Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: Evidence Review Group Report

Produced by Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE), University of York

Authors Eldon Spackman, Research Fellow, CHE
Jane Burch, Research Fellow, CRD
Rita Faria, Research Fellow, CHE
Belen Corbacho, Research Fellow, CHE
David Fox, Information Specialist, CRD
Nerys Woolacott, Senior Research Fellow, CRD

Correspondence to Nerys Woolacott
Senior Research Fellow, CRD, University of York, York, YO10 5DD

Date completed *04/02/2011*

THE UNIVERSITY of York

Source of funding: This report was commissioned by the NIHR HTA Programme as project number: HTA 09/43.

Declared competing interests of the authors
None.

Acknowledgements
The ERG would like to thank Dr Derick Todd and Dr Chris Pepper for providing clinical advice throughout the project. We would also like to acknowledge the advice of Professor Steve Palmer.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Spackman, E, Burch, J, Faria, R, Corbacho, B, Fox, D, Woolacott, N. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. A Single Technology Appraisal. Centre for Reviews and Dissemination and Centre for Health Economics, 2011.

Contributions of authors
Eldon Spackman, Rita Faria and Belen Corbach: Health economists wrote the economic sections of the report and performed the economic modelling.
Jane Burch and Nerys Woolacott (Project manager): Systematic reviewers critiqued the clinical reviews and wrote the clinical sections of the report.
David Fox: Information specialist critiqued the manufacturer's search strategies.

Contents

List of tables

List of figures

Table of abbreviations

Abbreviation	Definition
A+C	Aspirin plus clopidogrel
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ASA	Aspirin
bid	Twice daily
BIOSIS	BioSciences Information Service of Biological Abstracts
CAD	Coronary artery disease
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CHA_2DS_2-VASc	An adaptation of $CHADS_2$
$CHADS_2$	A clinical prediction rule to estimate the risk of stroke in people with AF
CI	Confidence interval
COX	Cyclooxygenase
CrCl	Creatinine clearance
CTR	Clinical trial report
CVA	Cerebrovascular accident
DARE	Database of Abstracts of Reviews of Effects
DE	Dabigatran etexilate
DBG	Dabigatran
ECH	Extracranial haemorrhage
ED	Extended dominance
EED	Economic Evaluation Database
ERG	Evidence review group
FDA	US Food and Drug Administration
GI	Gastrointestinal
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
INR	International normalised ratio
IQR	Interquartile range
ISPOR	International Society on Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
LVEF	Left ventricular ejection fraction
mg	Milligram
MI	Myocardial infarction
mRS	Modified Rankin scale
MS	Manufacturer's submission
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NR	Not reported
od	Once daily
PAS	Patient access scheme
PbR	Payment by results
PE	Pulmonary embolism
PETRO	Prevention of embolic and thrombotic events
PETRO-ex	PETRO trial extension
PROBE	Prospective Randomised Open trial with Blinded outcome Evaluation
PSS	Personal social services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RE-LY	Randomised evaluation of long-term Anticoagulant Therapy
RELY-able	Long-term extension of the RE-LY trial
RR	Relative risk/risk ratio
SD	Standard deviation
TIA	Transient ischaemic attack
TTO	Time trade off
TTR	Time in therapeutic range
UK	United Kingdom
VKA	Vitamin K antagonist
WFN	Warfarin

1 SUMMARY

1.1 Scope of the manufacturer submission

The manufacturer's submission (MS) explored three regimens of dabigatran for the prevention of stroke in patients with atrial fibrillation (AF): 110 mg bid (referred to as dabigatran 110 mg), 150 mg bid (referred to as dabigatran 150 mg), and 150 mg bid followed by 110 mg bid once the patient reached the age of 80 (referred to as dabigatran sequence), compared primarily to dose-adjusted warfarin (referred to as warfarin). Aspirin monotherapy and clopidogrel plus aspirin were considered secondary comparators. The aim of the MS was to demonstrate that dabigatran was as effective as warfarin, and potentially better, in preventing stroke without a concomitant increase in bleeding.

Compared to the NICE scope, the population in the MS seem to be at higher risk of stroke than the population considered eligible in the UK NHS; the definition of moderate risk in the MS includes those aged 75 years and over with no additional risk factors, whereas the NICE scope specifies people aged 65 years and over with no additional risk factors. In terms of outcomes, the MS reported the outcomes specified in the NICE scope (stroke, non-central nervous system embolism, myocardial infarction (MI), mortality, adverse effects of treatment including haemorrhage and health-related quality of life), however, all stroke was only reported as a component of composite outcomes.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

Based on a single randomised controlled trial (RCT; RE-LY) non-inferiority of both doses of dabigatran was established for the primary outcome of stroke (including haemorrhagic)/systemic embolism (SE); the relative risk reductions in stroke/SE for dabigatran 110 mg and 150 mg compared to warfarin were 10% and 35%, respectively (test for non-inferiority: $p<0.0001$ for both dabigatran doses at both margins). Once non-inferiority was established for the primary outcome, further analyses investigated superiority of dabigatran over warfarin.

Dabigatran 150 mg was significantly better than warfarin in preventing the primary outcome of stroke/SE (hazard ratio (HR) 0.65, 95% CI 0.52 to 0.81); ischaemic stroke (HR 0.75, 95% CI 0.58 to 0.97) and vascular mortality (HR 0.85, 95% CI 0.72 to 0.99); non-inferiority of dabigatran was established for all-cause mortality. Dabigatran 110 mg demonstrated a lower

level of efficacy, and failed to show non-inferiority for ischaemic stroke at the lower margin preferred by the FDA of 1.38. Neither dose was significantly different from warfarin for the risk of SE (dabigatran 110 mg: relative risk (RR) 0.71, 95% CI 0.37 to 1.38; dabigatran 150 mg: RR 0. 61, 95% CI 0.30 to 1.21). The results for acute MI, an efficacy outcome included in the economic model, indicated a small but non-significant increased risk with both doses of dabigatran (dabigatran 110 mg: HR 1.29, 95 % CI 0.96 to 1.75; dabigatran 150 mg: HR 1.27, 95 % CI 0.96 to 1.75).

In terms of safety the main risk of treatment considered was increased bleeding. Compared to warfarin, both dabigatran doses were associated with a significantly lower rate of haemorrhagic stroke (dabigatran 150 mg: HR 0. 26, 95% CI 0.14 to 0.49; dabigatran 110 mg: HR 0. 31, 95% CI 0.17 to 0.56), life-threatening bleeds (dabigatran 150 mg: HR 0. 80, 95% CI 0.66 to 0.98; dabigatran 110 mg: HR 0. 67, 95% CI 0.54 to 0.82), and intracranial haemorrhage (ICH) including haemorrhagic stroke (dabigatran 150 mg: HR 0. 41, 95% CI 0.28 to 0.61; dabigatran 110 mg: HR 0. 30, 95% CI 0.19 to 0.45) and excluding haemorrhagic stroke (dabigatran 150 mg: HR 0. 52, 95% CI 0.32 to 0.84; dabigatran 110 mg: HR 0. 32, 95% CI 0.18 to 0.57). Dabigatran 110 mg was also associated with a decreased rate of major bleeds (HR 0. 80, 95% CI 0.70 to 0.93), but the 150 mg dose was not (HR 0.93, 95% CI 0.81 to 1.07). However, both doses of dabigatran were associated with a higher rate of gastrointestinal (GI) bleeds (dabigatran 150 mg: HR 1. 52, 95% CI 1.35 to 1.72; dabigatran 110 mg: HR 1.35, 95% CI 1.19 to 1.53) and dabigatran 150 mg was associated with increased major GI bleeds (HR 1.47, 95% CI 1.17 to 1.85); and life-threatening GI bleeds (HR 1.62, 95% CI 1.17 to 2.26).

Overall discontinuation rates across the three RE-LY trial arms were similar, however, the discontinuation rates for the two dabigatran doses are higher in the early stages of the trial compared to warfarin.

For the subgroup analyses of patients under and over the age of 80 years, efficacy results were reported only for ischaemic stroke, SE, transient ishaemic attack (TIA) and MI: these are the outcomes included in the economic model. These results for both sub groups generally reflected the general population but in the over 80s, there was better response in some outcomes including a benefit in the risk of TIA with dabigatran 110 mg (HR 0.45, 95%

CI 0.23 to 0.89). In terms of safety, dabigatran 150 mg in the over 80's was not associated with an increased risk of haemorrhagic stroke or intracranial haemorrhage, but was associated with an increased risk of extracranial haemorrhage (ECH; HR 1.61, 95% CI 1.19 to 2.18). Dabigatran 110 mg was associated with a significant reduction in the incidence of haemorrhagic stroke (HR 0.26, 95% CI 0.07 to 0.91) and ICH (HR 0.29, 95% CI 0.10 to 0.88), but, as with dabigatran 150 mg, was associated with an increased risk of ECH (HR 1.44, 95% CI 1.05 to 1.97). It is unclear what proportion of those with ECH would have been major/life-threatening bleeds or GI bleeds, as these outcomes were not reported for this subgroup.

When results were presented separately for patients who were warfarin experienced or naïve, the results for stroke/SE did not differ for either sub group of patients compared with the general population. However, the reduction in major bleed was more pronounced with dabigatran 110 mg (HR 0.74, 95% CI 0.60 to 0.91) than 150 mg (HR 0.93, 95% CI 0.76 to 0.1.12) in warfarin experienced patients. A medical review by the Center for Drug Evaluation and Research (FDA) included subgroup analyses that showed the benefit of dabigatran in the prevention of stroke/SE was greater in those with poor warfarin control, and that dabigatran showed efficacy, but not superiority over warfarin, in patients who achieved the international normalised ratio (INR control) above the centre-level median (67%).

A mixed treatment comparison (MTC) which included the two doses of dabigatran, dose-adjusted vitamin K antagonist (VKA), aspirin, aspirin plus clopidogrel, and placebo was presented. It also included a weighted average of two subgroups (under 80years of age randomised to dabigatran 150 mg and over 80 years of age randomised to dabigatran 110 mg) in order to investigate the effectiveness and safety of a reduction in the dose of dabigatran at aged 80 ('dabigatran sequence'). The results from the MTC for dabigatran compared to warfarin, were similar to those from the direct comparison in the RE-LY trial (the constructed dabigatran sequence gave similar results to the dabigatran 150 mg dose). The MTC found that compared with aspirin or aspirin plus clopidogrel the relative treatment effect favoured all doses of dabigatran for most outcomes (some statistically significantly so).

Overall, the evidence shows that dabigatran 150 mg is efficacious in preventing ischaemic stroke and vascular death, without a significant concomitant increase in the incidence of

haemorrhagic stroke or major bleeding, although, the incidence of GI bleeds is increased with dabigatran 150 mg compared to warfarin. There seems to be some benefit in a dose reduction in the elderly in terms of haemorrhagic outcomes, and the beneficial effects of dabigatran compared with warfarin seem to be most pronounced in those with poor INR control.

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

The MS included two generally well-conducted systematic reviews: the first of dabigatran trials in the relevant indication, and the second of all potentially relevant pharmacological interventions for the prevention of stroke in patients with AF. The ERG found no relevant studies that were not discussed in the submission.

