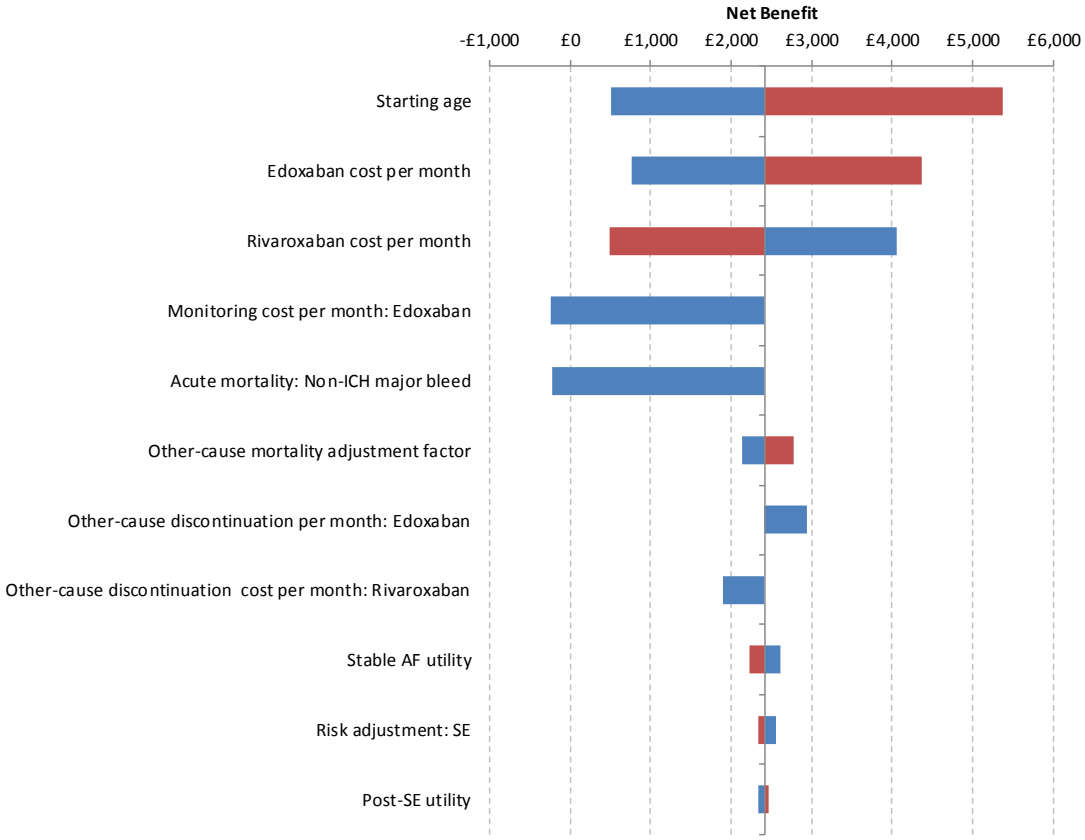
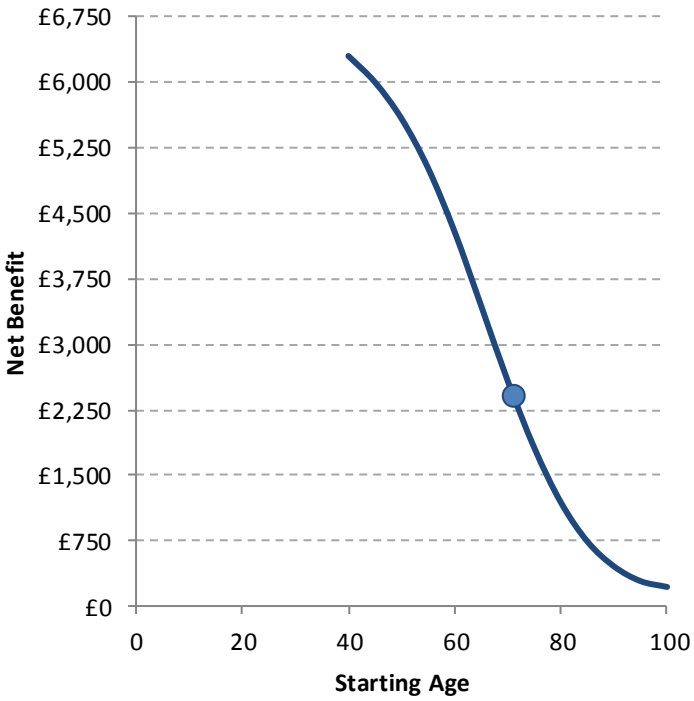
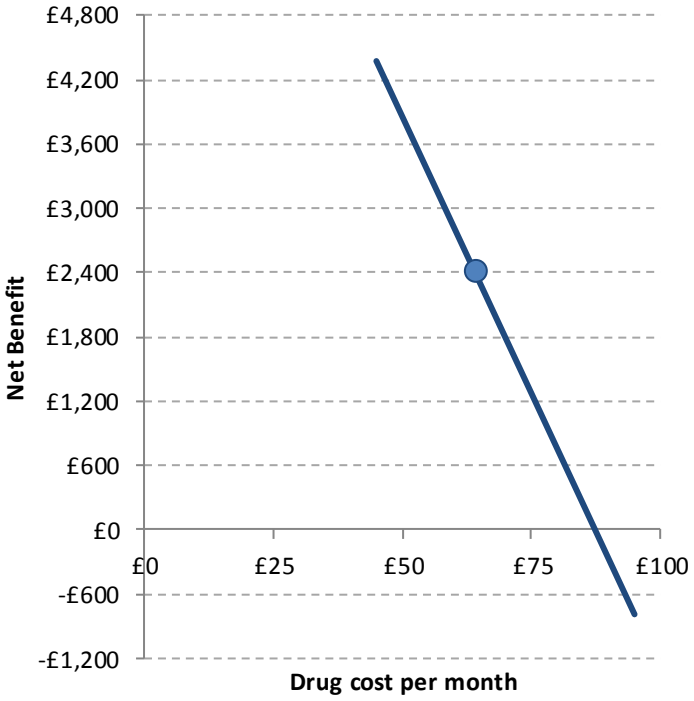


Figure 31: Sensitivity analysis; Starting age (Edoxaban vs rivaroxaban)



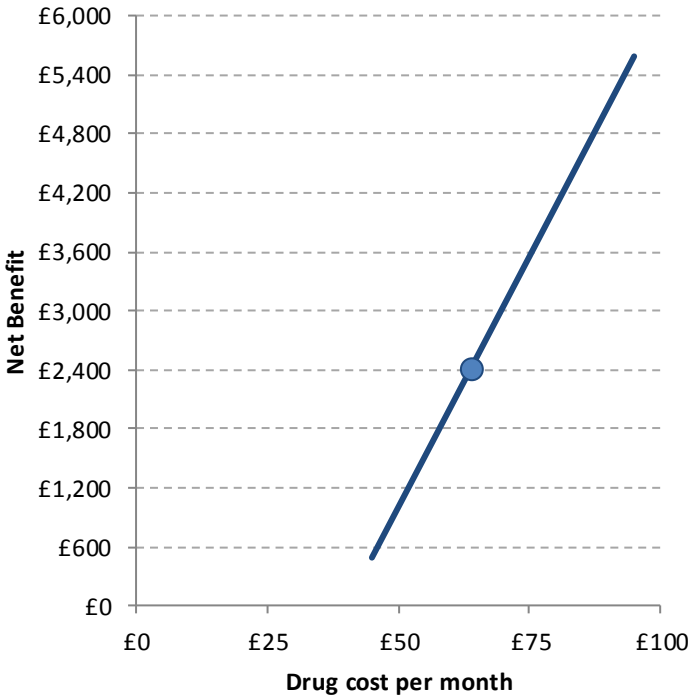
The chart shows the effect on net benefit as the starting age increases. If the starting age is 45 the net benefit is £6,302, compared to £1,193 when the starting age is 80.

Figure 32: Sensitivity analysis; Edoxaban, total drug cost per month (Edoxaban vs rivaroxaban)



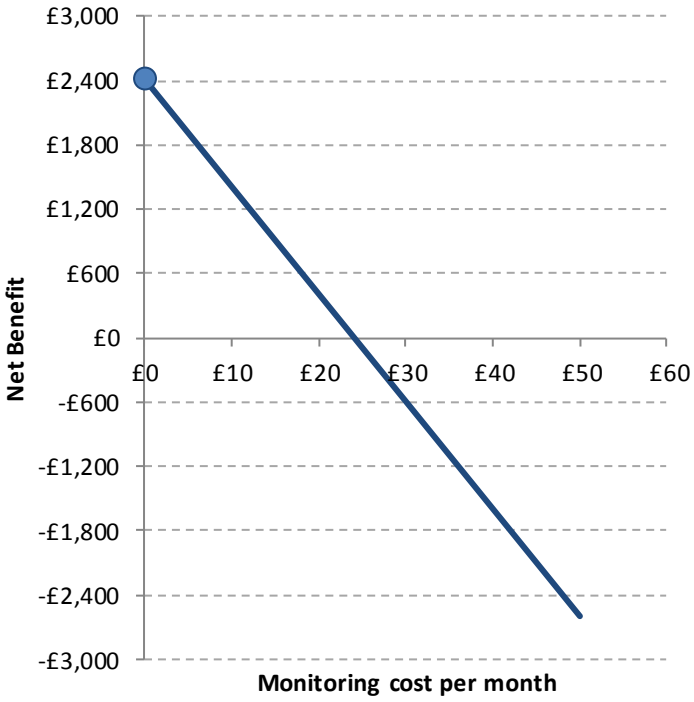
The chart shows the effect on net benefit as the monthly cost of edoxaban changes. At a monthly cost of £45 the net benefit is £4,374, compared to -£788 when the cost is £95.

Figure 33: Sensitivity analysis; Rivaroxaban, total drug cost per month (Edoxaban vs rivaroxaban)



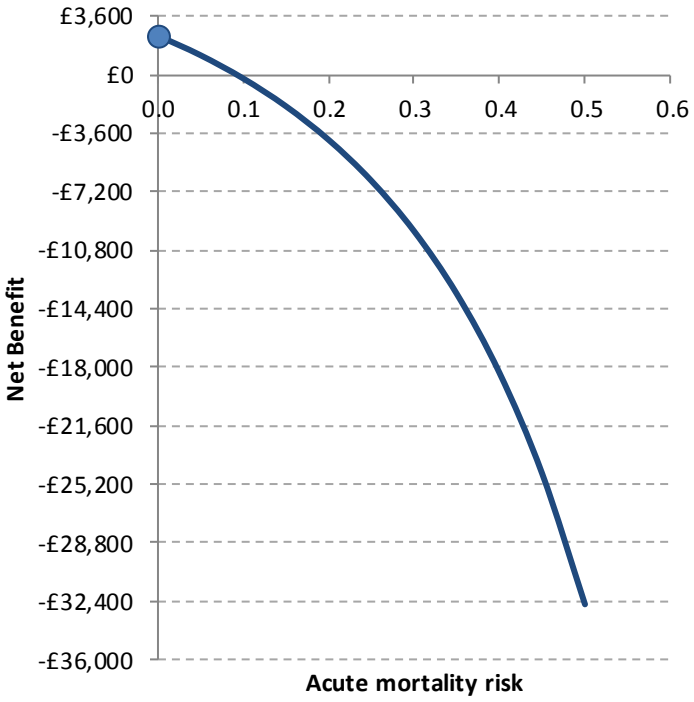
The chart shows the effect on net benefit as the monthly cost of rivaroxaban changes. At a monthly cost of £45 the net benefit is £491, compared to £5,591 when the cost is £95.

Figure 34: Sensitivity analysis; Monthly monitoring cost for edoxaban (Edoxaban vs rivaroxaban)



The chart shows the effect on net benefit as the monthly monitoring cost for edoxaban is varied. At a monthly cost of £0 the net benefit is £2,400, compared to -£2,596 when the cost is £50.

Figure 35: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs rivaroxaban)



The chart shows the effect on net benefit as the acute mortality risk of a non-ICH major bleed increases. At a risk of 0% the net benefit is £2,420, compared to -£32,609 when the risk is 50%.