For the review of trials of dabigatran in the relevant indication the manufacturer identified three trials that directly compared dabigatran with warfarin: RE-LY, PETRO and 1160.49. The MS appropriately concentrated on the results of the RE-LY trial. The RE-LY trial was a good quality trial with blinded doses of dabigatran and an open-label dose warfarin arm. The other two trials were smaller phase II dose-finding studies with safety as the primary objective. The RE-LY trial was designed to demonstrate the non-inferiority of dabigatran compared to warfarin. This was appropriate given the well established efficacy of warfarin. Non-inferiority trials have limitations, particularly in relation to the establishment of the non-inferiority margin and the population on which to base analyses. However, the ERG feel that the manufacturer took adequate measures to reduce the impact of the potential biases associated with these limitations by using two margins of non-inferiority (1.46 and 1.38) and by analysing the results for both the intention to treat (ITT) and per protocol populations.

The software chosen to run the MTC had some limitations: the inability to include trials with zero counts; and the use of a fixed effect model that produced narrower confidence intervals which may not have reflected the heterogeneity across the trials. In addition, adjustment was made for only a single covariate in the analysis, and no justification as to the choice of that covariate over another that showed significant impact on the results of four major outcomes was given. The impact of the introduction of a fourth arm to the RE-LY trial into the MTC (and potentially double counting a large number of patients) on the relative effect of dabigatran, not only compared to dose-adjusted VKA, but also compared to aspirin monotherapy and aspirin plus clopidogrel, is uncertain. The importance of the MTC in the

manufacturer's submission was limited: only the comparison with aspirin and aspirin plus clopidogrel were utilised in the economic model's base-case; the primary comparator in clinical practice for dabigatran is warfarin. It is worth noting that in the economic section of the submission, the manufacturer defines two 'dabigatran sequences' that fed into the model: neither of these were the dabigatran sequence arm that was created for the MTC.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer did not identify any previously published cost-effectiveness studies of dabigatran for the prevention of stroke or SE in patients with AF. Therefore the manufacturer's *de novo* economic evaluation, adapted from a previous evaluation of warfarin, formed the basis of the submitted economic evidence.[1] Subsequent to the MS a separate study was published on the cost-effectiveness of dabigatran.[2]

The manufacturer's evaluation was based on a cost utility analysis designed to compare the costs and outcomes of dabigatran against treatments used in the UK (warfarin, aspirin, aspirin plus clopidogrel). Three dabigatran regimens were examined by the manufacturer: dabigatran 110 mg, dabigatran 150 mg and sequential treatment. Sequential treatment allowed patients to be treated differentially by age, patients less than 80 years old were treated with dabigatran 150 mg and patients 80 years or older were treated with dabigatran 110 mg (this is not the constructed 'dabigatran sequence' arm included in the MTC).

The manufacturer developed a Markov model; three levels of disability were used to define health states, independent, moderate, severe and dead. Patients at risk of haemorrhagic and ischemic events transitioned between health states when a clinical event occurred and their disability status changed. As a consequence of the different clinical events the model also allowed for discontinuation or switch to a second-line treatment. The patient cohort reflected the patients participating in the RE-LY trial and was stratified according to $CHADS_2$ score and stroke history. The simulation provided the number of clinical events, costs and QALYs for each sub-group. The final results were obtained by averaging the results of each sub-subgroup, weighted by $CHADS_2$ distribution. No results were provided by the manufacturer for individual sub-groups. The relative event risk for all treatment strategies was applied to the baseline risk of events in patients treated with warfarin in the RE-LY trial. The relative risk for dabigatran 110 mg and dabigatran 150 mg for the various clinical events was

obtained from the RE-LY trial. As described above MTCs were undertaken and provided relative risks for aspirin, aspirin plus clopidogrel, and no treatment. No treatment was informed by the placebo arm. Two MTCs were performed, one using SAS and the other using WinBUGS. The manufacturer chose the SAS MTC for the base-case analysis.

In the model, INR affected the risk of clinical events. Patients with an INR between 2 and 3 were considered to be in the appropriate therapeutic target range for AF patients. An INR below 2 increased the risk of ischemic events and an INR above 3 increased the risk of haemorrhagic events. In the MS INR response was weighted to reflect patients in the RE-LY trial. All results presented by the manufacturer were a weighted average of patients with and without INR control. No subgroup results were presented by patients' INR response.

The economic evaluation incorporated the health-related quality of life associated with disability status and disutility incurred due to the various clinical events.

The model considered the resource costs associated with antithrombotic treatment (including INR monitoring), acute events costs and long term follow-up costs resulting from disability. The national payment by results (PbR) tariff was used to estimate unit costs where applicable. Systematic reviews were conducted to estimate costs if no published unit costs were available. The manufacturer also sponsored a new study to assess the cost of stroke in patients with AF within the Oxford Vascular Study (OXVASC).

Structural, univariate and probabilistic sensitivity analyses (PSA) were performed by the manufacturer. The original MS does not provide a full incremental analysis of all treatments under assessment, instead a selection of pair wise comparisons were made. In the MS dabigatran 110 mg and dabigatran 150 mg were not compared. The ERG requested a full incremental analysis of all treatments. Aspirin is associated with the lowest costs. Warfarin is associated with greater costs and health benefits than aspirin. The incremental cost-effectiveness ratio (ICER) for warfarin compared to aspirin is £2,502 per additional Quality adjusted life year (QALY). The combination of aspirin plus clopidogrel is associated with higher costs and less health benefits than warfarin. Therefore this intervention is dominated by warfarin. Dabigatran 150 mg results in higher costs but greater health benefits than warfarin, the ICER comparing dabigatran 150 mg to warfarin is £6,261 per additional QALY.

Dabigatran 110 mg and sequential treatment are associated with greater costs and lower health benefits than dabigatran 150 mg, and are therefore dominated.

The manufacturer considered dabigatran 110 mg and sequential treatment to be cost effective compared to the treatments available in current practice, because both are associated with increased health benefits and costs compared to warfarin. However, neither was cost-effective when compared to dabigatran 150 mg. The PSA base-case analysis takes into account the uncertainty surrounding the input parameters. The inclusion of uncertainty into the model results in similar conclusions to the deterministic analysis. The probabilistic ICER for dabigatran 150 mg is higher than in the deterministic analysis; £7,940 per QALY compared to £6,261 per QALY.

All results presented by the manufacturer represented the total AF population. When sub-group analyses were undertaken by the ERG results varied substantially.

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

A detailed critique of the manufacturer's initial submission and revised model following points for clarification was undertaken by the ERG. The economic model structure was considered appropriate for the decision problem, and the general approach employed by the manufacturer to estimate lifetime cost-effectiveness was deemed appropriate and met the requirements of the NICE reference case approach. However, the ERG identified a few alternative assumptions to those used in the model. The ERG's analysis considered:

1. The generalisability of the RE-LY trial data to the UK-AF population
2. The cost-effectiveness of dabigatran for patients with different $CHADS_2$ scores
3. The effect of INR control on cost-effectiveness
4. The cost of annual INR monitoring
5. How treatment affected stroke disability
6. The long-term consequences of AMI and SE
7. The disutility of dabigatran in the RE-LY Quality of life (QoL) sub-study.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The description of the underlying health problem in the MS is appropriate to the submission and technology under appraisal. The systematic reviews were generally well-conducted, and the evidence for the effectiveness and safety was based primarily on a good quality trial, that demonstrated that overall, dabigatran was not inferior to warfarin in terms of efficacy and safety.

The economic model structure was considered appropriate for the decision problem as it captures both the acute and longer-term consequences of the clinical events included. At the same time, the general approach employed by the manufacturer to estimate lifetime cost-effectiveness met the requirements of the NICE reference case approach.

All the important comparators reflecting the standard practice in the UK are included in the model. The manufacturer conducted extensive literature reviews that provided relevant studies representing up-to-date clinical evidence. For the primary comparison, dabigatran versus warfarin, the key clinical evidence comes from the pivotal RE-LY study. Structural, univariate and probabilistic sensitivity analysis (PSA) were performed to reflect uncertainty in the model inputs and assumptions and these were informative in exploring the robustness of the results and identifying potential key drivers of cost-effectiveness.

The ERG also acknowledges that the manufacturer provided detailed additional information in response to the clarification points which were central to key aspects of the ERG's review.

1.6.2 Weaknesses and areas of uncertainty

The two main potential weaknesses of the MS are related to the sequence of treatments and the cost of anticoagulation monitoring.

Currently the MS considers sequential treatment to be dose adjustment of dabigatran for elderly patients. However treatment sequence also refers to the timing of different treatments along a patient's treatment pathway. One of the weaknesses of the economic model is that it allows the evaluation of a restricted number of treatment sequences. Specifically the model

and the MS assume that warfarin and dabigatran are mutually exclusive alternatives. In the model once a patient has been prescribed dabigatran, the second-line treatment will be aspirin plus clopidogrel, aspirin or no treatment. Unfortunately the structure of the model fails to allow the sequence of treatment to be fully explored. For example, starting on dabigatran and then switching to warfarin is a reasonable treatment sequence based on the clinical expert opinion we received. The manufacturer's model assumes a patient cannot switch to warfarin if dabigatran was the first treatment. It is not clear that a health system that approves dabigatran will no longer use warfarin, this has important implications for the incremental costs since this means dabigatran is unlikely to offset the fixed costs of warfarin.

The costs of monitoring, together with the acquisition cost of dabigatran, are the key drivers of the model in terms of resources and costs. There appear to be a wide range of plausible estimates for the annual cost of monitoring. The ERG considers the average cost of monitoring has been overestimated in the model and that the results may be biased in favour of dabigatran. Equally important, clinical advisors to the ERG were concerned with the high variability of monitoring costs in practice. Those with well controlled INR will have much lower costs than uncontrolled patients. This heterogeneity has not been considered in the MS. The uncertainty around the monitoring costs was also inadequately modelled in the MS.

In terms of the assessment of the clinical evidence, two main areas of uncertainty are worth particular attention:

1. How the results would be affected by the inclusion of people over 65 with AF but no other risk factors for stroke to the trial population. The inclusion of this potentially large subgroup of patients would reflect the NICE scope more closely, and reduce the overall risk level of the population. Additionally since the threshold for anticoagulation use continues to fall it is not clear how dabigatran will perform in less severe populations.
2. The relative effect of dabigatran to aspirin monotherapy in patient whom warfarin is not suitable remains unknown, therefore this aspect of the NICE scope has not been addressed. However, given a contraindication to warfarin would also mean a contraindication to dabigatran, this comparison is likely to only be relevant in the small number of patients who have an allergy to warfarin. In addition, atrial

appendage occlusion devices would also be considered a comparator to dabigatran in these patients.

1.7 Summary of additional work undertaken by the ERG

The most significant assumptions for which the ERG considered there to be justified alternatives were: (i) adapting the characteristics of the RE-LY patients simulated in the economic model to the characteristics of the UK AF patients; (ii) testing cost effectiveness of dabigatran across the different distributions of $CHADS_2$ scores groups; (iii) considering the patients able to maintain INR within the target range of 2 and 3 as a separate subpopulation for the economic evaluation; (iv) testing different approaches to estimate the cost of annual monitoring; (v) disability of stroke considered to be independent of treatment; and (vi) considering disutility associated with dabigatran from the RE-LY QoL sub-study.

The characteristics of the patients in the RE-LY trial may not reflect the characteristics of the UK patients suffering AF. The ERG explored an alternative scenario using the results of a UK study which suggests the UK-AF population is less severe than that of the RE-LY trial, but older. When the ERG altered these assumptions the ICER for dabigatran 150 mg for the UK population increases to £10,455 per QALY. The analysis suggests that first dabigatran 150 mg is more cost effective than warfarin, and second that treating patients with dabigatran 110 mg is not cost effective compared to dabigatran 150 mg regardless of age.

The ERG tested the cost effectiveness of dabigatran across the different distributions of $CHADS_2$ score groups. The results of this analysis suggested that dabigatran 150 mg is more cost effective in patients with higher $CHADS_2$ scores. Across all $CHADS_2$ scores dabigatran 110, and sequential treatment, are dominated by dabigatran 150 mg.

Considering the patients able to maintain INR within the target range of 2 and 3 as a separate subpopulation for the economic evaluation, the ERG demonstrated that warfarin was the most cost-effective intervention for patients who are able to keep INR within range. The ICER of dabigatran 150 mg compared to warfarin increases to £60,895 per QALY; dabigatran 110 mg and the sequence model are dominated by warfarin. These results show that INR control is a key parameter in the economic evaluation, and at the same time highlight the need to explore the scenario of warfarin as first-line treatment with dabigatran as second-line treatment.

The cost of anticoagulant monitoring is a key driver of the model in term of resources and costs. The ERG considers that the manufacturer approach to estimate the annual cost of monitoring is limited and might be biased in favour of dabigatran due to the inclusion of fixed costs of monitoring. These fixed costs will only be offset if warfarin is no longer used in the UK. Three alternatives approaches were then used to recalculate this cost. Adjusting the model to test each individual assumption increased the ICER up to £15,701.

Incorporating disutility associated with dabigatran treatment increased the ICER for dabigatran 150 mg slightly, however it did not change the overall conclusions regarding the cost-effectiveness of this intervention.

Finally, the ERG investigated an alternative 'base-case' analyses to the one presented by the manufacturer. The ERG base-case assumes that: (i) a patient cohort representative of the AF patient population in the UK, using the data reported by Gallagher *et al.*, 2008; (ii) The variable (per patient) costs of anticoagulant monitoring are £115.14; (iii) patients suffer from dyspepsia during dabigatran treatment, not only for three months; (iv) disability and mortality risks after stoke are treatment independent; (v) disutility associated with dabigatran is 0.016 during the first 12 months of treatment, as per the RE-LY QoL sub-study. The ICER for dabigatran 150 mg is £24,173 per QALY for the ERG base-case scenario. In this scenario dabigatran 110 mg and sequential treatment are dominated by dabigatran 150 mg, as in the manufacturer's results.

1.8 Conclusions

Based primarily on a single trial (RE-LY), dabigatran 150 mg bid was shown to be non-inferior, and subsequently superior, to dose-adjusted warfarin in the prevention of stroke/SE. Dabigatran 150 mg bid was also shown to be efficacious in preventing ischaemic stroke and vascular death, without significant concomitant increases in the incidence of haemorrhagic stroke or major bleeding. However, the incidence of GI bleeds, including major GI bleeds and life-threatening GI bleed, was increased with dabigatran 150 mg bid compared to dose adjusted warfarin.

Results for those under 80 years of age were similar to those of the whole population, both in terms of effectiveness and safety. However, there seems to be some benefit in a dose reduction in the elderly in terms of haemorrhagic outcomes, with dabigatran 110 mg bid showing a significant reduction in the incidence of haemorrhagic stroke and ICH compared to dose-adjusted warfarin, but not dabigatran 150 mg bid. In addition, although dabigatran is efficacious in patients with good warfarin control, the beneficial effects of dabigatran seem to be most pronounced in those with poor INR control.

The main uncertainty surrounding the evaluation of the clinical evidence is the generalisability of the results to the AF population in the UK NHS. The population in the RE-LY trial, on which the assessment of efficacy and safety relied, had a higher risk of stroke than that specified in the NICE scope. Furthermore, according to clinical experts advising the ERG, the threshold for treatment with warfarin seems to be decreasing, therefore decreasing the risk of stroke in the eligible AF population, making the population in the RE-LY trial less representative of clinical practice over time.

The economic model structure was considered appropriate for the decision problem, and the general approach employed by the manufacturer to estimate lifetime cost-effectiveness was deemed appropriate and met the requirements of the NICE reference case approach. However, the ERG identified a few alternative assumptions to those used in the model. By instituting these assumptions the cost-effectiveness of dabigatran 150 mg bid compared to warfarin ranged from £24,173 to £29, 131 per QALY.

The main uncertainty surrounding the economic evaluation is the cost-effectiveness of dabigatran in the heterogeneous groups of the UK population. In the additional work undertaken by the ERG we showed that the cost-effectiveness of dabigatran differs by severity and that it is not cost-effective for patients who can maintain adequate INR levels. Since it is unclear from treatment outset which patients will have INR control it may be possible to use warfarin and dabigatran sequentially. The cost-effectiveness of warfarin with second-line dabigatran compared to first-line dabigatran will depend on the risk associated with warfarin until INR control can be decided.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem.

The description of the underlying health problem in the MS is appropriate to the submission and technology under appraisal.

2.2 Critique of manufacturer's overview of current service provision

The submission states that the anticipated indication for dabigatran is the prevention of stroke and systemic embolism (SE) in adult patients with atrial fibrillation (AF). Dabigatran does not currently have marketing authorisation for this indication in the UK; marketing authorisation for the use of dabigatran in the prevention of stroke and SE in adult patients with AF is expected in [redacted]. Authorisation is currently available for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The NICE scope specified the target population as people with AF who are at moderate to high risk of stroke or SE. The definitions of moderate and high risk of stroke or SE in adults with AF in the NICE clinical guidance 36 are:

- Moderate
    - Aged ≥65 with no high risk factors
    - Aged <75 with hypertension, diabetes or vascular disease
- High
    - Previous ischaemic stroke/transient ischaemic attack (TIA) or thromboembolic event
    - Ages ≥75 with hypertension, diabetes or vascular disease
    - Clinical evidence of valve disease or heart failure, or impaired left ventricular function on echocardiography.

The definition of moderate/high risk of stroke or SE considered in the MS is that used in the main trial of dabigatran (RE-LY[3, 4]):

- History of stroke, TIA or SE

- Left ventricular ejection fraction (LVEF) <40%
- Symptomatic heart failure
- Age ≥ 75 years
- Age ≥ 65 years and one of the following:
    - Diabetes mellitus on treatment
    - Documented coronary artery disease
    - Hypertension requiring medical treatment.

Therefore the population in the MS seem to be at higher risk of stroke than the population considered eligible in the UK NHS, as the definition of moderate in the MS does not include people over 65 years of age with no additional risk factors.

3.2 Intervention

The intervention specified in the manufacturer's decision problem is dabigatran etexilate (Pradaxa®) 110 mg or 150 mg twice daily (bid). Three regimens of dabigatran were explored in the MS: 110 mg bid, 150 mg bid, and 150 mg bid followed by 110 mg bid once the patient reached the age of 80. The manufacturer was asked to provide evidence to justify the reduction in dose at the age of 80. The manufacturer stated that the regimens incorporating dose reduction at the age 80 were implemented based on interim feedback from the regulatory authority (European Medicines Agency) and the posology reflected in the Canadian approval of dabigatran. The ERG note it does not reflect the licence in the USA, which does not recommend an age-related dose reduction. Clinical advisors to the ERG considered the reduction in dose at 80 years of age was based upon the known increased risk of bleeding with warfarin, and the pharmacology of dabigatran with decreased renal function. The ERG's clinical advisors considered the reduction in dose in the elderly to be a reasonable precaution, and would reflect clinical practice.

3.3 Comparators

The comparators specified in the NICE scope were warfarin and antiplatelet agents such as aspirin in people for whom warfarin is inappropriate. In the MS, warfarin was the primary comparator. Aspirin monotherapy and clopidogrel plus aspirin were considered secondary comparators, but not in the context of patients for whom warfarin was inappropriate. Clinical advisors to the ERG agreed with the NICE scope; they considered clopidogrel to have a

limited role in this indication, being considered only in those who are intolerant to warfarin and who suffer side effects of aspirin. Further treatments were included in the MTC network were Ximelagatran and vitamin K antagonists (VKA) other than warfarin, although the results of these comparators were not considered in the MS. The use of a left atrial appendage occlusion device may be considered a comparator to dabigatran in a small minority of patients who cannot use oral warfarin. Other agents (dipyridamole, idraparinux (anticoagulant administered by injection), ximelagatran (oral direct thrombin inhibitor), indobufen (Cyclooxygenase (COX)-inhibitor), and truifusal (salicylate)) were not considered in the MS as comparators to dabigatran. The omission of the above treatments from the MS was deemed appropriate by clinical advisors to the ERG.

3.4 Outcomes

The outcomes identified in the NICE scope as appropriate for the population being studied were:

- Stroke
- Non-central nervous system embolism
- Myocardial infarction
- Mortality
- Adverse effects of treatment including haemorrhage
- Health-related quality of life.

These outcomes were considered in the MS, although all stroke was only used as a component of composite outcomes; both all-cause mortality and vascular mortality were reported. A range of additional outcomes were considered by the manufacturer:

- Compliance/discontinuation of treatment

Effectiveness:

- Ischaemic stroke
- Other stroke
- Pulmonary embolism (PE)
- Symptomatic, clinical MI
- Silent MI

- Total MI
- TIA
- Hospitalisation

Safety

- Haemorrhagic stroke (included in the effectiveness section of the MS)
- Major bleeding
- Intracranial haemorrhage (ICH; with and without haemorrhagic stroke)
- Extracranial haemorrhage (ECH)
- Life-threatening bleed
- Major GI bleed
- Life-threatening GI bleed
- Any GI bleed
- Minor bleeding
- Any bleeding

A range of composite outcomes were also reported:

- Stroke/SE
- Stroke/SE/all-cause mortality
- Stroke/SE/vascular mortality/PE/MI
- Stroke/SE/vascular mortality/PE/MI
- Ischaemic stroke/SE/hospitalisation or all-cause mortality/PE/MI/TIA
- Net clinical benefit (stroke/SE/all-cause mortality or major bleed/PE/MI).

Of the outcomes listed above, ischaemic stroke, SE, MI (total), TIA, haemorrhagic stroke, ICH, ECH, and minor bleed, were included in the economic model.

3.5 Quality assessment

The manufacturer's assesses study quality using appropriate criteria: method of randomisation; allocation concealment; similarity at baseline across groups; blinding (participants, carers, outcome assessors); imbalances in drop-outs (and adjustments made); evidence of selective reporting; the use of an intention to treat (ITT) analysis.

3.6 Other relevant factors

[redacted]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

The MS included two systematic reviews: the first of dabigatran trials in the relevant indication, and the second of all potentially relevant pharmacological interventions for the prevention of stroke in patients with AF.