Figure 36: Tornado diagram; Edoxaban vs dabigatran 110mg

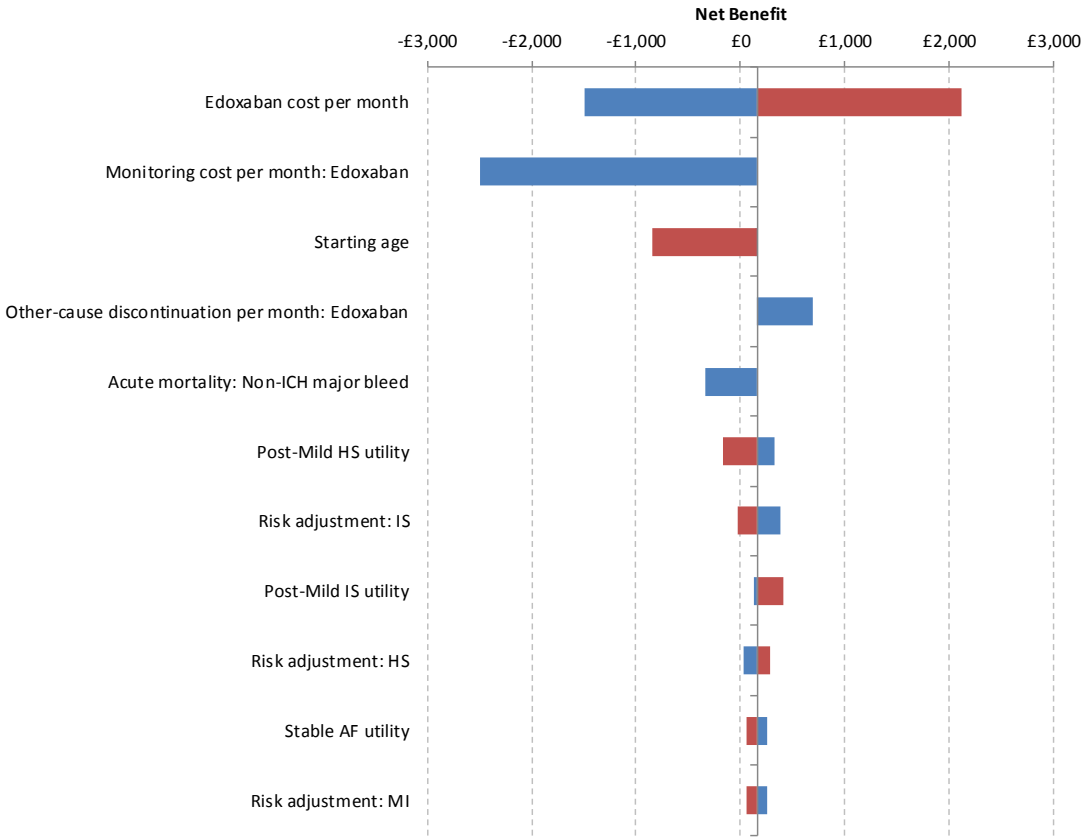
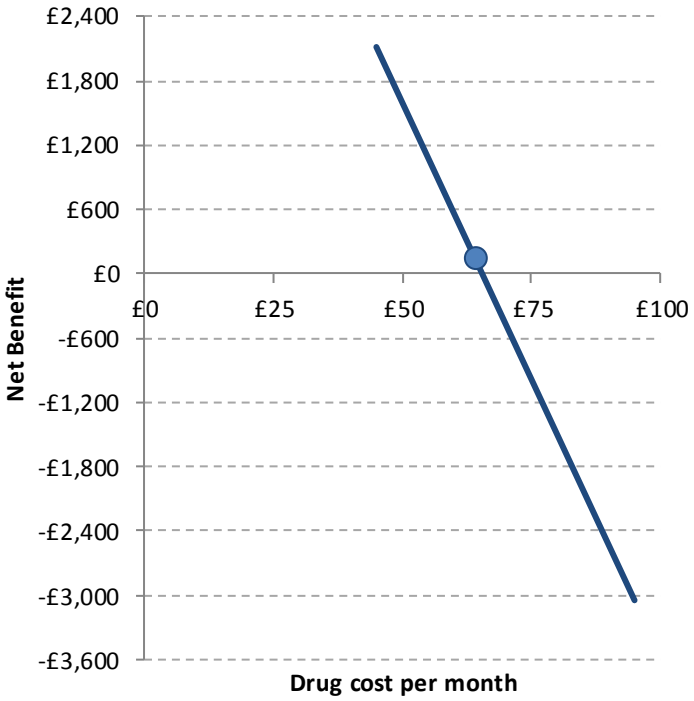
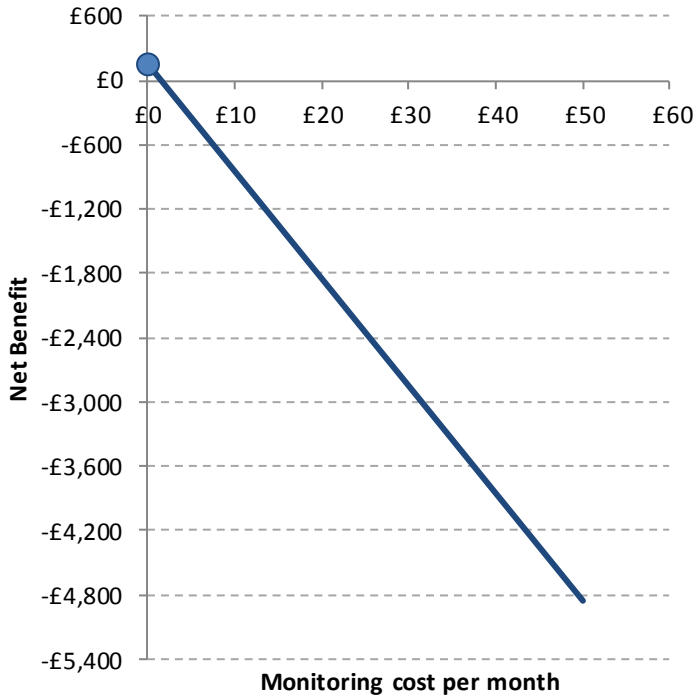


Figure 37: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs dabigatran 110mg)



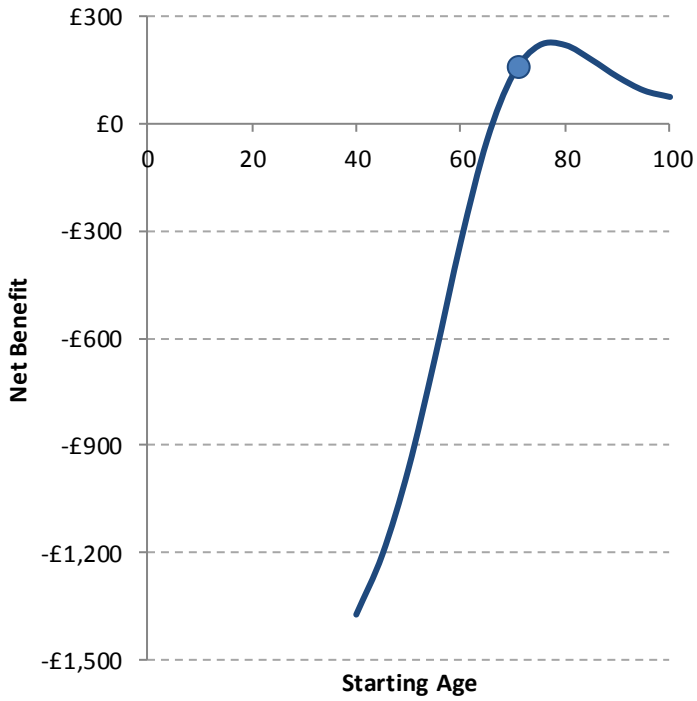
The chart shows the effect on net benefit as the monthly cost of edoxaban changes. At a monthly cost of £95 the net benefit is -£3,046, compared to -£2,116 when the cost is £45.

Figure 38: Sensitivity analysis; Edoxaban total monitoring cost per month (Edoxaban vs dabigatran 110mg)



The chart shows the effect on net benefit as the monthly monitoring cost for edoxaban changes. At a monthly cost of £0 the net benefit is £163, compared to -£4,845 when the monthly cost is £50.

Figure 39: Sensitivity analysis; Starting age (Edoxaban vs dabigatran 110mg)

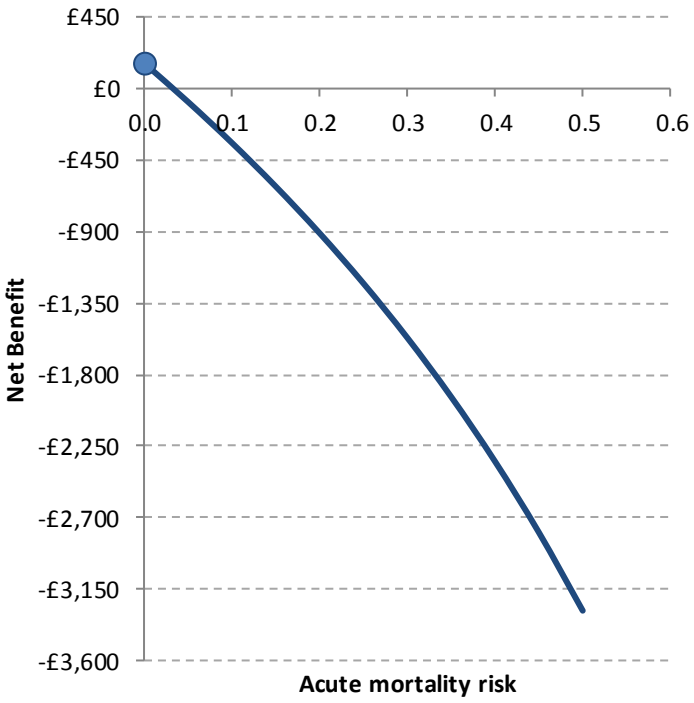


The chart shows the effect on net benefit as the starting age increases. At a starting age of 45 the net benefit is -£1,200, compared to £221 when the starting age is 80.

Figure 40: Sensitivity analysis; Edoxaban: Other-cause discontinuation per month (Edoxaban vs dabigatran 110mg)

The chart shows the effect on net benefit as other-cause discontinuation increases. At a discontinuation rate of 0% the net benefit is £163, compared to £1,223 when the rate is 11%.

Figure 41: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs dabigatran 110mg)



The chart shows the effect on net benefit as acute mortality of a non-ICH major bleed increases. At a risk of 0% the net benefit is £163, compared to -£3,286 when the risk is 50%.