4.1.1 Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate

The manufacturer conducted extensive searches using a range of databases. For the first review of dabigatran trials in the relevant indication MEDLINE, EMBASE, CENTRAL, the manufacturer's own internal databases (BILIT, pre-BILIT and IDEA), Clinicaltrials.gov, and the proceedings of five relevant conferences were searched. Only English language studies were sought for this review, therefore language bias can't be ruled out.

For the second review of all potentially relevant pharmacological interventions for the prevention of stroke in patients with AF, MEDLINE, EMBASE, CENTRAL, CDSR, DARE, BIOSIS, and the reference lists of articles, reviews and meta-analyses were searched. No date or language restrictions were applied to the searches for the second review.

The search strategies used were reported in full for each section of the clinical review (clinical evidence, mixed treatment comparison (MTC), non-RCT evidence, adverse events) and seem appropriate; no relevant studies appear to have been missed.

4.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion and exclusion criteria applied in the MS to select studies for the first review of the efficacy and safety of dabigatran, were appropriate:

Population:	Adults (≥18 years) with AF
Intervention:	Dabigatran
Comparator:	Another treatment modality or placebo
Outcomes:	Prevention of stroke
Study design:	Randomised controlled trials or observational studies.

The inclusion and exclusion criteria applied to select studies for the second review of other therapeutic regimens, were also appropriate:

Population:	Adults (≥18 years) with AF
Intervention:	Any treatment used to prevent stroke in AF
Comparator:	Any alternative treatment used to prevent stroke in AF or placebo
Outcomes:	Prevention of stroke
Study design:	Randomised controlled trials.

The inclusion criteria were applied by more than one reviewer in both reviews, reducing the potential for selection bias and missed studies.

4.1.3 Data extraction

Data were extracted in order to calculate hazard ratios (HR) or risk ratios (RR) with 95% confidence intervals (CI) by more than one reviewer, reducing the potential for data extraction errors.

4.1.4 What studies were included in the clinical effectiveness review and what were excluded?

The trials included in the review of dabigatran are discussed in this section. The broader group of trials included in the MTC are discussed later (Section 4.4).

The manufacturer identified three trials that directly compared dabigatran with warfarin: RE-LY, PETRO and 1160.49 (Table 1). Uncontrolled extensions of the RE-LY and PETRO trials, where only the patients receiving dabigatran were followed-up, were also identified: RELY-ABLE and PETRO-Ex (Table 1). RE-LY was the primary source of effectiveness data in the submission; PETRO and 1160.49 were phase II dose-finding studies with safety as the primary objective.

Table 1: Studies included in the MS

	Intervention	**Comparator**	**Patient numbers**
RE-LY[4]	• Dabigatran 110 mg bid (N = 6,015) • Dabigatran 150 mg bid (N = 6,076)	Adjusted-dose warfarin Target INR 2.0-3.0 (N = 6,022)	18,113
RELY-ABLE[5]	• Dabigatran 110 mg bid • Dabigatran 150 mg bid	None	6,200 (Estimated)
PETRO[6]	• Dabigatran 50 mg bid (N=58) • Dabigatran 50 mg bid + ASA 81 mg od (N=20) • Dabigatran 50 mg bid + ASA 325 mg od (N=27) • Dabigatran 150 mg bid (N=99) • Dabigatran 150 mg bid + ASA 81 mg od (N=34) • Dabigatran 150 mg bid + ASA 325 mg od (N=33) • Dabigatran 300 mg bid (N=98) • Dabigatran 300 mg bid + ASA 81 mg od (N=33) • Dabigatran 300 mg bid + ASA 325 mg od (N=30)	Adjusted-dose warfarin Target INR 2.0-3.0 (N = 70)	502
PETRO-Ex[7]	All patients were initially maintained on the same Dabigatran doses as in PETRO except the 50 mg bid dose group who were switched to 150 mg od. Due to higher frequency of major bleeding events in 300 mg bid group and thromboembolic events in 150 mg od group, these patients were subsequently switched to Dabigatran 300 mg od or 150 mg bid.	None	361
1160.49[8]	• Dabigatran 110 mg bid • Dabigatran 150 mg bid	Adjusted-dose warfarin Target INR 2.0-3.0 (1.6 to 2.6 for patients aged 70 or over)	174

ASA, aspirin; bid, twice daily dosing; INR, International Normalised Ratio; od, once-daily dosing

4.1.5 Relevant studies not discussed in the submission

The ERG found no relevant studies that were not discussed in the submission.

4.2 Summary and critique of submitted clinical effectiveness evidence

4.2.1 Summary and critique of the RE-LY trial

The RE-LY trial was designed as a non-inferiority trial in which two blinded doses of dabigatran (110 mg bid and 150 mg bid) were compared with open-label dose-adjusted warfarin (target international normalised ratio (INR) of 2.0 to 3.0) for the prevention of stroke and SE in patients with non-valvular AF and at least one additional risk factor for stroke. Therefore the initial objective of the trial was to show that the response to dabigatran was not clinically inferior to that of the most clinically relevant comparative agent, dose-adjusted warfarin; improvement of any size meets the definition of non-inferiority.[9] This primary objective was appropriate, given that a placebo controlled trial would not be ethical, and the efficacy of warfarin is well established.

Non-inferiority trials, however, have a number of limitations, including the establishment of the non-inferiority margin and the population on which to base analyses; these can result in the introduction of bias.[9] Two margins were used to assess non-inferiority of the RE-LY trial in the MS: 1.46 and 1.38. To show non-inferiority, the upper bound of the confidence interval (CI) of the hazard ratio (HR) for dabigatran versus warfarin had to be less than the margin specified. The derivation of the value of 1.46 was not reported in the MS; 1.38 was specified as the preferred margin of non-inferiority of the US Food and Drug Administration (FDA).

When analysing the result of a non-inferiority trial, the use of an ITT population (where data is included in the analysis for patients who have discontinued the study drug) tends to bias the results toward equivalence, which could make a truly inferior treatment appear to be non-inferior.[9] However, an analysis based on a per protocol population (where data from patients with major protocol violations is excluded) can substantially bias the results in either direction. Therefore, analyses of non-inferiority trials using both the ITT and per-protocol populations are recommended, and the trial considered positive if both analyses support non-inferiority.[9] The primary non-inferiority analyses of the RE-LY trial reported in the MS was conducted on the ITT population. However, the RE-LY clinical trial report (CTR) stated that non-inferiority was also assessed in a secondary analysis using the per protocol population; although the results of this analysis were not reported, it was stated that they supported those of the ITT analysis.

The RE-LY trial was a large Prospective Randomised Open trial with Blinded outcome Evaluation (PROBE) study, with two doses of dabigatran allocated in a concealed fashion and the dose of dabigatran blinded to patients, carers and outcome assessors, and an open label warfarin arm. Blinded adjudicators were used to assess study outcomes. This study design was used due to the requirement for regular INR tests for patients receiving warfarin; although sham INR testing is possible, it was considered by the trialists to be complex, time consuming and undesirable. The trialists also considered this an appropriate study design as most placebo-controlled warfarin trials have been open label in design. Although the open label nature of the warfarin arm in the trial could introduce bias, this would be primarily in subjective outcome measures and patient reported outcomes. The majority of the clinical outcomes measured in the RE-LY trial are less prone to such subjective judgements. In addition, the outcome assessors were blinded, reducing the risk of detection bias. Therefore the use of the PROBE study design is not considered by the ERG to be a major threat to study quality in this circumstance, and the quality of the RE-LY trial was considered good.

Randomisation was conducted within 14 days of the screening visit at which AF was identified/confirmed. Participants were randomly allocated to 1 of 3 treatment groups: dabigatran 110 mg bid (referred to as dabigatran 110 mg), dabigatran 150 mg bid (referred to as dabigatran 150 mg), or dose-adjusted warfarin (referred to as warfarin); the allocation ratio was 1:1:1 with a block size of 3, 6, and 9. The trial recruited 18,133 patients across 44 countries; 6,015 received 110 mg dabigatran, 6,076 received 150 mg dabigatran and 6,022 received warfarin. The numbers recruited exceeded those calculated as being required to detect non-inferiority at a margin of 1.46 at 90% power and a one-sided α=0.025. A power calculation using the lower margin of 1.38 was not provided. Participants were followed up at 2 weeks by telephone, and then visits were undertaken at 1, 3, 6, 9, and 12 months after randomisation and then every 4 months for the duration of the trial up to a maximum of 36 months; minimum follow-up was 1 year, and median follow-up was 23.7 months. From Table 2, it can be seen that there is similarity across the three treatments arms for all variables measured at baseline.

Table 2: Baseline characteristics of the participants in RE-LY

	Dabigatran 110 mg (n=6,015)	Dabigatran 150 mg (n=6,076)	Warfarin (n=6,022)
Mean age, yrs (SD)	71.4 (8.6)	71.5 (8.8)	71.6 (8.6)
Male	3,865 (64.3%)	3,840 (63.2%)	3,809 (63.3%)
Weight, kg (SD)	82.9 (19.8)	82.4 (19.3)	82.6 (19.6)
Duration of disease	<3 mo: 1,843 (30.6%) 3 mo to 2 yrs: 1,324 (22.0%) >2yrs: 2,842 (47.2%)	<3 mo: 1,854 (30.5%) 3 mo to 2 yrs: 1,344 (22.1%) >2yrs: 2,875 (47.3%)	<3 mo: 1,929 (32.0%) 3 mo to 2 yrs: 1,315 (21.8%) >2yrs: 2,776 (46.1%)
Type of AF	Persistent: 1,950 (32.4%) Paroxysmal: 1,928 (32.1%) Permanent: 2,131 (35.4%)	Persistent: 1,909 (31.4%) Paroxysmal: 1,977 (32.5%) Permanent: 2,188 (36.0%)	Persistent: 1,930 (32.0%) Paroxysmal: 2,036 (33.8%) Permanent: 2,055 (34.1%)
$CHADS_2$ score	0: 151 (2.5%) 1: 1,809 (30.1%) 2: 2,088 (34.7%) 3+: 1,966 (32.7%) Mean: 2.1	0: 146 (2.4%) 1: 1,815 (29.9%) 2: 2,136 (35.2%) 3+: 1,979 (32.6%) Mean: 2.1	0: 155 (2.6%) 1: 1,707 (28.3%) 2: 2,229 (37.0%) 3+: 1,931 (32.1%) Mean: 2.1
Mean CrCl, mL/min (SD)	73.0 (27.7)	72.7 (28.2)	73.0 (27.4)
Long-term VKA therapy	3,008 (50.0%)	3,047 (50.1%)	2,929 (48.6%)
Previous cardioversion	1,658 (27.6%)	1,683 (27.7%)	1,651 (27.4%)
Previous ablation	119 (2.0%)	136 (2.2%)	132 (2.2%)
Diabetes	1,409 (23.4%)	1,402 (23.1%)	1,410 (23.4%)
Hypertension	4,738 (78.8%)	4,795 (78.9%)	4,750 (78.9%)
Previous stroke	761 (12.7%)	756 (12.4%)	756 (12.6%)
Previous TIA	548 (9.1%)	587 (9.7%)	528 (8.8%)
Prior MI	1,008 (16.8%)	1,029 (16.9%)	968 (16.1%)
Heart failure	1,937 (32.2%)	1,934 (31.8%)	1,922 (31.9%)
Aspirin	2,384 (39.6%)	2,338 (38.5%)	2,431 (40.4%)
Anti-hypertensive	4,830 (80.3%)	4,895 (80.6%)	4,784 (79.4%)
Beta-Blocker	3,789 (63.0%)	3,887 (64.0%)	3,722 (61.8%)
Amiodarone	647 (10.8%)	672 (11.1%)	657 (10.9%)
Statins	2,702 (44.9%)	2,682 (44.1%)	2,673 (44.4%)
Proton-pump inhibitor	847 (14.1%)	878 (14.5%)	842 (14.0%)
H_2-receptor antagonist	239 (4.0%)	257 (4.2%)	262 (4.4%)

CrCl, creatinine clearance; MI, myocardial infarction; mo: month; SD, standard deviation; TIA, transient ischaemic attack; VKA, vitamin K antagonist; yrs: years.

The risk of stroke at baseline in patients in the RE-LY trial was classified according to the $CHADS_2$ score (Table 3). The $CHADS_2$ score is a clinical prediction rule for the risk of stroke in patients with AF. Each risk factor is given a score (Table 3), and the total is then translated into a percentage risk of stroke (Table 4).[10] A score of 0 is low risk, 1 is moderate risk, and 2 and above is high risk. As can be seen from Table 3, the age at which a person is considered to be at risk of stroke is 75 years, rather than the 65 years specified in the NICE definition of moderate risk. A recent modification of the $CHADS_2$ prediction rule has been

suggested (CHA_2DS_2-VASc score),[11] where people aged 65 and over are considered at risk, and those over 75 years at a further increased risk; gender is also included in the modified score (Table 5). A score of 0 or 1 indicates a low risk of stroke; 2 or above is moderate to high risk. This score was not available at the time of the RE-LY trial, however, it may be considered more appropriate for use in future trials in this indication as it reflects the NICE definition more closely.

Table 3: The $CHADS_2$ clinical prediction rule

	Condition	Points
C	Congestive heart failure	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or on anti-hypertensive medication)	1
A	Age 75 years or over	1
D	Diabetes mellitus	1
S_2	Prior Stroke or TIA	2

Table 4: The percentage risk of stroke for each $CHAD_2$ score

$CHADS_2$ Score	Stroke Risk % (95% CI)
0	1.9 (1.2–3.0)
1	2.8 (2.0–3.8)
2	4.0 (3.1–5.1)
3	5.9 (4.6–7.3)
4	8.5 (6.3–11.1)
5	12.5 (8.2–17.5)
6	18.2 (10.5–27.4)

Table 5: The CHA_2DS_2-VASc score for the risk of stroke in patients with AF[11]

	Feature	Score if present
C	Congestive Heart Failure/left ventricular dysfunction	1
H	Hypertension	1
A	Age ≥ 75 years	2
D	Diabetes mellitus	1
S	Stroke/TIA/embolism	2
V	Vascular disease (previous MI, peripheral arterial disease or aortic plaque)	1
A	Age between 65 and 74 years	1
S	Female	1

A range of exclusion criteria were applied in the RE-LY trial (P55 of MS). The exclusion of some subgroups of patients may affect the generalisability of the results of the trial to clinical practice to some extent. The main subgroups of patient excluded to which this may apply are:

- Severe, disabling stroke within the previous 6 months or any stroke within the previous 14 days: Recent stroke is associated with a risk of haemorrhagic transformation (bleeding in the infarct area) and anticoagulation would normally be delayed. The reason for the 6 month rule is not clear, but it would likely reduce the risk profile of the cohort and lower the power of the study, thus disadvantaging dabigatran.

- History of heart valve disorders: Dabigatran has not yet been trialled in valvular AF (especially prosthetic valves) due to the higher rate of thrombosis.
- Severe renal impairment: This reflects the pharmacology of the drug. The FDA has approved a (non-trialled) lower dose of 75 mg in this group.

Those in whom warfarin was contraindicated were also excluded from the RE-LY trial. With the exception of those patients with an allergy to warfarin, a contraindication to warfarin would be regarded as a contraindication to dabigatran. The clinical advisors to the ERG do not believe that the exclusion of these subgroups of patients from the RE-LY trial would limit its generalisability for clinical practice.

Several analysis sets were defined in the RE-LY trial:

- Randomised (ITT) set: All patients were analysed in the groups to which they were randomised.
- Safety set: All randomised subjects who received at least one dose of study medication
- Per protocol set: All patients who were randomised and treated and did not have important protocol violations
- Treated set: All randomised subjects who took the randomised study medication for ≥70% of the time in the study or prior to the onset of a primary outcome event.

A large number of subgroup analyses were conducted on the primary outcome of the RE-LY trial (16 planned a priori and a further 16 additional post hoc analyses; P73/4 of the MS). The manufacturer acknowledged that with such a large number of subgroup analyses, some treatment by subgroup interactions may turn out to be statistically significant by chance. The results of seven of these analyses were reported in the MS for the primary outcome (Table 34, P88 of the MS). Results for a wider range of outcomes were reported for two patient subgroups:

- Under and over 80 years of age (*post hoc* subgroup)
- Warfarin naïve (received 2 months or less of any Vitamin K antagonist (VKA)) treatment in their life time up to the time of randomisation) and warfarin experienced (received more than 2 months VKA treatment) patients.

According to the RE-LY CTR, imbalances across the VKA subgroups were noted. Compared to VKA naïve patients, more VKA experienced patients had previously undergone cardioversion (38.1% versus 17.1%); had a prior stroke/SE/TIA (25.1% versus 18.6%); had an implanted device (pacemaker 13.4% vs. 8.0% or defibrillator 2.9% versus 1.5%) or had undergone AV nodal ablation (3.5% vs. 0.8%); were receiving oral anticoagulants at baseline (92% versus 33%). VKA experienced patients were also more likely to have had AF diagnosed more than two years prior to randomisation (67.5%; 55.9% of VKA naïve had new onset AF compared to 5.8% in the VKA experienced group). These factors would make the VKA experienced group at a higher risk of stroke than the VKA naïve group. The data for the population switching to 110 mg at aged 80 years was derived *post hoc* from the relevant subgroups. The differences at baseline between the under and over 80 years subgroups were not reported in the MS.

The effectiveness of warfarin is related to the maintenance of INR control. It is possible that the effectiveness of dabigatran relative to warfarin would differ in patients who can maintain good INR control to those who cannot. A sub-group analysis based on INR control was not reported in the MS; the results of such an analysis was presented in the submission to the FDA (see Section 4.3.2.1).[12]

4.2.2 Summary and critique of the PETRO trial

PETRO was a 12-week study of dabigatran, alone or in combination with aspirin (ASA), compared to warfarin (target INR 2.0 to 3.0) in patients with AF. Three doses of dabigatran were investigated (50, 150, and 300 mg bid); only the 150 mg bid dose is comparable to the doses administered in the RE-LY trial and relevant to the decision problem (Table 6). The results were presented descriptively due to low numbers of events. The quality of the PETRO trial was considered good. The study design was similar to that of the RE-LY trial, with the allocation of two doses of dabigatran concealed and blinded to patients, carers and outcome assessors, and open label warfarin and aspirin arms. From Table 6, it can be seen that the warfarin arm of the trial had a greater proportion of patients being prescribed angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), indicating a greater number of patients with hypertension and/or heart failure in this arm, and therefore patients at a greater risk of stroke. Compared to the RE-LY trial, the PETRO trial had a lower proportion of females (lowering the risk profile), a greater proportion of patients with prior

stroke and statin use (increasing the risk profile), and there was no indication as to the distribution of the different types of AF.

4.2.3 Summary and critique of the 1160.49 trial

[redacted]

4.3 Results for clinical effectiveness

4.3.1 Compliance and treatment discontinuation

Compliance and treatment discontinuation were assessed in the RE-LY trial. Compliance with dabigatran was calculated as the number of capsules taken, divided by the number of capsules that should have been taken; days when dabigatran was temporarily or permanently discontinued were not considered in the calculation. Given the requirement for optimisation of the therapeutic effect of warfarin, compliance was defined as within 80-120% INR control, and the percentage of time the INR was within the required target range of 2 to 3 was calculated. The first week after randomisation and the days while study warfarin was temporarily or permanently stopped were excluded from the calculation.

Compliance was reported as 94.8% (SD 11.3) for dabigatran 110 mg and 94.6% (SD 11.7) for dabigatran 150 mg. The time in therapeutic INR range (TTR) with warfarin was 64.4% (SD 19.8). The TTR for warfarin is not directly comparable to the compliance rates of

dabigatran, and therefore these rates may give a false impression of the relative rates of compliance of the two drugs. In response to a point of clarification, the manufacturer supplied Kaplan-Meier estimates of treatment adherence for the RE-LY population at different durations of follow-up:

- 30 days: dabigatran 110 mg, [redacted]%; dabigatran 150 mg, [redacted]%; warfarin, [redacted]%
- 90 days: dabigatran 110 mg, [redacted]%; dabigatran 150 mg, [redacted]%; warfarin, [redacted]%
- 360 days: dabigatran 110 mg, [redacted]%; dabigatran 150 mg, [redacted]%; warfarin, [redacted]%
- 720 days: dabigatran 110 mg, [redacted]%; dabigatran 150 mg, [redacted]%; warfarin, [redacted]%.

From these more comparable calculations, it can be seen that adherence to warfarin is slightly better than to dabigatran over a 2 year period of follow-up. It is worth noting that INR monitoring offers a benefit of warfarin over dabigatran in clinical practice, as a person not complying with warfarin would be identified by poor INR control. There would be no such monitoring with dabigatran and therefore identifying patients who are non-compliant with dabigatran treatment would be more difficult, leaving them at a higher risk of stroke/SE.

Overall discontinuation rates across the three trial arms were similar (Table 7). However, from Figure 1, it can be seen that the discontinuation rates for the two dabigatran doses are higher in the early stages of the trial, probably due to the higher rate of gastrointestinal (GI) adverse effects with dabigatran.