Figure 42: Tornado diagram; Edoxaban vs dabigatran 150mg

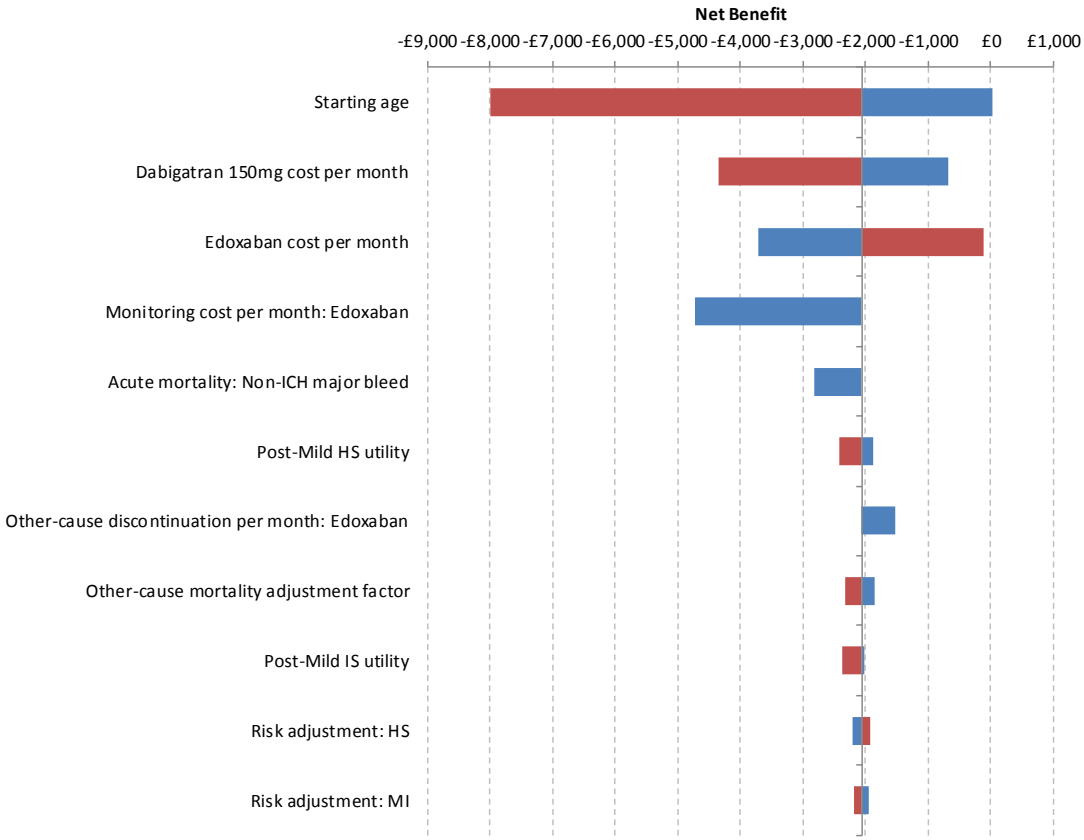
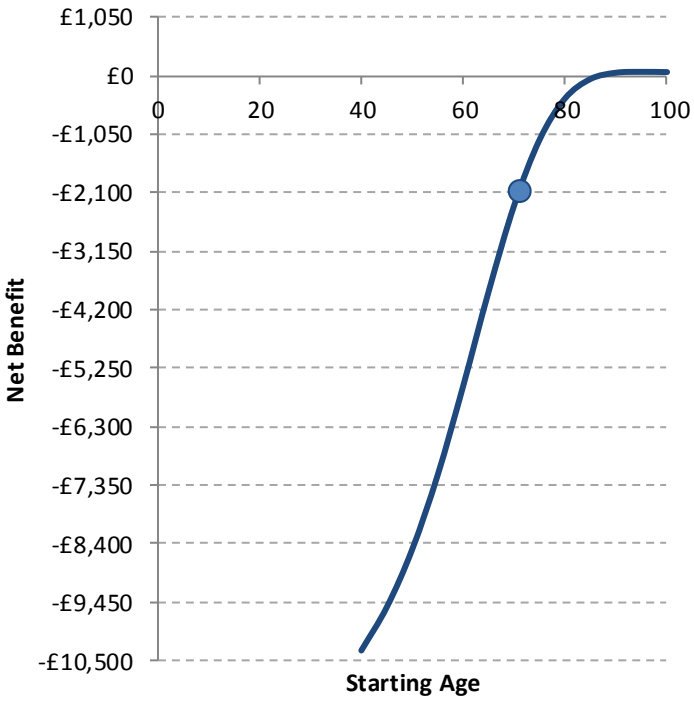
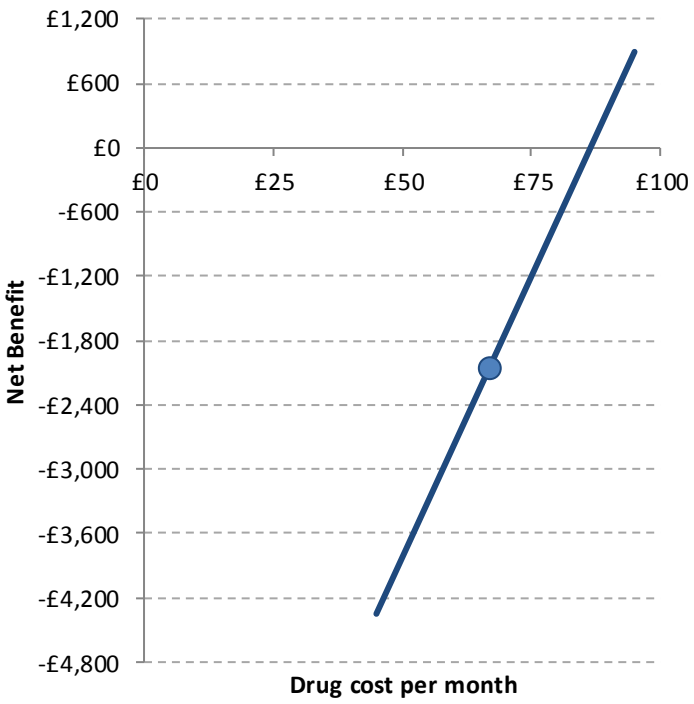


Figure 43: Sensitivity analysis; Starting age (Edoxaban vs dabigatran 150mg)



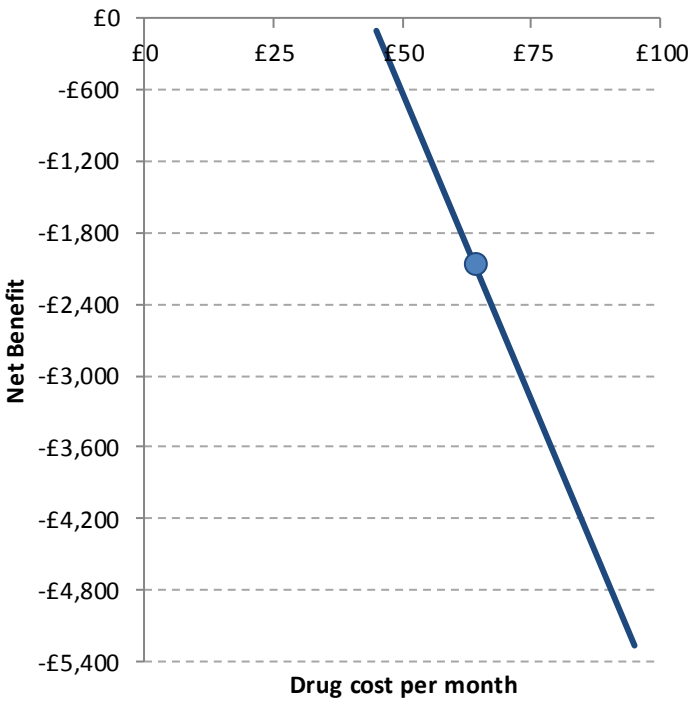
The chart shows the effect on net benefit as the starting age is varies. At a starting of 45 the net benefit is £9,544, compared to -£405 when the age is 80.

Figure 44: Sensitivity analysis; Dabigatran total drug cost per month (Edoxaban vs dabigatran 150mg)



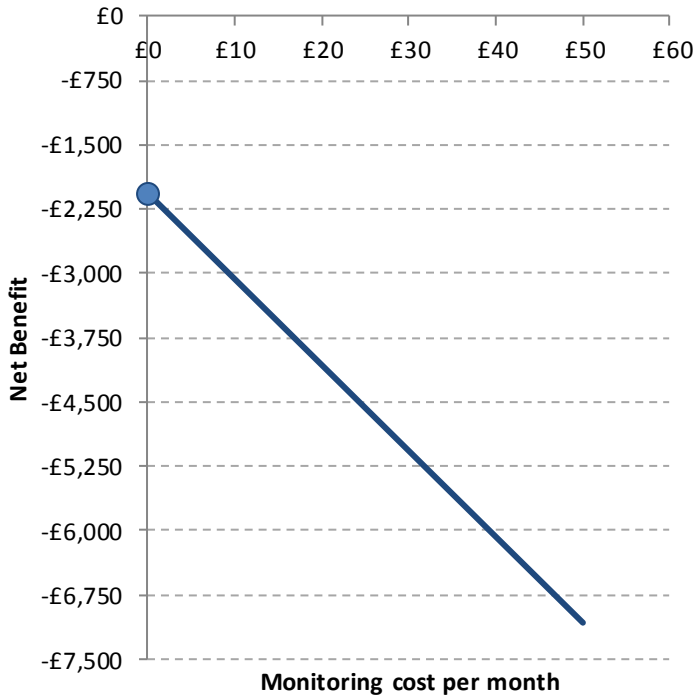
The chart presents the effect on net benefit as the monthly cost of dabigatran is varied. At a monthly cost of £50 the net benefit is -£4,350, compared to £895 when the cost is £95.

Figure 45: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs dabigatran 150mg)



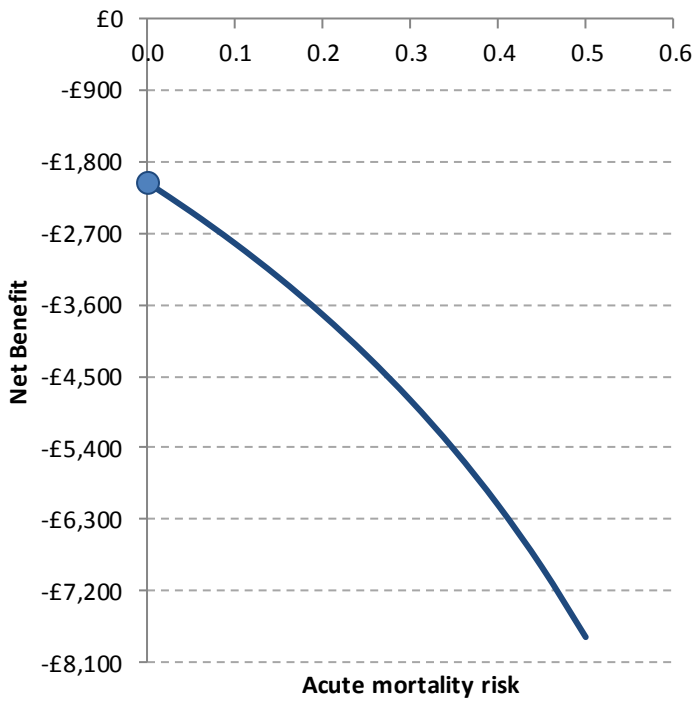
This chart shows the effect on net benefit as the monthly cost of edoxaban is varied. At a monthly cost of £45 the net benefit is -£103, compared to -£5,265 when the cost is £95.

Figure 46: Sensitivity analysis; Edoxaban total monitoring cost per month (Edoxaban vs dabigatran 150mg)



The chart shows the effect on net benefit as the monthly monitoring cost for edoxaban is increased. At a monthly cost of £0, the net benefit is -£2,000 compared to -£7,074 when the monthly cost is £50.

Figure 47: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs dabigatran 150mg)



The chart shows the effect on net benefit as the acute mortality risk for a non-ICH major bleed is increased. At a risk of 0%, the net benefit is -£2,056 compared to -£7,785 when the risk is 50%.

Figure 48: Tornado diagram; Edoxaban vs warfarin

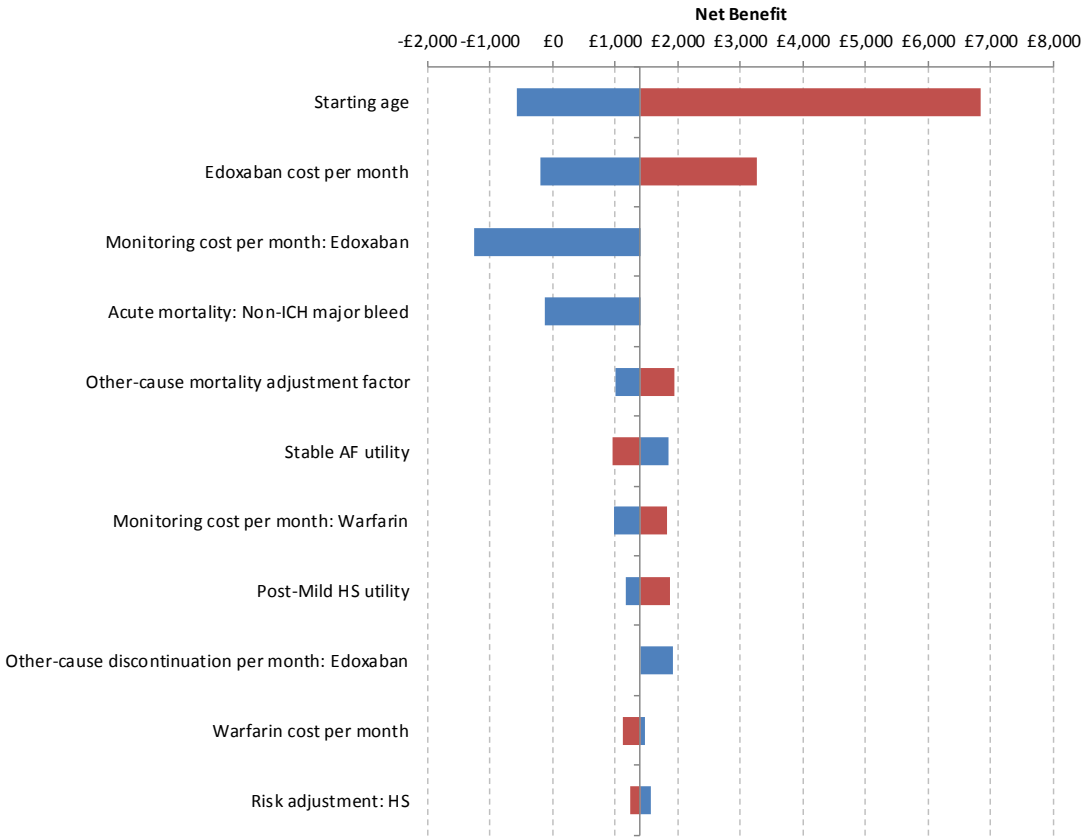
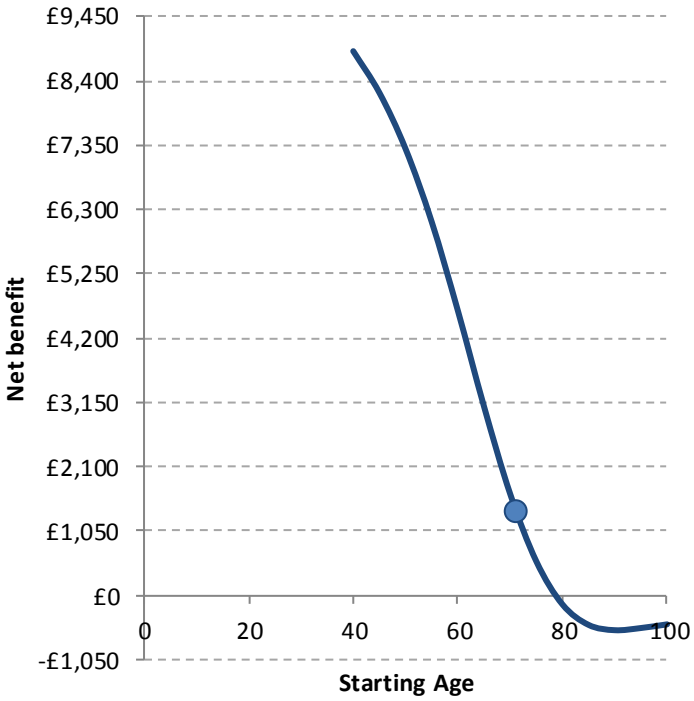
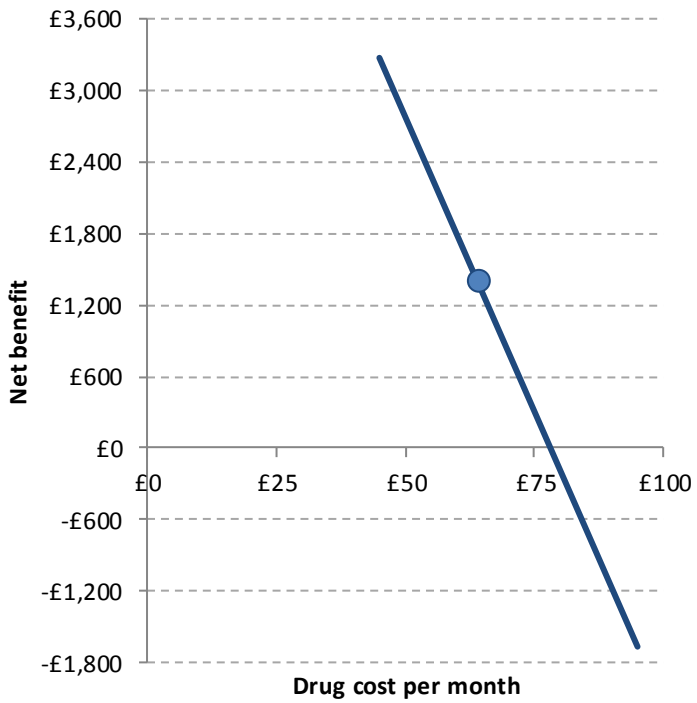


Figure 49: Sensitivity analysis; Starting age (Edoxaban vs warfarin)



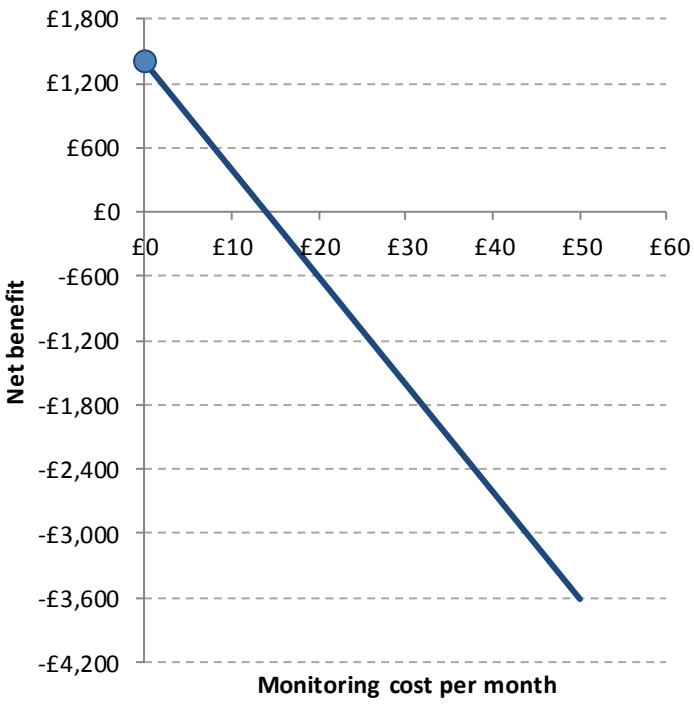
The chart shows the effect on net benefit as the starting age is varied. At a starting age of 45 the net benefit is £8,206, compared to -£149 when the starting age is 80.

Figure 50: Sensitivity analysis; Edoxaban total drug cost per month (Edoxaban vs warfarin)



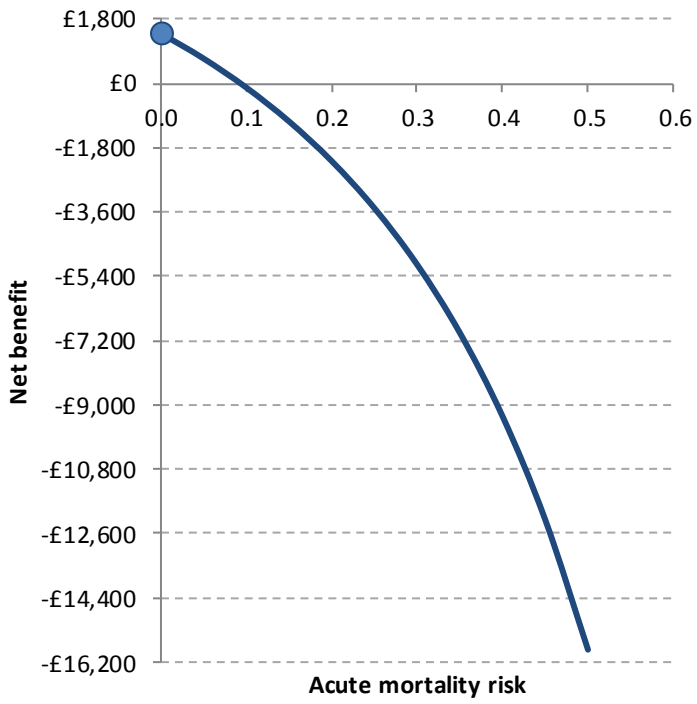
This chart presents the effect on net benefit as the monthly cost of edoxaban is varied. At a monthly drug cost of £95, the net benefit is -£1,667 compared to £3,227 when the monthly cost is £45.

Figure 51: Sensitivity analysis; Edoxaban total monitoring cost per month (Edoxaban vs warfarin)



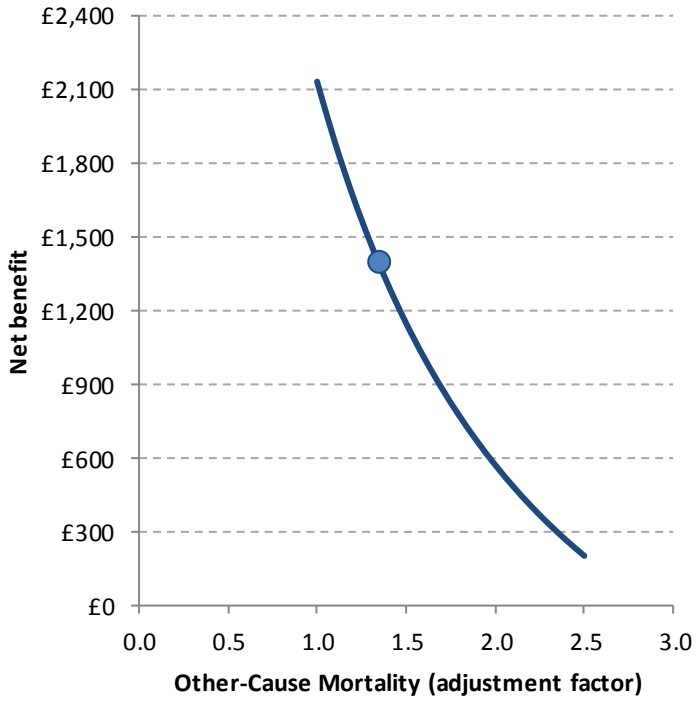
The chart shows the effect on net benefit as the monthly monitoring cost for edoxaban is increased. At a monthly cost of £0 the net benefit is £1,406, compared to -£3,661 when the cost is £50.

Figure 52: Sensitivity analysis; Acute mortality: Non-ICH major bleed (Edoxaban vs warfarin)



The chart shows the effect on net benefit as the acute mortality for non-ICH major bleed is varied. When the mortality risk is equal to 0%, the net benefit is £1,406, compared to -£15,851 when the risk is 50%.

Figure 53: Sensitivity analysis; Other-cause mortality adjustment factor (Edoxaban vs warfarin)



The chart shows the effect on net benefit as the other-cause mortality adjustment factor is varied. When the adjustment factor is equal to 1 (no increase in risk over time), the net benefit is £2,135, compared to £204 when the adjustment factor is 2.5.

7.7.8 **Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.**

Figure 54 to Figure 58 present scatter plots displaying the incremental results of the PSA, for edoxaban compared with each comparator arm in the model.