Table 6: Baseline characteristics of the participants in the relevant arms of the PETRO and 1160.49 trials

	PETRO		1160.49		
Parameter	**Dabigatran 150 mg (n=166)**	**Warfarin (n=70)**	**Dabigatran 110 mg (n=[redacted])**	**Dabigatran 150 mg (n=[redacted])**	**Warfarin (n=[redacted])**
Mean age, yrs (SD)	70 (8.1)	69 (8.3)	[redacted]	[redacted]	[redacted]
Female	31 (18.7%)	11 (15.7%)	[redacted]	[redacted]	[redacted]
Weight, kg (SD)	89.4 (17.0)	92.0 (21.1)	[redacted]	[redacted]	[redacted]
Type of AF	Not reported	Not reported	[redacted]	[redacted]	[redacted]
Median duration of disease, yrs (IQR)	3.9 (6.6)	3.4 (5.0)	[redacted]	[redacted]	[redacted]
Previous TIA or stroke	29 (17.5%)	13 (18.6%)	[redacted]	[redacted]	[redacted]
Hypertension	118 (71%)	49 (70%)	[redacted]	[redacted]	[redacted]
Diabetes	45 (27%)	15 (21.4%)	[redacted]	[redacted]	[redacted]
Heart failure	52 (31.3%)	24 (34.3%)	[redacted]	[redacted]	[redacted]
CAD	104 (63%)	42 (60%)	[redacted]	[redacted]	[redacted]
Current/former smoker	120 (72.3%)	53 (75.7%)	[redacted]	[redacted]	[redacted]
Beta-blockers	121 (73%)	49 (70%)	[redacted]	[redacted]	[redacted]
ACE inhibitor/ARB	116 (69.8%)	57 (81.4%)	[redacted]	[redacted]	[redacted]
Verapamil/dilatiazem	31 (18.7%)	14 (20%)	[redacted]	[redacted]	[redacted]
Other calcium inhibitors	37 (2.3%)	14 (20%)	[redacted]	[redacted]	[redacted]
Amiodarone	9 (5.4%)	6 (8.5%)	[redacted]	[redacted]	[redacted]
Digoxin	75 (45%)	32 (45.7%)	[redacted]	[redacted]	[redacted]
Diuretic	89 (53.6%)	44 (63%)	[redacted]	[redacted]	[redacted]
Statin	100 (60%)	37 (53%)	[redacted]	[redacted]	[redacted]
Aspirin	Not reported	Not reported	[redacted]	[redacted]	[redacted]
Warfarin experienced	Not reported	Not reported	[redacted]	[redacted]	[redacted]
Mean CrCl, mL/min (SD)	Not reported	Not reported	[redacted]	[redacted]	[redacted]

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CrCl, creatinine clearance; IQR, interquartilerange; SD, standard deviation; TIA, transient ischaemic attack

Table 7: Discontinuation rates for dabigatran and warfarin in the RE-LY trial

	Dabigatran 110 mg		Dabigatran 150 mg		Warfarin	
	Number of patients	**Annual rate**	**Number of patients**	**Annual rate**	**Number of patients**	**Annual rate**
No treatment interruption	2,910	48.6%	2,881	47.5%	2,878	48.0%
Permanent discontinuation	1,318	22.0%	1,382	22.8%	1,073	17.9%
Reason for permanent discontinuation:						
Subject refused study drug	424	7.1%	459	7.6%	405	6.8%
Outcome event	261	4.4%	246	4.1%	177	3.0%
Minor bleed	67	1.1%	76	1.3%	37	0.6%
Other	471	7.9%	507	8.4%	372	6.2%

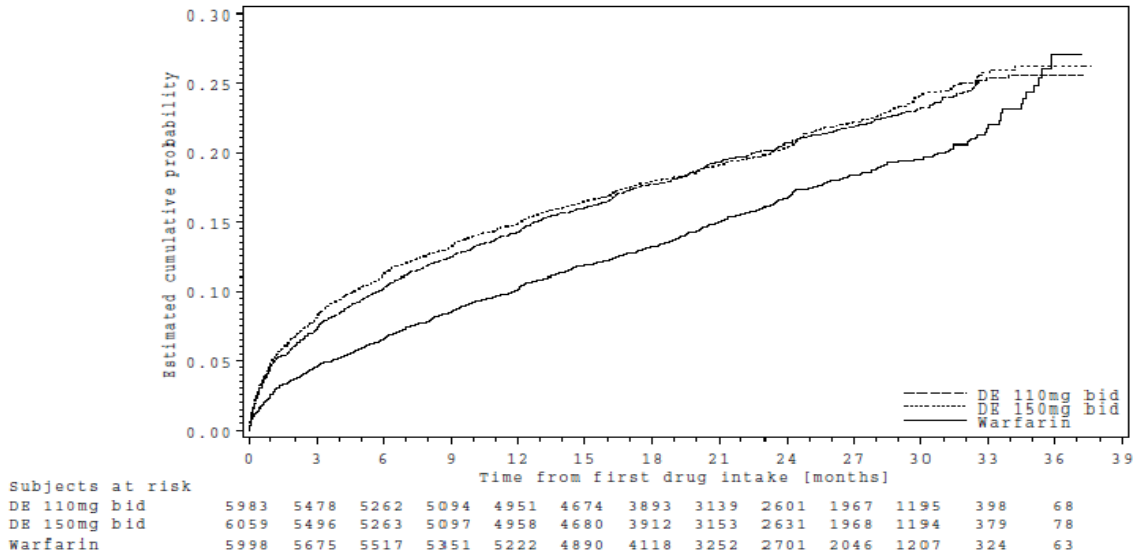


Figure 1: Kaplan-Meier curve for the discontinuation of dabigatran (DE) 110 mg, 150 mg, and warfarin

4.3.2 Treatment effectiveness

4.3.2.1 The RE-LY trial

The submission included a large number of effectiveness results from the RE-LY trial; the primary effectiveness outcome was the incidence of all stroke (including haemorrhagic) or SE (stroke/SE); there were a range of secondary and composite outcomes presented (see Section 3.4). These outcomes were not consistently reported across analyses; notably stroke/SE was not reported for all patient populations/subgroups. Where possible, this report presents the results of selected effectiveness outcomes: stroke/SE, SE, ischaemic stroke, all-cause mortality, vascular mortality, TIA, MI and PE; results for all strokes were not presented separately in the MS, only as a component of composite outcomes. Full results of the analyses of superiority can be found on P82 to P90 of the MS. The manufacturer discusses the incidence of haemorrhagic stroke in the effectiveness section of the submission. As this is an adverse event of treatment, this outcome is discussed in the safety section of this report to avoid repetition of results (Section 4.3.3).

Non-inferiority of dabigatran compared to warfarin was established for the primary outcome stroke/SE at both margins investigated (1.46 and 1.38); the relative risk reductions in stroke/SE for dabigatran 110 mg and 150 mg compared to warfarin were 10% and 35%,

respectively (test for non-inferiority: $p<0.0001$ for both dabigatran doses at both margins). Once non-inferiority was established for the primary outcome, further analyses investigated superiority of dabigatran over warfarin. Given the magnitude of superiority of dabigatran over warfarin for the primary outcome, this seems appropriate. Clinical advisors to the ERG have indicated that non-inferiority would mean dabigatran would be considered an efficacious alternative to warfarin in similar clinical circumstances, with benefits of ease of administration and lack of monitoring, and superiority of dabigatran over warfarin would not be a requirement for its introduction into clinical practice.

Dabigatran 150 mg was significantly better than warfarin in preventing the primary outcome of stroke/SE; the beneficial effect of dabigatran 150 mg was also demonstrated in terms of ischaemic stroke and vascular mortality (Table 8). Although superiority was not established in terms of all-cause mortality, dabigatran demonstrated non-inferiority. Dabigatran 110 mg was not significantly different from warfarin for stroke/SE, ischaemic stroke, vascular mortality, and failed to show non-inferiority for ischaemic stroke at the lower margin preferred by the FDA of 1.38 . The results for acute MI, an efficacy outcome included in the economic model, showed a small but non-significant increased risk with both doses of dabigatran. The annual rates of SE alone and PE were reported (Table 8), but the manufacturer did not present a HR for these outcomes in the clinical section of the submission. Relative risks from the MS or calculated by the ERG are presented. SE alone was one of only five outcomes reported for the subgroup analysis by age (under 80 years/80 years or over) below.

For the subgroup analyses of patients under 80 years of age and those of 80 years or older, results were reported only for ischaemic stroke, SE, TIA and MI; these are the outcomes included in the economic model. There was no statistically significant difference between dabigatran and warfarin for any of the outcomes measured in those under 80 years of age (Table 8), but there was a statistically significant reduction in the incidence of TIA in those over 80 years of age with dabigatran 110 mg.

When results were presented separately for patients who were warfarin experienced or naïve, the results for the primary outcome of stroke/SE was similar to the primary analysis of all patients (Table 8). The RE-LY CTR reported that there was no significant treatment by VKA

use interaction for the primary outcome (p=0.89). The only other outcome presented for this subgroup was stroke/SE/all-cause mortality; it is unclear why only these outcomes were reported for these subgroups of patients.

Table 8: Results for treatment effectiveness from the RE-LY trial (HR (95% CI))

	Dabigatran 110 mg versus warfarin	**Dabigatran 150 mg versus warfarin**
All patients		
Stroke/SE	0.90 (0.74 to 1.10)	**0.65 (0.52 to 0.81)**
Ischaemic stroke	1.13 (0.89 to 1.42)	**0.75 (0.58 to 0.97)**
Vascular mortality	0.90 (0.77 to 1.06)	**0.85 (0.72 to 0.99)**
All-cause mortality	0.91 (0.80 to 1.03)	0.88 (0.77 to 1.00)
MI	1.29 (0.96 to 1.75)	1.27 (0.96 to 1.75)
SE only*	Annual rates: 0.13%, 0.11% and 0.18% for dabigatran 110 mg, 150 mg and warfarin, respectively; a HR was not reported	
PE*	Annual rates: 0.12%, 0.15% and 0.10% for dabigatran 110 mg, 150 mg and warfarin, respectively; a HR was not reported	
TIA*	Annual rates: 0.62%, 0.72% and 0.84% for dabigatran 110 mg, 150 mg and warfarin, respectively; a HR was not reported	
Under 80 years		
Ischaemic stroke	[redacted]	0.77 (0.58 to 1.03)
MI	[redacted]	1.26 (0.89 to 1.26)
SE only	[redacted]	0.66 (0.30 to 1.47)
TIA	[redacted]	0.92 (0.66 to 1.29)
Stroke/SE	Not reported	
Vascular mortality		
All-cause mortality		
PE		
Over 80 years		
Ischaemic stroke	0.82 (0.51 to 1.33)	[redacted]
MI	1.39 (0.74 to 2.60)	
SE only	0.51 (0.13 to 2.06)	
TIA	**0.45 (0.23 to 0.89)**	
Stroke/SE	Not reported	
Vascular mortality		
All-cause mortality		
PE		
VKA naïve		
Stroke/SE	0.93 (0.70 to 1.24)	**0.63 (0.46 to 0.87)**
Ischaemic stroke	Not reported	
Vascular mortality		
All-cause mortality		
MI		
SE only		
PE		
VKA experienced		
Stroke/SE	0.87 (0.66 to 1.15)	**0.63 (0.49 to 0.89)**
Ischaemic stroke	Not reported	
Vascular mortality		
All-cause mortality		
MI		
SE only		
PE		

* RRs for SE (MS Table 74, P162): dabigatran 110 mg versus warfarin 0.71 (95% CI 0.37 to 1.38); dabigatran 150 mg versus warfarin 0. 61 (95% CI 0.30 to 1.21).
* ERG calculated RRs for PE: dabigatran 110 mg versus warfarin 1.17 (95% CI 0.54 to 2.52); dabigatran 150 mg versus warfarin 1.49 (95% CI 0.72 to 3.08) Data taken from Table 31, page 83 of the MS.
* ERG calculated RRs for TIA: dabigatran 110 mg versus warfarin 0.75 (95% CI 0.55 to 1.01); dabigatran 150 mg versus warfarin 0.87 (95% CI 0.65 to 1.16).