Figure 54: Edoxaban vs. apixaban

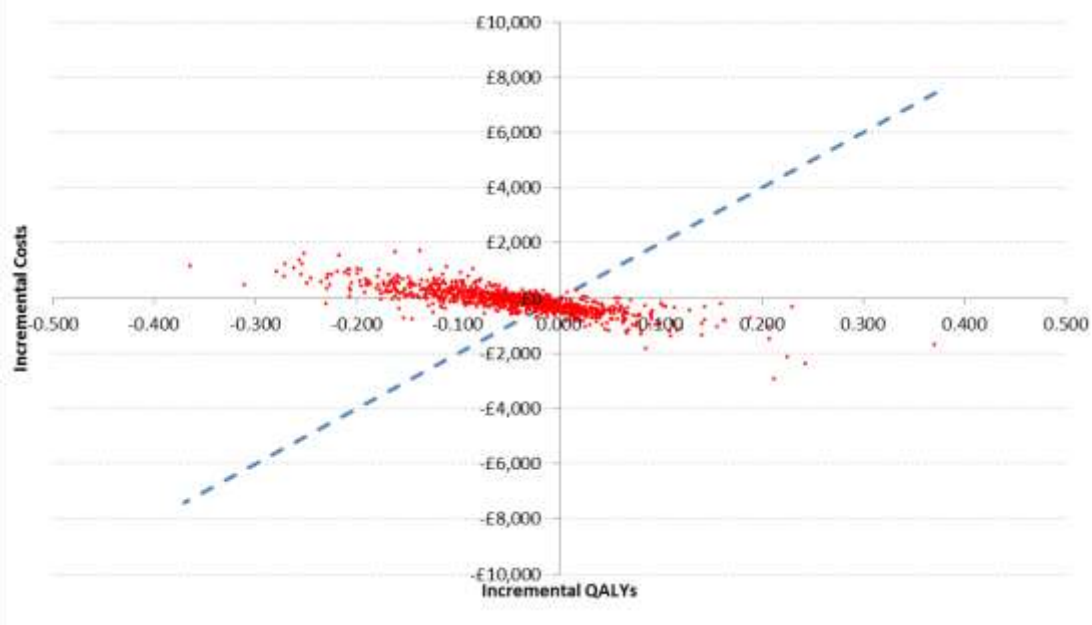


Figure 55: Edoxaban vs. rivaroxaban

Figure 56: Edoxaban vs. dabigatran 110mg

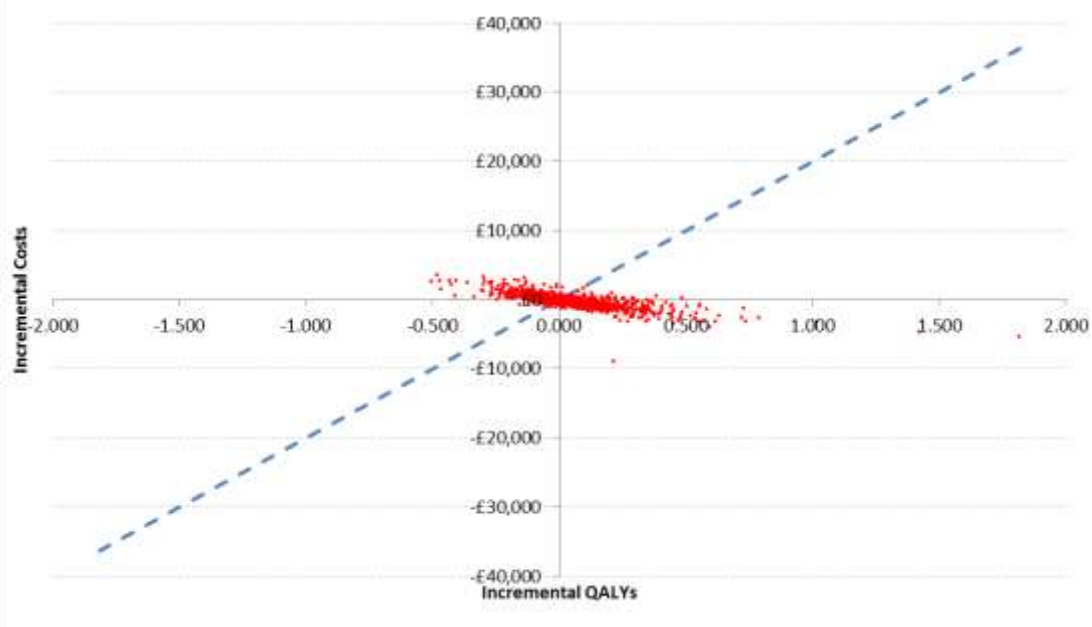


Figure 57: Edoxaban vs. dabigatran 150 mg

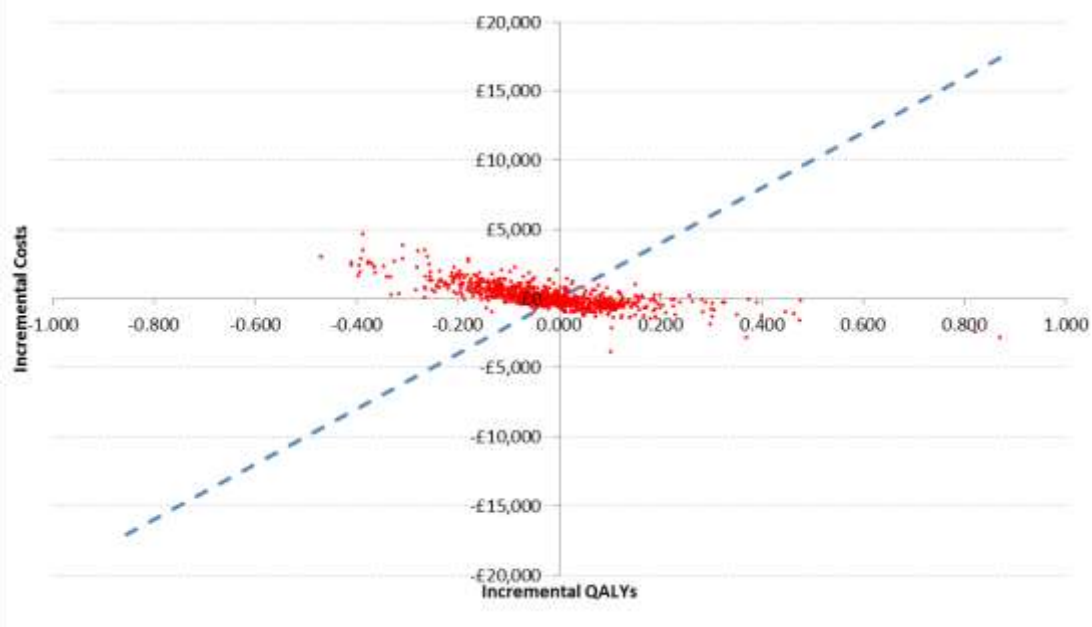


Figure 58: Edoxaban vs. warfarin

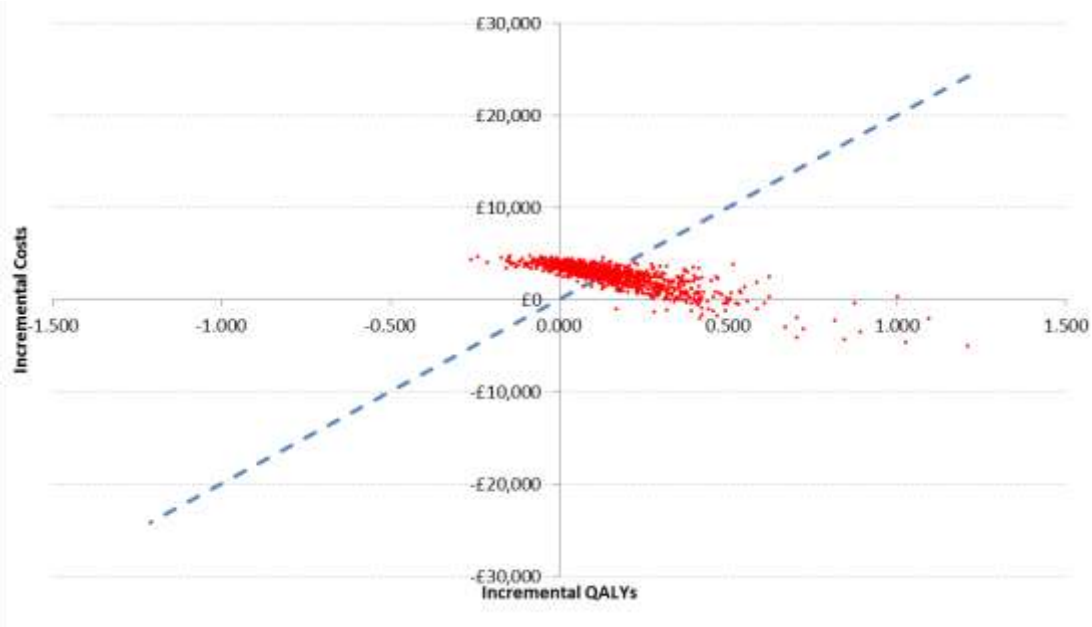


Figure 59 and Figure 60 present the cost-effectiveness acceptability curves (CEACs). Table 81 displays the probability of each treatment option being the most cost-effective option for each willingness to pay threshold, and Table 82 displays the probability of edoxaban being cost-effective compared to each comparator arm.

Figure 59: Cost-effectiveness acceptability curve (probability of being most cost-effective option)

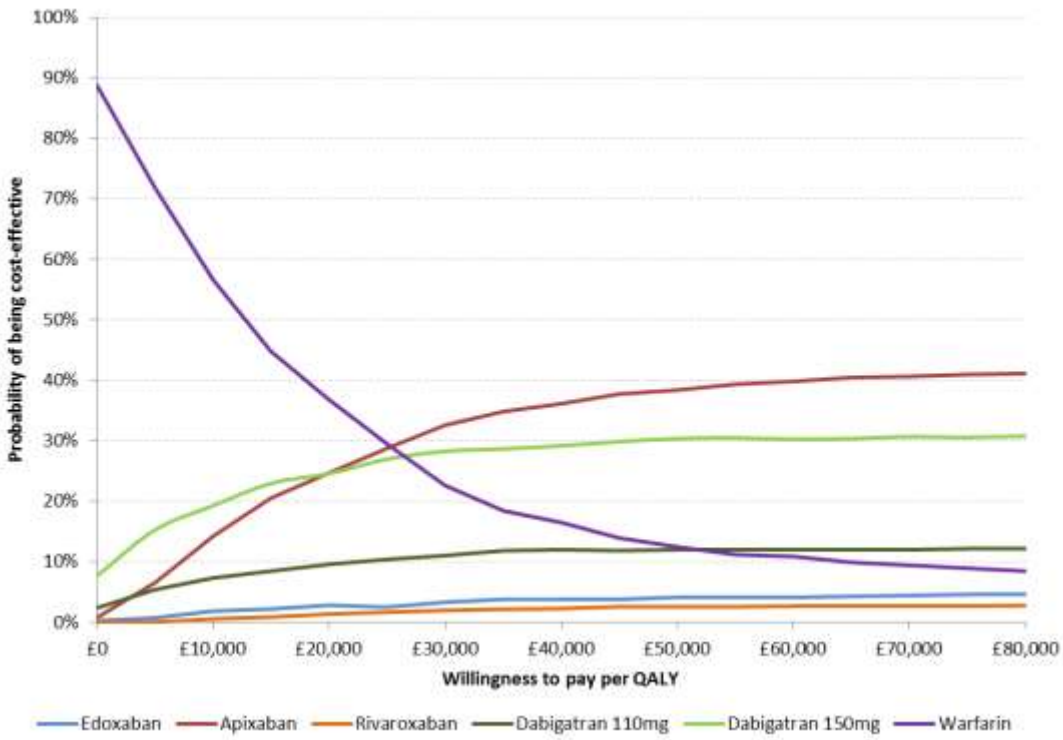


Figure 60: Cost-effectiveness acceptability curve (pairwise comparison of the probability of edoxaban being cost-effective compared to each comparator)

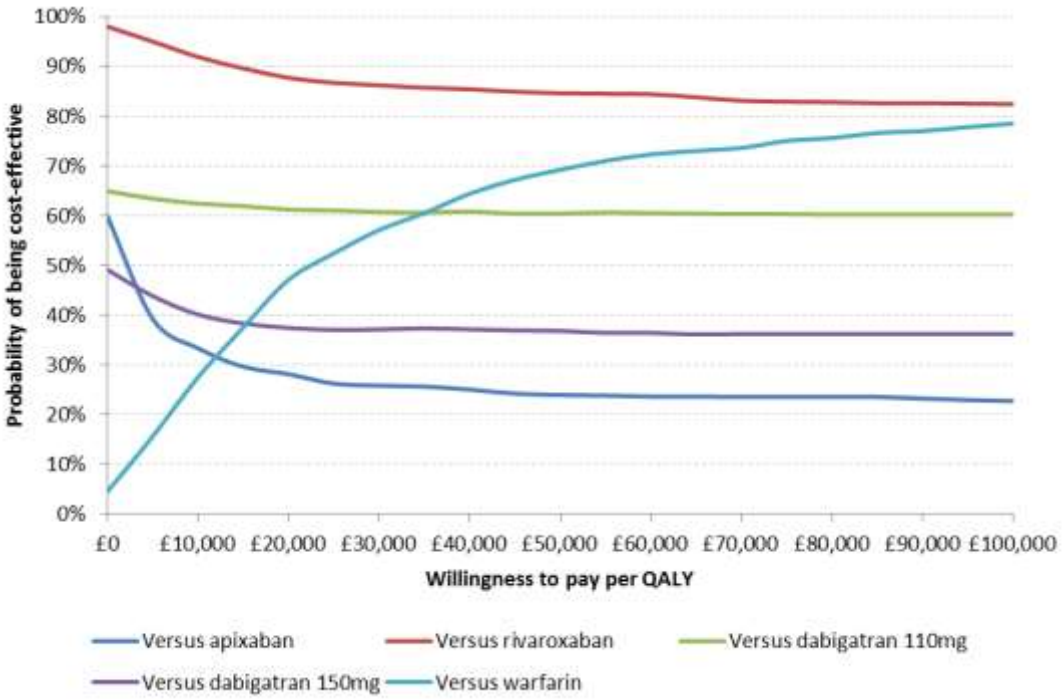


Table 81: Probability of being most cost-effective option, at different WTP thresholds

Comparator	£20,000	£30,000
Edoxaban	2.9%	3.4%
Apixaban	24.7%	32.6%
Rivaroxaban	1.4%	2.0%
Dabigatran 110mg	9.6%	11.1%
Dabigatran 150mg	24.6%	28.3%
Warfarin	36.8%	22.6%

Table 82: Probability of edoxaban being cost-effective versus each comparator arm, at different WTP thresholds

Comparator	£20,000	£30,000
Edoxaban	-	-
Apixaban	28.1%	25.8%
Rivaroxaban	87.7%	86.2%
Dabigatran 110mg	61.2%	60.7%
Dabigatran 150mg	37.4%	37.1%
Warfarin	47.1%	57.1%

7.7.9 **Please present the results of scenario analysis. Include details of structural sensitivity analysis.**

Scenario analyses were undertaken around hazard ratios for TIA and CRNMB. The base case analysis assumes values of 1 where data were not available; in the

scenario analysis, all values of 1 were changed to 0.93 and 0.72 for TIA and 1.19 and 1.25 for CRNBM.

When a value of 0.93 or 0.72 was used there was no difference to the overall results, i.e. treatment options were in the same order as the base case. Table 83 to Table 86 show the results of the scenario analysis.