A submission by the manufacturer to the FDA included an analysis of the primary outcome by INR control (Table 9).[12] From these results it can be seen that dabigatran 150 mg has a beneficial effect on the risk of stroke/SE over warfarin in patient who achieve INR control (time in therapeutic range (TTR)) of ≥65% or ≥68%. However, in that submission, lower levels of control were not reported: in the RE-LY trial average INR control is 64.4% (Table 29 MS). The medical review produced by the Center for Drug Evaluation and Research includes this comparison for the outcome of stroke/SE (Table 10).[13] This analysis showed a greater benefit of dabigatran in those who achieved poor warfarin control than those who were well controlled (threshold being the centre-level median of 67%). The report concluded that although the results showed efficacy of dabigatran in patients who achieved INR control above the centre-level median, they did not show superiority, as statistical significance was not reached in those who are well controlled.[13] The medical review went on to further subdivide patients by INR control (<58.5%%, ≥58.5 and <66.8%, ≥66.8 and <74.2%, ≥74.2%). It can be seen that the greatest benefit of dabigatran was in the lowest quartile of INR control (Table 10). This demonstrates that in people achieving good INR control with warfarin, little or no additional benefit in terms of effectiveness would be gained with dabigatran.

Table 9: The incidence of stroke/SE related to warfarin control[12]

Dabigatran 110 mg n/N	Dabigatran 150 mg n/N	Warfarin n/N	Dabigatran 110 mg vs. warfarin HR (95% CI)	Dabigatran 150 mg vs. warfarin HR (95% CI)
TTR threshold ≥65%				
133/5983	88/6059	76/3194	1.03 (0.78 to 1.36)	0.68 (0.50 to 0.92)
TTR threshold ≥68%				
133/5983	88/6059	65/2807	1.05 (0.78 to 1.42)	0.70 (0.51 to 0.96)

CI: Confidence interval; HR: Hazard ratio: TTR: Time in therapeutic range

Table 10: The incidence of stroke/SE and major bleeding (HR (95% CI)) related to warfarin control[13]

Relative effectiveness of dabigatran versus warfarin for the risk of stroke/SE using the median centre-level INR control as the threshold (67%)			
<median		**≥median**	
Dabigatran 110 mg	**Dabigatran 150 mg**	**Dabigatran 110 mg**	**Dabigatran 150 mg**
0.86 (0.66 to 1.12)	0.57 (0.42 to 0.76)	0.96 (0.71 to 1.30)	0.77 (0.56 to 1.06)
Relative effectiveness of dabigatran versus warfarin for the risk of stroke/SE using the quartiles of centre-level INR control as the threshold			
	Dabigatran 110 mg	**Dabigatran 150 mg**	
<58.5%	0.95 (0.64 to 1.40)	0.60 (0.39 to 0.94)	
≥58.5 and <66.8%	0.79 (0.54 to 1.16)	0.53 (0.35 to 0.81)	
≥66.8 and <74.2%	0.97 (0.65 to 1.44)	0.65 (0.42 to 1.02)	
≥74.2%	0.92 (0.59 to 1.44)	0.90 (0.57 to 1.41)	

CI: Confidence interval; HR: Hazard ratio; INR: International normalised ratio

4.3.2.2 The PETRO trial

Only two thromboembolic events occurred during the 12-week treatment period of the PETRO trial; neither occurred in the dabigatran 150 mg bid or warfarin arms of the trial (both occurred in the dabigatran 50 mg bid arm).[6]

4.3.2.2 The 1160.49 trial

In the 1160.49 trial, [redacted]

4.3.3 Safety analyses

4.3.3.1 The RE-LY trial

The safety analysis was based almost entirely on the RE-LY trial. This report presents the results for selected safety outcomes, including haemorrhagic stroke, major bleed, life threatening major bleeding, ICH, ECH and gastrointestinal (GI) bleeding; full results of the safety analyses can be found on P130 to P137 of the MS. For the subgroup analysis of under and over 80 years of age only those outcomes included in the economic model were presented in the MS (haemorrhagic stroke, ICH (excluding haemorrhagic stroke), ECH and minor bleed). Dabigatran was not associated with an increase in intracranial bleeds.

Compared to warfarin, both doses of dabigatran were associated with a significantly lower rate of haemorrhagic stroke, life-threatening bleeds, and intracranial haemorrhage (ICH) with

and without haemorrhagic stroke; dabigatran 110 mg also showed a significant reduction in major bleeding compared to warfarin (Table 11). Where dabigatran wasn't statistically significantly different from warfarin, non-inferiority was established. In contrast, warfarin has statistically significantly fewer GI bleeds compared to both doses of dabigatran, and significantly fewer major GI bleeds and life-threatening GI bleeds than dabigatran 150 mg.

The results of those safety outcomes reported for the under 80's were similar to those of the overall population. In the over 80's, dabigatran 110 mg was associated with a significantly decreased incidence of haemorrhagic stroke. The incidence of GI bleeds was not specifically reported for the age-related subgroups, and cannot be calculated from the data provided. However, the risk of ECH [redacted] when compared to warfarin in the over 80's (Table 11). The incidence of ECH was not reported for the overall population, but an estimated RR can be calculated by subtracting the numbers of patients with ICH (including haemorrhagic stroke) from the numbers of patients experiencing a major bleed. This is only a rough estimate to facilitate comparison between the overall population and the age-related subgroups, as some patients may have experienced both outcomes. Compared to warfarin, the RR is 0.95 (95% CI 0.82 to 1.11) for dabigatran 110 mg, and 1.08 (0.93 to 1.25) for dabigatran 150 mg. These RRs are most similar to the HRs for the under 80's.

The only outcome to be reported for the warfarin experienced and naïve patients was major bleeding; no increased risk was seen with dabigatran 150 mg in either subgroup and a small benefit of dabigatran 110 mg was seen in those who were warfarin experienced (Table 11). The medical review produced by the Center for Drug Evaluation and Research presented an analysis for major bleeds subdividing patients by INR control (<58.5%%, ≥58.5 and <66.8%, ≥66.8 and <74.2%, ≥74.2%); as with the effectiveness outcome of stroke/SE, the greatest benefit of dabigatran was in the lowest quartile of INR control (<58.5%%, 110 mg: HR 0.64 (95% CI 0.46 to 0.88); 150 mg: HR 0.68 (95% CI 0.50 to 0.93)).

Table 11: Results for safety from the RE-LY trial (HR (95% CI))

	Dabigatran 110 mg vs. warfarin	Dabigatran 150 mg vs. warfarin
All patients		
Haemorrhagic stroke	**0.31 (0.17 to 0.56)**	**0.26 (0.14 to 0.49)**
Major bleeding	**0.80 (0.70 to 0.93)**	0.93 (0.81 to 1.07)
Life threatening major bleed	**0.67 (0.54 to 0.82)**	**0.80 (0.66 to 0.98)**
ICH(including haemorrhagic stroke)	**0.30 (0.19 to 0.45)**	**0.41 (0.28 to 0.61)**
ICH(excluding haemorrhagic stroke)	**0.32 (0.18 to 0.57)**	**0.52 (0.32 to 0.84)**
GI bleeding	**1.35 (1.19 to 1.53)**	**1.52 (1.35 to 1.72)**
GI major bleed	1.07 (0.84 to 1.36)	**1.47 (1.17 to 1.85)**
GI Life threatening bleeding	1.17 (0.82 to 1.67)	**1.62 (1.17 to 2.26)**
ECH	Not reported*	
Under 80 years		
Haemorrhagic stroke	[redacted]	**0.21 (0.09 to 0.47)**
ICH(excluding haemorrhagic stroke)	[redacted]	**0.48 (0.27 to 0.85)**
ECH	[redacted]	0.93 (0.78 to 1.11)
Life threatening major bleed	Not reported	
ICH(including haemorrhagic stroke)		
Major bleeding		
GI bleeding		
GI major bleed		
GI Life threatening bleeding		
Over 80 years		
Haemorrhagic stroke	**0.26 (0.07 to 0.91)**	[redacted]
ICH(excluding haemorrhagic stroke)	**0.29 (0.10 to 0.88)**	[redacted]
ECH	**1.44 (1.05 to 1.97)**	[redacted]
Life threatening major bleed	Not reported	
ICH(including haemorrhagic stroke)		
Major bleeding		
GI bleeding		
GI major bleed		
GI Life threatening bleeding		
VKA naïve		
Major bleeding	0.87 (0.71 to 1.07)	0.94 (0.77 to 1.14)
Haemorrhagic stroke	Not reported	
Life threatening major bleed		
ICH(including haemorrhagic stroke)		
ICH(excluding haemorrhagic stroke)		
ECH		
GI bleeding		
GI major bleed		
GI Life threatening bleeding		
VKA experienced		
Major bleeding	**0.74 (0.60 to 0.91)**	0.93 (0.76 to 1.12)
Haemorrhagic stroke	Not reported	
Life threatening major bleed		
ICH(including haemorrhagic stroke)		
ICH(excluding haemorrhagic stroke)		
ECH		
GI bleeding		
GI major bleed		
GI Life threatening bleeding		

CI: Confidence interval; ECH: Extracranial haemorrhage; GI: Gastrointestinal; HR: Hazard ratio; ICH: Intracranial haemorrhage

* RR calculated by ERG (see text) 0.95 (95% CI 0.82 to 1.11) for dabigatran 110 mg, and 1.08 (0.93 to 1.25) for dabigatran 150 mg

4.3.3.2 The PETRO trial

During the 12 weeks of the trial, dabigatran administered at any dose studied without aspirin did not appear to result in increased bleeding rates compared to warfarin dosed to an INR of 2.0 to 3.0.

4.3.3.3 The 1160.49 trial

[redacted]

4.3.4 Meta-analysis

Meta-analysis of the three trials comparing dabigatran to warfarin was not conducted for either the effectiveness or safety outcomes; PETRO and 1160.49 were short-term drug safety trials with no primary efficacy outcome and low incidence of safety outcomes, and the RE-LY was substantially larger than the other two trials. This decision seems appropriate.

4.3.5 Summary of the direct evidence of treatment effect of dabigatran compared to dose-adjusted warfarin

The primary source of data for the effectiveness and safety of dabigatran compared to warfarin was the RE-LY trial. Results of this trial, showed both dabigatran 150 mg to be non-inferior to warfarin in the prevention of stroke/SE. Dabigatran 150 mg was shown to be superior to warfarin in terms of stroke/SE, ischaemic stroke and vascular mortality; a reduction in all-cause mortality was also observed, and although this did not reach statistical significance, it showed dabigatran to be non-inferior to warfarin. Dabigatran 110 mg was generally less effective that 150 mg. The results for acute MI showed a small non-significant increased risk with both doses of dabigatran, with neither dose showing non-inferiority to warfarin.

The beneficial effect of dabigatran in the reduction in the risk of stroke/SE remained significant in those with good warfarin control (TTP ≥65% and ≥68%), however, an analysis in the medical review produced by the Center for Drug Evaluation and Research concluded that although dabigatran showed efficacy in patients who achieved good INR control, it did not show superiority over warfarin.

In terms of adverse bleeding events, both doses of dabigatran resulted in fewer haemorrhagic strokes, life-threatening bleeds and ICH than warfarin; a significant reduction in terms of major bleeding was only observed with the 110 mg dose. In contrast, dabigatran was associated with a higher rate of GI bleeding, with 150 mg bid resulting in significantly greater incidences of major GI bleeding and life-threatening GI bleeding.