Table 83: Data gaps for TIA hazard ratios: 0.93

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,413	8.547	6.32	-	-	-	-	-
Dabigatran 150mg	£15,565	8.888	6.60	£1,798	0.437	0.28	£6,421	£6,421
Dabigatran 110mg	£15,935	8.869	6.58	-£22	0.08	0.07	£9,700	Strictly dominated
Edoxaban	£15,957	8.789	6.51	-£117	-0.007	0	£13,389	Strictly dominated
Apixaban	£16,074	8.796	6.51	£509	-0.092	-0.09	£14,005	Strictly dominated
Rivaroxaban	£16,740	8.694	6.43	£805	-0.175	-0.15	£30,245	Strictly dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 84: Data gaps for TIA hazard ratios: 0.72

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,413	8.547	6.32	-	-	-	-	-
Dabigatran 150mg	£15,570	8.902	6.61	£2,157	0.45	0.29	£7,438	£7,438
Dabigatran 110mg	£15,921	8.869	6.58	£351	-0.033	-0.03	£9,646	Strictly dominated
Edoxaban	£15,957	8.789	6.51	£36	-0.08	-0.07	£13,389	Strictly dominated
Apixaban	£16,074	8.796	6.51	£117	0.007	0	£14,005	Strictly dominated
Rivaroxaban	£16,726	8.694	6.58	£652	-0.102	0.07	£12,742	Strictly dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 85: Data gaps for CRNMB hazard ratios: 1.19

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,413	8.547	6.32	-	-	-	-	-
Dabigatran 150mg	£15,778	8.883	6.60	£2,365	0.34	0.28	£8,446	£8,446
Edoxaban	£15,957	8.789	6.51	£179	-0.09	-0.09	£13,389	Strictly dominated
Dabigatran 110mg	£16,156	8.869	6.58	£199	0.08	0.07	£10,550	Strictly dominated
Apixaban	£16,287	8.796	6.51	£131	-0.07	-0.07	£15,126	Strictly dominated
Rivaroxaban	£16,774	8.694	6.43	£487	-0.10	-0.08	£30,555	Strictly dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 86: Data gaps for CRNMB hazard ratios: 1.25

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,413	8.547	6.32	-	-	-	-	-
Dabigatran 150mg	£15,846	8.883	6.60	£2,433	0.34	0.28	£8,689	£8,689
Edoxaban	£15,957	8.789	6.51	£111	-0.09	-0.09	£13,389	Strictly dominated
Dabigatran 110mg	£16,224	8.869	6.58	£267	0.08	0.07	£10,812	Strictly dominated
Apixaban	£16,355	8.796	6.51	£131	-0.07	-0.07	£15,484	Strictly dominated
Rivaroxaban	£16,774	8.694	6.43	£419	-0.10	-0.08	£30,555	Strictly dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

7.7.10 What were the main findings of each of the sensitivity analyses?

The deterministic sensitivity analysis shows that there for all the comparators the cost of treatment, monitoring cost and patients starting age are among the top five variables with the largest effect on the results. Acute mortality for major non-ICH bleed was a clinical input which had one of the greater impacts on NMB. Utility values in the model had limited effect on the results with the utility of stable AF and post-event utility of MI and HS being in the top 10 variables.

7.7.11 What are the key drivers of the cost-effectiveness results?

As identified by the deterministic sensitivity analysis, the key inputs driving the results of the model include the patients starting age, costs associated with the intervention (drug and monitoring costs), utility of patients in the Stable AF health state, and rate of other-cause discontinuation.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Validation was assessed using two primary criteria, internal (verification) and external consistency (validation). Internal validity addresses whether the model has been implemented correctly, and examines the extent to which the mathematical calculations are performed correctly and are consistent with the model's specifications. Face validation helps ensure a model is constructed and used in accord with most current medical science and best available evidence. This process enhances credibility with experts and increases acceptance of results.

Internal validity was assessed firstly using the techniques of extreme value analysis, where minimum and maximum values for appropriate parameter values were substituted, parallel inputs for all interventions for efficacy, costs and utilities, and logical consistency tests. Secondly, equations (i.e. those for converting rates to probabilities) were validated against their source, and coding accuracy was checked by verification of separate parts of a model one by one.

External consistency was assessed by assessing the face validity of the model, and comparing the results of the analysis against published results (cross validation). For the model structure, it was assessed whether the model includes all aspects of the patient pathway considered important, and whether they are related in ways consistent with medical science. It was also assessed whether the best available data sources were used, and whether the setting, population, interventions, outcomes, assumptions, and time horizons correspond to those of decision problem. A comparison of the results of the model with the results of published models is discussed in further detail in Section 7.10.1.

7.9 Subgroup analysis

7.9.1 **Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.**

Subgroup analysis was undertaken focusing on groups of patients with different risks of stroke ($CHADS_2 \geq 3$), and time in therapeutic range (cTTR ≥ 60%). Subgroups were selected in line with the NICE scope.

7.9.2 **Please clearly define the characteristics of patients in the subgroup.**

Details of the patients in the subgroups are presented in Section 6.3.7.

7.9.3 **Please describe how the statistical analysis was undertaken.**

Hazard ratios for each event for each comparator compared with edoxaban were generated from the NMA. Limited data was available to inform the NMA for the subgroups (data availability is presented in Section 7.3.1). Baseline annual event rates for edoxaban were extracted from the ENGAGE AF-TIMI 48 trial for each subgroup. Transition probabilities were calculated using the methodology presented in Section 7.3.2, where the edoxaban annual event rates were converted to a monthly probability and adjusted for patient age in each cycle of the model, and the hazard ratios were applied multiplicatively to the edoxaban monthly probabilities to generate monthly probabilities for each comparator arm. Where there were no available data for an event, it was assumed that the hazard ratio was equivalent to the hazard ratio estimated in the base case analysis (i.e. for all patients).

7.9.4 **What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).**

Results of the subgroup analyses are presented in Table 87 and Table 88. The ICERs for the $CHADS_2 \geq 3$ subgroup were lower than those for the base case scenario, while the ICERs for the cTTR ≥ 60% subgroup were higher than those for the base case scenario.

Table 87: Subgroup analysis - patients with $CHADS_2 \geq 3$

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£14,773.64	8.23	6.04	-	-	-	-	-
Dabigatran 150mg	£16,401.32	8.67	6.41	£1,627.68	0.44	0.37	£4,379.32	Extendedly dominated
Apixaban	£16,538.65	8.79	6.51	£137.33	0.12	0.10	£3,719.30	£3,719.30
Edoxaban	£16,815.02	8.58	6.33	£276.38	-0.21	-0.18	£7,012.02	Strictly dominated
Dabigatran 110mg	£16,921.57	8.58	6.31	£106.54	0.00	-0.01	£7,751.80	Strictly dominated
Rivaroxaban	£17,617.49	8.50	6.25	£695.92	-0.08	-0.06	£13,166.30	Strictly dominated

Table 88: Subgroup analysis - cTTR ≥ 60%

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£12,926.46	8.60	6.36	-	-	-	-	-
Dabigatran 150mg	£15,486.55	8.87	6.58	£2,560.09	0.27	0.22	£11,738.32	£11,738.32
Dabigatran 110mg	£15,947.46	8.79	6.50	£460.91	-0.08	-0.08	£22,267.98	Strictly dominated
Edoxaban	£15,957.51	8.79	6.51	£10.05	0.01	0.01	£20,375.95	Strictly dominated
Apixaban	£16,003.09	8.86	6.57	£45.57	0.07	0.06	£14,662.97	Strictly dominated
Rivaroxaban	£16,724.55	8.71	6.45	£721.46	-0.15	-0.13	£46,795.19	Strictly dominated

7.9.5 **Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.**

No relevant subgroups specified in the scope were excluded from the analysis.

7.10 Interpretation of economic evidence

7.10.1 **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

The systematic review detailed in Section 7.1 did not identify any economic evaluations which estimated the cost-effectiveness of edoxaban in AF. However, one economic evaluation was identified that was based in a UK setting, which compared apixaban to dabigatran and rivaroxaban in AF patients suitable for VKA therapy. [130] This analysis used a Markov model with a lifetime time horizon. In this study, apixaban was estimated to be a cost-effective option when compared to the other NOACs: the estimated ICER for dabigatran 110mg versus apixaban was £4,497, for dabigatran 150mg the ICER was £9,611, and for rivaroxaban the ICER was £5,305. In the current study, apixaban is a dominant treatment strategy compared to rivaroxaban and dabigatran 110mg, while compared to the dabigatran 150mg comparator, apixaban produces fewer QALYs.

Differences in results between this evaluation and previously published evaluation may result from several key data inputs used between the models, notably the patient age (age was demonstrated to be a key driver of the model in Section 7.7.11; patients in this evaluation are younger than patients in the apixaban and rivaroxaban evaluations), quality of life for Stable AF patients, and assumptions around discontinuation. The patients in the ENGAGE AF-TIMI 48 trial had a $CHADS_2$ score of 2 or greater, while in the trials for the other comparators (dabigatran and apixaban), a third of patients had a $CHADS_2$ score of less than 2. Therefore the baseline event rates and patient characteristics in this model will not reflect the same patient population as these two comparators. The differences in the results may also reflect the differences in the different model structures: in this evaluation, there was no limit placed on the number of recurrent events that a patient could experience, while in previous submissions, patients were limited to one recurrent event.

The results in the submission should be given more credence than preceding evaluations due to the research methods and assumptions employed in the evaluation. The model was designed based on previous economic analyses that were submitted to NICE, since the critique from the ERGs provided a firm basis on which to inform the best techniques and assumptions to use in the model. Utility values for Stable AF patients were collected in the ENGAGE AF-TIMI 48 clinical trial, and are therefore more representative of the patients in the evaluation than estimated published in the literature relating to other studies.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Edoxaban is licensed for use in adult patients with nonvalvular atrial fibrillation with one of more of the following risk factors: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. The inclusion criteria for the ENGAGE AF-TIMI 48 trial was patients with a $CHADS_2$ score of 2 or greater. Therefore the baseline event rates and patient characteristics in the model may not be fully representative of the licensed patient population since patients with a $CHADS_2$ score of 1 are not included.

For both the primary efficacy and safety endpoints the HRs are stable across the range of $CHADS_2$ scores and therefore it is reasonable to expect that the overall HR for the study as a whole for subjects with $CHADS_2$ scores of 2 to 6 would also apply to subjects with a $CHADS_2$ score of 1. Furthermore the ENGAGE AF-TIMI 48 study enrolled a large number of subjects with $CHADS_2$ score of 2 and so the extrapolation to $CHADS_2$ 1 scores is reasonable.

Extrapolating the results for subjects with a $CHADS_2$ score of 2 and higher to those with a $CHADS_2$ score of 1 is appropriate because there is no fundamental difference in the pathophysiology of a subject's coagulation system by different levels of $CHADS_2$ score. The ESC has made similar extrapolations in the recommendations for other anticoagulants e.g. VKA and rivaroxaban for which studies included $CHADS_2$ scores greater than or equal to 2, as was done for edoxaban.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the economic evaluation lies in the comprehensive model structure fed by a robust clinical trial and extensive research to populate it. The economic model builds on recommendations from previous technology appraisals and good practice in published economic models.

The model was developed over the course of the ENGAGE AF-TIMI 48 study in consultation with UK clinical and health economic experts (as described in Section 7.3.5), ensuring that the model clinical pathway is in line with UK clinical practice and the most appropriate inputs are utilised.

The main weakness of the analysis is the lack of evidence for certain parameters which were not found despite a thorough systematic review. Evidence for all outcomes of interest were not published for all comparators e.g. full details of stroke severity for all modified Rankin scale categories, and outcomes on TIA not included in comparators clinical trials.

Data on baseline risk and patient characteristics were based on the ENGAGE AF-TIMI 48 trial, which enrolled patients who may not completely representative of UK AF patients or the patients who are licensed for edoxaban.

There are often concerns that the effectiveness of different treatments in clinical practice will be less than that the efficacy observed in clinical trials, and that event

costs underestimated and quality of life overestimated in economic models as a result. The strengths of the analysis and the extensive sensitivity analysis suggest that the results of the model are robust.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Extensive sensitivity analyses (deterministic and probabilistic) were undertaken to determine the robustness of the results. Further evidence generation programmes may improve the overall robustness of the analysis, such as a head-to-head trial of the licensed NOACS and warfarin.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The eligible population in Egland and wales was estimated based on population statistics, prevalence and incidence of AF and treatment patterns. Estimations were based on the following assumptions:

- The population size for people aged over 18 years old in England and Wales was estimated to be 43,404,300 in 2015 [78] and was assumed to grow at a 0.5% annual rate.
- The prevalence of AF (existing cases) was estimated at 1.76% per year in England, according to the GRASP-AF registry[5] and 1.85% in Wales according to data from the National Health Service (NHS) Quality and Outcomes Framework for 2012/2013.[6] This led to a weighted average of 1.765%
- The incidence of AF (new cases) was assumed to be 0.05% per year. [51]
- The proportion of patients with non-valvular AF was further assumed to be 75% [45], and 78.8% of these patients at risk of stroke (i.e., with a $CHADS_2$ risk score ≥1)[46].
- Of those patients with NVAF at risk of stroke, approximately 90% was assumed to seek treatment for their condition in 2015-2017, and approximately 91% in 2018 onwards.

Table 89: Estimation of population eligible for treatment with edoxaban

	2015	2016	2017	2018	2019
Population	43,404,300				
Annual population growth	0.5%	0.5%	0.5%	0.5%	
Prevalence rate	1.765%				
Incidence rate		0.05%	0.05%	0.05%	0.05%
Number of eligible patients	766,086	787,514	809,039	830,664	852,388
Proportion of NVAF	75.00%	75.00%	75.00%	75.00%	75.00%
Proportion at risk of stroke	78.80%	78.80%	78.80%	78.80%	78.80%
Proportion of patients treated	90.0%	90.0%	90.0%	91.0%	91.0%
Proportion of patients non-OAC (Aspirin / Clopidogrel)	14.7%	11.3%	10.0%	10.0%	10.0%
Number of OAC treated patients	**347,724**	**371,399**	**387,209**	**402,066**	**412,581**

8.1 What assumption(s) were made about current treatment options and uptake of technologies?

Current treatment options included warfarin, rivaroxaban, dabigatran, apixaban and edoxaban. No additional treatment was assumed to be entering the market in the next 5 years, and none of the NOACs will be available as generics in the period. NOACs were assumed to be used increasingly instead of warfarin.

8.2 What assumption(s) were made about market share (when relevant)?

Warfarin was assumed to have the highest market share currently and over the next five years.

NOACS were assumed to be used increasingly, with their joint market share doubling over 5 years.

Within the NOAC market, we assumed edoxaban would take market shares from the other NOACs proportionally to their respective market shares, i.e. mostly from dabigatran, followed by apixaban and then rivaroxaban.

Table 90 outlines the detailed market shares without edoxaban and the projected uptake of edoxaban assuming a positive recommendation for preventing stroke and systemic embolism in people with atrial fibrillation presenting for treatment.

Table 90: Current and future competitor market share

	2015	2016	2017	2018	2019
World without edoxaban					
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NOACs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within NOACs:					
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with edoxaban					
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NOACs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within NOACs:					
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.3 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The cost-effectiveness model described in Section 7.2 was used to derive annual costs of AF with each treatment at a five-year time horizon. These annual costs include intervention costs, including monitoring for patients receiving warfarin, and the costs of stroke, other cardiovascular events (i.e. myocardial infarction), and adverse events such as bleeds.

Table 91 lists these annual costs by treatment option.

Table 91: Annual costs used in budget impact calculations

	Year 1	Year 2	Year 3	Year 4	Year 5
Edoxaban	£1,290	£1,346	£1,373	£1,387	£1,385
Apixaban	£1,294	£1,344	£1,367	£1,379	£1,374
Rivaroxaban	£1,353	£1,416	£1,446	£1,463	£1,461
Dabigatran	£1,259	£1,303	£1,323	£1,335	£1,332
Warfarin	£937	£1,030	£1,087	£1,129	£1,152

8.4 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Table 92 presents the unit costs assumed in the budget impact calculations. These are the same as presented in Section 7.5 with the cost-effectiveness model.

Table 92: Unit costs used in budget impact calculations

	Unit cost	Source
Intervention costs		
Edoxaban	£ 2.10	Daiichi Sankyo
Apixaban	£ 2.20	BNF 68 [121]
Rivaroxaban	£ 2.10	BNF 68 [121]
Dabigatran	£ 2.20	BNF 68 [121]
Warfarin	£ 0.11	BNF 68 [121]
Monitoring (per month)	£ 22.09	NHS Costing Template for dabigatran

	Unit cost	Source
Acute event costs		
Ischaemic stroke	£ 3,683 - £ 26 240	Luengo-Fernandez *et al*. 2012 [123]
Haemorrhagic stroke	£ 10,723 - £ 46,598	Luengo-Fernandez *et al*. 2012 [123]
Systemic embolism	£ 4,285	Luengo-Fernandez *et al*. 2012 [123]
Myocardial infarction	£ 2,446	NHS Reference Costs 2013 [124]
Other ICH	£ 2,589	NHS Reference Costs 2013 [124]
TIA	£938	NHS Reference Costs 2013 [124]
Non-ICH major bleed	£ 1,803	NHS Reference Costs 2013 [124]
CRNM bleed	£ 883	NHS Reference Costs 2013 [124]
Post-event costs (per month)		
Ischaemic stroke	£ 193 - £ 571	Luengo-Fernandez *et al*. 2012 [123]
Haemorrhagic stroke	£ 193 - £ 571	Luengo-Fernandez *et al*. 2012 [123]
Systemic embolism	£ 193	Luengo-Fernandez *et al*. 2012 [123]
Myocardial infarction	£ 4	NHS Reference Costs 2013 [124]
Cost of death		
Death	£ 2,902	Luengo-Fernandez *et al*. 2012 [123]

8.5 Were there any estimates of resource savings? If so, what were they?

Edoxaban is not expected to lead to any additional resource savings than those realised by preventing strokes and adverse events.

8.6 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact of edoxaban for the NHS in England and Wales is approximately £9,731 in Year 1 rising to approximately £323,115 in Year 5 (

Table **93**).

Table 93. Annual budget impact for NHS in England and Wales

	2015	2016	2017	2018	2019
World without edoxaban					
Warfarin	£256,052,108	£297,357,221	£324,313,771	£346,482,420	£360,768,880
NOACs					
Rivaroxaban	£10,065,883	£11,189,012	£11,833,289	£12,272,492	£12,431,854
Dabigatran	£66,465,127	£74,626,018	£80,741,349	£86,611,070	£90,667,953
Apixaban	£18,570,624	£21,071,877	£23,008,247	£24,949,668	£26,350,671
Total cost	**£351,153,742**	**£404,244,127**	**£439,896,657**	**£470,315,650**	**£490,219,357**
World with edoxaban					
Warfarin	£256,052,108	£297,357,221	£324,313,771	£346,482,420	£360,768,880
NOACs					
Rivaroxaban	£9,973,708	£11,055,785	£11,663,858	£12,070,811	£12,211,790
Dabigatran	£65,856,493	£73,667,552	£79,358,577	£84,696,303	£88,291,071
Apixaban	£18,400,569	£20,795,646	£22,596,629	£24,358,975	£25,598,708
Edoxaban	£880,596	£1,415,151	£2,077,862	£2,925,154	£3,672,024
Total cost	**£351,163,473**	**£404,291,355**	**£440,010,697**	**£470,533,663**	**£490,542,472**
Budget impact	**£9,731**	**£47,228**	**£114,041**	**£218,013**	**£323,115**

8.7 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

9 References

(1) Bunch TJ, Gersh BJ. Rhythm Control Strategies and the Role of Antiarrhythmic Drugs in the Management of Atrial Fibrillation: Focus on Clinical Outcomes. J Gen Intern Med 26[5], 531-537. 2011.

(2) Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm SocietyEuropace. Circulation 114, e257-e354. 2006.

(3) Kannel W, Benjamin E. Status of the epidemiology of atrial fibrillation. Med Clin North Am 92[1], 17-40. 2008.

(4) Lloyd-Jones D, Adams RJ, Brown TM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; 121:e46-e215.

(5) Cowan C, Healicon R, Robson I, Long WR, Barrett J, Fay M et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. *Heart* 2013; 99(16):1166-1172.

(6) The Welsh Government. Information from the General Medical Services Quality and Outcomes Framework Statistics for Wales, 2012-13. The Welsh Government [2014 [cited 2014 June 4]; Available from: URL:http://wales.gov.uk/statistics-and-research/general-medical-services-contract/?lang=en

(7) National Institute for Health and Care Excellence. NICE guidelines [CG180] - Atrial fibrillation: the management of atrial fibrillation. 2014.

(8) Royal College of Physicians Clinical Effectiveness and Evaluation Unit on behalf of the Intercollegiate Stroke Working Party. Sentinel Stroke National Audit Programme.Clinical audit first pilot public report. 2013.

(9) Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369[22], 2093-2104. 2013.

(10) Stambler BS. A new era of stroke prevention in atrial fibrillation: comparing a new generation of oral anticoagulants with warfarin. *International archives of medicine* 2013; 2013/11/01:46.

(11) Turpie AG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. 2007; 2007/03/24:1238-1247.

(12) Weitz JI, Bates SM. New anticoagulants. *J Thromb Haemost* 2005; 2005/08/17:1843-1853.

(13) Ogata KM-H. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010; 50(7):743-753.

(14) Edoxaban Summary of Product Characteristics. Daiichi Sankyo. 2015.

(15) Mendell J, Zahir H, Matsushima N, Noveck R, Lee F, Chen S et al. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. *Am J Cardiovasc Drugs* 2013; 13(5):331-342.

(16) Bounameaux H, Camm AJ. Edoxaban: an update on the new oral direct factor Xa inhibitor. *Drugs* 2014; 74(11):1209-1231.

(17) Gonzalez-Quesada CJ, Giugliano RP. Comparison of the phase III clinical trial designs of novel oral anticoagulants versus warfarin for the treatment of nonvalvular atrial fibrillation: implications for clinical practice. *Am J Cardiovasc Drugs* 2014; 14(2):111-127.

(18) Bathala MS, Masumoto H, Oguma T, He L, Lowrie C, Mendell J. Pharmacokinetics, biotransformation, and mass balance of edoxaban, a selective, direct factor Xa inhibitor, in humans. *Drug Metab Dispos* 2012; 40(12):2250-2255.

(19) De CR, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol* 2012; 59(16):1413-1425.

(20) Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the esc guidelines for the management of atrial fibrillation: An update of the 2010 esc guidelines for the management of atrial fibrillation developed with the special contribution of the european heart rhythm association. Europace 14, 1385-1413. 2012.

(21) National Institute for Health and Care Excellence. NICE Commissioning guides [CMG49] - Support for commissioning: anticoagulation therapy. 2013.

(22) Desai N, Giugliano R. Can we predict outcomes in atrial fibrillation? Clin Cardiol 35[Suppl 1], 10-14. 2012.

(23) Fuster V, Rydén LE, Asinger RW, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. Circulation 104, 2118. 2001.

(24) Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ et al. Management of atrial fibrillation in seven European countries after

the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events--European Registry in Atrial Fibrillation (PREFER in AF). *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2014; 2013/10/03:6-14.

(25) Apostolakis S, Lip GYH. Atrial Fibrillation. In: Hoffman R, Benz E.J, Silberstein L.E, Heslop H.E, Weitz J.I, et al., editors. Hematology: Basic Principles and Practice. 6th ed. Churchill Livingstone; 2012. 2086-2093.

(26) Calum A. Symptoms in atrial fibrillation: Why keep score? Circulation 2, 215-217. 2009.

(27) Wolf PA, Abbott RD, Kannel WB, et al. Atrial fibrillation as an independent risk factor for stroke: The framingham study. Stroke 22, 983-988. 1991.

(28) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; 31(19):2369-2429.

(29) Odum LE, Cochran KA, Aistrope DS, Snella KA. The CHADS(2)versus the new CHA2DS2-VASc scoring systems for guiding antithrombotic treatment of patients with atrial fibrillation: review of the literature and recommendations for use. *Pharmacotherapy* 2012; 32(3):285-296.

(30) Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996; 27(10):1760-1764.

(31) Rivero-Ayerza M, Scholte op Reimer W, Lenzen M, et al. New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. Eur Heart J 29, 1618-1624. 2008.

(32) Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005; 36(6):1115-1119.

(33) Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006; 27(8):949-953.

(34) Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994-1998: analysis of data from the general practice research database. *Heart* 2001; 86(3):284-288.

(35) Caldwell JC, Contractor H, Petkar S, et al. Atrial fibrillation is under-recognized in chronic heart failure: insights from a heart failure cohort treated with cardiac resynchronization therapy. *Europace* 2009; 11(10):1295-1300.

(36) Barrios V, De la Figuera M, Coca A. Prevención de la fibrilación auricular en el paciente hipertenso. . 2007;128:148-54. Med Clin (Barc) 128, 148-154. 2007.

(37) Barrios V, Calderon A, Escobar C, et al. Patients with atrial fibrillation attended in primary care setting. The Val-FAAP study. Rev Esp Cardiol 65[1], 47-53. 2012.

(38) Townsend N. Coronary heart disease statistics 2012 edition. British Heart Foundation: London , 57. 2012.

(39) Fernandez MM, von Schéele B, Hogue S, et al. Review of challenges in optimizing oral anticoagulation therapy for stroke prevention in atrial fibrillation. Am J Cardiovasc Drugs 13[2], 87-102. 2013.

(40) McBride D, Mattenklotz AM, Willich SN, Bruggenjurgen B. The costs of care in atrial fibrillation and the effect of treatment modalities in Germany. *Value Health* 2009; 12(2):293-301.

(41) Reinhold T, Lindig C, Willich SN, Bruggenjurgen B. The costs of atrial fibrillation in patients with cardiovascular comorbidities - a longitudinal analysis of German health insurance data. *Europace* 2011; 13(9):1275-1280.

(42) Jonsson L, Eliasson A, Kindblom J, Almgren O, Edvardsson N. Cost of illness and drivers of cost in atrial fibrillation in Sweden and Germany. *Applied health economics and health policy* 2010; 8(5):317-325.

(43) Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. *Age and ageing* 2009; 38(1):27-32.

(44) The Health and Social Care Information Centre. Quality and Outcomes Framework (QOF) for April 2012 - March 2013, England. The Health and Social Care Information Centre [2014 [cited 2014 June 4]; Available from: URL:http://www.hscic.gov.uk/catalogue/PUB12262

(45) The RealiseAF registry, Initial results. 2015.

(46) Gallagher AM, van Staa TP, Murray-Thomas T, et al. Population-based cohort study of warfarin-treated patients with atrial fibrillation: incidence of cardiovascular and bleeding outcomes. BMJ Open 4. 2014.

(47) Office for National Statistics. Life expectancy at birth and at age 65 for the United Kingdom and constituent countries, 2008-10. Office for National Statistics [2014 [cited 2014 June 4]; Available from: URL:http://www.ons.gov.uk/ons/dcp171778_277684.pdf

(48) Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98[10], 946-952. 1998.

(49) NICE technology appraisals [TA249]. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. 2012.

(50) NICE technology appraisals [TA256]. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. 2012.

(51) NICE technology appraisals [TA275]. Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. 2013.

(52) Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. CHEST Journal 2004;126(3_suppl):204S-33S. CHEST journal 126[3 Suppl], 204S-233S. 2004.

(53) You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141[2 Suppl], e531S-75S. 2012.

(54) Mearns ES, White CM, Kohn CG, Hawthorne J, Song JS, Meng J et al. Quality of vitamin K antagonist control and outcomes in atrial fibrillation patients: a meta-analysis and meta-regression. *Thrombosis journal* 2014; 12(1):14.

(55) Hedner E, Carlsson J, Kulich KR, Stigendal L, Ingelg+Ñrd A, Wiklund I. An instrument for measuring health-related quality of life in patients with Deep Venous Thrombosis (DVT): development and validation of Deep Venous Thrombosis Quality of Life (DVTQOL) questionnaire. *Health and quality of life outcomes* 2004; 2(1):30.

(56) Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Archives of internal medicine 165[10], 1095-1106. 2005.

(57) Diener H-C, Verheugt F. Introduction. *Eur Heart J Suppl* 2005; 7(Supple E):E3.

(58) Anderson N, Fuller R, Dudley N. 'Rules of thumb or reflective practice?' Understanding senior physicians' decision-making about anti-thrombotic usage in atrial fibrillation. *QJM* 2007; 100(5):263-269.

(59) Zahir H, Brown KS, Vandell A, Desai M, Maa JF, Dishy V et al. Edoxaban Effects on Bleeding Following Punch Biopsy and Reversal by a 4-Factor Prothrombin Complex Concentrate. *Circulation* 2014.

(60) Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)
1. *Chest* 2008; 133(6 Suppl):160S-198S.

(61) European Medicines Agency (EMA). Xarelto -EMEA/H/C/000944 -II/0023 - Summary of product characteristics. 2013.

(62) European Medicines Agency (EMA). Pradaxa -EMEA/H/C/000829 -II/0055. 2014.

(63) Laliberté F, Nelson WW, Lefebvre P, Schein JR, Rondeau-Leclaire J, Duh MS. Impact of daily dosing frequency on adherence to chronic medications among nonvalvular atrial fibrillation patients. *Advances in therapy* 2012; 29(8):675-690.

(64) Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous

thromboembolism: a cost-effectiveness analysis. *Am J Med* 2001; 111(2):130-139.

(65) Weitz J, Connolly SJ, Patel I, Salazar D, Rohatagi S, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost* 2010; 104(3):633-641.

(66) Chung NJ. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thrombosis and Haemostasis* 2011; 105(3):535-545.

(67) Yamashita TK. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. *Circ J* 2012; 76(8):1840-1847.

(68) Daiichi Sankyo PD. Clinical Study Report DU176b-C-U301, Version 2.0, 15 Nov 2013. 2013.

(69) Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. RE-LY Steering Committee and Investigators. N Engl J Med 361, 1139. 2009.

(70) Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365[11], 981-992. 2011.

(71) Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. the ROCKET AF Investigators. N Engl J Med 365, 883. 2011.

(72) Kuroda Y, Hirayama C, Hotoda H, Nishikawa Y, Nishiwaki A. Postmarketing safety experience with edoxaban in Japan for thromboprophylaxis following major orthopedic surgery. *Vasc Health Risk Manag* 2013; 9:593-598.

(73) Edwards SJ HVTNNLKCTE. Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation: A Single Technology Appraisal. 2012.

(74) Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CD, Heuschmann PU. Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. *J Neurol Neurosurg Psychiatry* 2009; 80(9):1012-1018.

(75) Altman D. Practical Statistics for Medical Research. London: Chapman & Hall ed. 1991.

(76) Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke* 2003; 34(8):2060-2065.

(77) Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; 154(13):1449-1457.

(78) Office for National Statistics. UK life tables. 2014. 3-11-2014.

(79) Flegel KM, Hanley J. Risk factors for stroke and other embolic events in patients with nonrheumatic atrial fibrillation. *Stroke* 1989; 20(8):1000-1004.

(80) Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med* 2011; 154(1):1-11.

(81) Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke* 1988; 19(12):1497-1500.

(82) van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; 19(5):604-607.

(83) Janes F, Gigli GL, D'Anna L, Cancelli I, Perelli A, Canal G et al. Stroke incidence and 30-day and six-month case fatality rates in Udine, Italy: a population-based prospective study. *Int J Stroke* 2013; 8 Suppl A100:100-105.

(84) Scarborough S BPWKSKMCRM. Coronary Heart Disease Statistics. 2010.

(85) Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *Eur Heart J* 2007; 28(19):2346-2353.

(86) Centre for Health Equity Studies. The Causes of Death Register. 2014. 3-11-2014.

(87) Bronnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. *Stroke* 2001; 32(9):2131-2136.

(88) Henriksson KM, Farahmand B, Johansson S, Asberg S, Terent A, Edvardsson N. Survival after stroke--the impact of CHADS2 score and atrial fibrillation. *Int J Cardiol* 2010; 141(1):18-23.

(89) Huybrechts KF, Caro JJ, Xenakis JJ, Vemmos KN. The prognostic value of the modified Rankin Scale score for long-term survival after first-ever stroke. Results from the Athens Stroke Registry. *Cerebrovasc Dis* 2008; 26(4):381-387.

(90) Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013; 15(5):625-651.

(91) Frost L, Engholm G, Johnsen S, Moller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch Intern Med* 2001; 161(2):272-276.

(92) EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16(3):199-208.

(93) Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ* 1993; 306(6890):1440-1444.

(94) Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol* 2004; 126(4):557-564.

(95) Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med* 1996; 156(16):1829-1836.

(96) Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. *J Epidemiol Community Health* 2003; 57(8):622-627.

(97) Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 2011; 31(6):800-804.

(98) Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. *Pharmacoeconomics* 2006; 24(10):1021-1033.

(99) Meinertz T, Kirch W, Rosin L, Pittrow D, Willich SN, Kirchhof P. Management of atrial fibrillation by primary care physicians in Germany: baseline results of the ATRIUM registry. *Clin Res Cardiol* 2011; 100(10):897-905.

(100) Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol* 2007; 49(5):572-577.

(101) Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006; 26(4):410-420.

(102) Berg J, Lindgren P, Nieuwlaat R, Bouin O, Crijns H. Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. *Qual Life Res* 2010; 19(3):381-390.

(103) Doyle SL. Public perception of atrial fibrillation and treatment-related adverse events in the UK. 2011.

(104) Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995; 274(23):1839-1845.

(105) Goren A, Liu X, Gupta S, Simon TA, Phatak H. Quality of life, activity impairment, and healthcare resource utilization associated with atrial fibrillation in the US National Health and Wellness Survey. *PLoS One* 2013; 8(8):e71264.

(106) Ho JC, Chang AM, Yan BP, Yu CM, Lam YY, Lee VW. Dabigatran compared with warfarin for stroke prevention with atrial fibrillation: experience in Hong Kong. *Clin Cardiol* 2012; 35(12):E40-E45.

(107) Monz BU, Connolly SJ, Korhonen M, Noack H, Pooley J. Assessing the impact of dabigatran and warfarin on health-related quality of life: results from an RE-LY sub-study. *Int J Cardiol* 2013; 168(3):2540-2547.

(108) Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014; 311(7):692-700.

(109) Reynolds MR, Morais E, Zimetbaum P. Impact of hospitalization on health-related quality of life in atrial fibrillation patients in Canada and the United States: results from an observational registry. *Am Heart J* 2010; 160(4):752-758.

(110) Roalfe AK, Bryant TL, Davies MH, Hackett TG, Saba S, Fletcher K et al. A cross-sectional study of quality of life in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation Treatment of the Aged study. *Europace* 2012; 14(10):1420-1427.

(111) Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. *J Health Serv Res Policy* 2001; 6(2):92-98.

(112) Radholm K, Ostgren CJ, Alehagen U, Falk M, Wressle E, Marcusson J et al. Atrial fibrillation (AF) and co-morbidity in elderly. A population based survey of 85 years old subjects. *Arch Gerontol Geriatr* 2011; 52(3):e170-e175.

(113) Steg PG, Alam S, Chiang CE, Gamra H, Goethals M, Inoue H et al. Symptoms, functional status and quality of life in patients with controlled and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry. *Heart* 2012; 98(3):195-201.

(114) Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Lancet* 2000; 355(9208):956-962.

(115) Selby RM. Long-term oral anticoagulant management associated with routine medical care (RMC) in patients with non-valvular atrial fibrillation (NVAF) in Canada. *Blood* 2011; Conference(var.pagings).

(116) Wynn GJW. Validation and modification of the EHRA symptom score for AF. *Heart Rhythm* 2013; Conference(var.pagings):S343.

(117) Gupta S.Gross. The impact of high risk of stroke patients diagnosed with atrial fibrillation on health-related quality of life, and health care use in 5EU. *Value Health* 2011; Conference(var.pagings):A385.

(118) Aves TO. Temporal trends in health related quality of life in atrial fibrillation: Outcomes from the multinational registry of atrial fibrillation (RECORD-AF). *European Heart Journal* 2010; Conference(var.pagings):September.

(119) Agency for Healthcare Research and Quality. Agency for Healthcare Research and Quality (AHRQ) Puf Documentation Files. 2003.

(120) Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997; 35(11):1095-1108.

(121) Formulary Committee Joint. British National Formulary, September 2014 (edition 68). 2014.

(122) Spackman E BJFRCBFDWN. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: Evidence Review Group Report. 2011.

(123) Luengo-Fernandez R, Yiin GS, Gray AM, Rothwell PM. Population-based study of acute- and long-term care costs after stroke in patients with AF. *Int J Stroke* 2013; 8(5):308-314.

(124) Department of Health. NHS Reference costs 2013. 2013.

(125) National Health Service England and Wales. Electronic Drug Tariff. In:NHS Prescription Services; December 2014. 2014.

(126) Curtis L. Unit Costs of Health and Social Care 2013. 2013.

(127) Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR et al. Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups. *Health Technol Assess* 2004; 8(41):iii-x, 1.

(128) Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995; 311(7001):376-380.

(129) Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making* 2003; 23(4):341-350.

(130) Lip GY, Kongnakorn T, Phatak H, Kuznik A, Lanitis T, Liu LZ et al. Cost-effectiveness of apixaban versus other new oral anticoagulants for stroke prevention in atrial fibrillation. *Clin Ther* 2014; 36(2):192-210.