The suggested reduction in dose at age 80 years is primarily driven by the increased risk of bleeding and reduction in renal function in the elderly. In those outcomes reported, the results of the safety analysis for the under 80's is similar to that of the whole population, both in terms of effectiveness and safety. In the over 80's, the effectiveness of dabigatran compared to warfarin are also similar to the overall population, although the beneficial reduction in the incidence of ischaemic stroke no longer reaches statistical significant with dabigatran 150 mg. In terms of safety, there is no significant difference between dabigatran 150 mg and warfarin in the incidence of haemorrhagic stroke, ICH, ECH, or minor bleeds. However, when dabigatran 110 mg is compared to warfarin, a significant reduction in the incidence of haemorrhagic stroke and ICH was evident. In contrast, those on warfarin had significantly fewer ECHs compared to both dabigatran doses; it is unclear what proportion of these would have been major/life-threatening bleeds or GI bleeds, as these outcomes were not reported for this subgroup.

4.4 Indirect comparisons (mixed treatment comparison (MTC))

4.4.1 Methods

4.4.1.1 Treatments included in the MTC

The manufacturer undertook an MTC of all potentially relevant pharmacological interventions for the prevention of stroke in patients with AF; the search strategy and selection criteria are discussed in Sections 4.1.1 and 4.1.2. The treatments considered to be relevant in this analysis were dabigatran 150 mg bid, dabigatran 110 mg bid, dose-adjusted warfarin, aspirin, clopidogrel plus aspirin, and placebo. In the light of the licensing authorities requirement for the use of a lower dose of dabigatran in patients aged 80 and over, an additional dabigatran treatment was introduced into the MTC, the 'dabigatran sequence' treatment. This was meant to represent the use of dabigatran 150 mg in patients up to the age of 80 years, and then dabigatran 110 mg in those aged 80 and over. This sequencing of dabigatran dosing has not been studied in any trial. The treatment effect for dabigatran sequence was calculated as a *post hoc* weighted average of two subgroups of patients from the RE-LY trial: patients aged 80 or under randomised to dabigatran 150 mg and patients aged over 80 years randomised to dabigatran 110 mg (footnote of Table 44, P107 of the MS).

Although in the trial allocation to the 110 mg and 150 mg dabigatran arms was random, and this constitutes a valid (albeit ad hoc) subgroup, this constructed treatment can only be an approximation of the use of dabigatran according to its licence in clinical practice. Specifically:

- The response of a patient to dabigatran 110 mg initiated when the patient is over 80 years may be different to that in a patient who had first been treated with 150 mg prior to turning 80.
- It cannot take into account any effect of dose reduction from 150 mg to 110 mg at age 80, nor (should the licence allow) can it reflect the use of the 110 mg dose in high risk younger patients.

Importantly, although this is not explicitly stated in the MS, it would appear that the constructed dabigatran sequence arm was included in the MTC that also included both dabigatran 110 mg and 150 mg. If this was the case then some adjustment of the number of patients considered in each arm of the trial was necessary to avoid double counting (i.e. using data from the same patient more than once in the MTC). By not making this adjustment, and

effectively double counting patients, the precision of the estimates obtained will be artificially increased. It is not possible to be sure how this would impact on the mean estimates obtained, so we cannot state that this would work in favour of dabigatran or against it. In general, it was difficult to ascertain which data were utilised within the MTC. A different number of trials informed each of the outcome evaluated and it would appear that absolute treatment effects were used. If adjustments were made to account for the multiple use of the same data, they were not reported.

Table 74 on P162 in the economic section of the MS presents the relative risks of the modelled clinical events. It should be noted that the results of the MTC were only used in a limited way in the manufacturer's base-case model: they used the MTC estimates for aspirin, aspirin plus clopidogrel and placebo, for the base-case analysis; estimates for dabigatran from the MTC were only used in sensitivity analyses. Table 74 includes two sequence doses of dabigatran used in the economic model, defined on P15 as:

- Dabigatran sequence <80 years: Patients aged less than 80 years only initiated on dabigatran 150 mg and switching to dabigatran 110 mg at age 80
- Dabigatran sequence ≥80 years: Patients aged more than 80 years only initiated on dabigatran 110 mg.

The data for the dabigatran sequence <80 years were derived from Tables 35 (P89) and 63 (P137); these data are for the under 80 subgroup receiving dabigatran 150 mg. The data for the dabigatran sequence ≥80 years were derived from Tables 36 (P90) and 64 (P137); these data are for the over 80 subgroup receiving dabigatran 110 mg. Therefore, these 'sequences' are the subgroups investigated in the frequentist analysis; neither are the constructed dabigatran sequence used in the MTC.

4.4.1.2 Software used to conduct the MTC

The MTC presented in the MS was conducted using PROC GLIMMIX in SAS. Due to the volume of evidence available and the use of the SAS PROC GLIMMIX procedure, the manufacturer was unable to incorporate a trial by treatment' random effect. The manufacturers make a statement to this effect (P109: With a large amount of data for analyses, an additional 'trial by treatment' random effect would be included. However in these analyses, there was not sufficient data to support the addition of this term).

One limitation of the SAS MTC noted by the ERG was the exclusion of trails with zero event arms. In response to a request by the ERG to justify the exclusion of these trails, the manufacturer stated that any statistical analysis that compares dichotomous treatment responses where at least one cell count is zero is problematic due to the need to divide by zero. Common methods to address this problem include adding 0.5 to each cell and recalculating, or exclusion of the data. Given the simulation nature of MTC modelling, the manufacturer attempted to run their analyses including the actual zero count data wherever it was observed. They found that the MTC model coped well with trial arms that have zero counts, but became unstable where there were:

- Zero counts for a particular treatment across all trials including that treatment or
- Trials that have zero counts across all arms.

The manufacturer attempted to rerun the models adding 0.5 to each cell, but found the model estimates were still unstable and gave wide confidence intervals. Therefore the manufacturer decided to exclude such treatments from the analyses. Given the manufacturers choice to use SAS to model their MTC, it seems reasonable to have excluded these treatments from the analysis.

It became apparent from the submitted economic models that the MTC was conducted in both PROC GLIMMIX and WinBUGS. The manufacturer was asked to justify the presentation of the results from the analysis using PROC GLIMMIX rather than those using WinBUGS, as the results of this analysis fed into the economic model. The manufacturer stated that WinBUGS is a powerful software program that is particularly adaptable and useful in the cases where true Bayesian methods are needed and in cases where the amount of data is very small. In the MTCs in the MS, the data sample was considered to be reasonably sized, and it was considered unnecessary to employ full Bayesian techniques (meaning non-informative priors were used). However, it is not clear if the manufacturer decision to present the SAS model as their base-case was justified. The model presented in WinBUGS was a random effects model, which may be a more appropriate given that the trials included, whilst similar enough to pool, are unlikely to be identical (i.e. the true effect size was not exactly the same). Further, within the WinBUGS analysis it may not have been necessary to exclude treatment with zero events. Whilst the mean estimates obtained using the two different models do not vary greatly, those from the SAS model are closer to the results from the direct comparisons in the RE-LY trial. In addition, the uncertainty around those means is lower and therefore

may not be reflecting the heterogeneity that is apparent across the trials. This is due to the computational methods of the two packages and the lack of trial by treatment random effect in the SAS model.

4.4.2 Outcomes reported in the MTC

The outcomes assessed in the MTC were: all stroke; ischaemic stroke; haemorrhagic stroke; fatal or disabling stroke; SE; PE; all-cause mortality; TIA; ICH; ECH; minor bleeds; acute MI; cardiovascular mortality; and all bleeding. Therefore, the outcomes identified in the NICE scope as appropriate for the population being studied were included in this analysis. However, the primary outcome of the RE-LY trial, stroke/SE, was not assessed.

4.4.3 Description of the included studies and network

For an MTC analysis a network of trials has to be established for each outcome measure to be analysed: not every trial will report every outcome of interest. The MS included a single network diagram (P105); 20 trials were included in the primary MTC, and one study was added during a sensitivity analysis. This was an overview of the included trials that reported at least one outcome of interest, the network does not accurately reflect a specific network for any specific outcome measure. In addition, the network includes treatments that are not considered relevant to clinical practice (ximelagatran, idraparinux, indobufen, trifusal, and fixed low or high dose warfarin), and does not include the dabigatran sequence arm constructed from the data from the RE-LY trial. In the network, the most studied links are dose-adjusted VKA versus aspirin, and dose-adjusted VKA versus placebo with six direct comparison trails each. However, most of the links in the network had only one trial and the number of trials indicated for each comparison reflects merely the number of trials with at least one outcome for the given comparison.

The 20 trials included in the primary MTC randomised 49,125 patients (range 75 to 18,113 in the RE-LY trial). Where reported, the mean age ranged from 65 to 83.5 years, and the proportion male from 41.3% to 100%; the values for the RE-LY trial were a mean age of 71.5 years, and 63.5% male. The proportion of time within INR ranged from 42% to 86%; in the RE-LY trial, time within INR was 64%. The mean length of follow-up ranged from 10.2 to 42 months; the mean length of follow-up was 24 months in the RE-LY trial.

The network presented by the manufacturer was compared by the ERG with that used in a prior MTC in patients with AF, conducted by researchers at Leicester University.[14] The Leicester networks were not directly relevant as they included all drugs for treatment of AF, not just anticoagulation/antiplatelet prescribed for stroke prevention. However, the links of the Leicester networks specifically relating to anticoagulation/antiplatelet treatments for stroke prevention corresponded to those in the network in the MS.

4.4.4 Investigation of heterogeneity

Several variables considered to be potential sources of heterogeneity across trials were identified by the manufacturer. These were:

- Mean length of follow-up (months)
- Mean age (years)
- Proportion male (range 0 to 1)
- Mean baseline $CHADS_2$ score (range 0 to 6); or possibly only a history of stroke or TIA
- Race proportions (range 0 to 1; categories determined after data collection)
- Proportion of patients with prior use of oral anticoagulants (range 0 to 1)

$CHADS_2$ scores, ethnicity and prior use of oral anticoagulants were considered by the manufacturer to be insufficiently reported, and were therefore not investigated or included as covariates in the MTC. Of the covariates considered for inclusion by the manufacturer, three were investigated as potential sources of heterogeneity (for four outcomes: ischaemic stroke, all-cause mortality, acute MI, ICH): mean length of follow-up (months); mean age (years); and proportion male (range 0 to 1). As a result of the analyses, mean age and mean follow-up had significant impacts on outcomes, and were considered suitable for inclusion in the MTC. However, the inclusion of both covariates reduced the stability of the MTC model, and therefore all MTC models were run using just mean length of follow-up as a covariate; justification for choosing mean length of follow-up rather than age as the covariate is not given. A potential source of heterogeneity not considered by the manufacturer was the VKA used, these included warfarin, acenocoumarol, and phenprocoumon (the VKA was not specified for all trials in the MS).

The manufacturer was asked to justify the selection of only four outcomes for the assessment of heterogeneity. The manufacturer stated that the endpoints explored with covariates were

selected for pragmatic reasons, and the exploration of the covariates for all endpoints would have been extensive, the effects could be reasonably examined by selecting a sample of endpoints, and the endpoints selected were those that were deemed to be major model determinants.

4.4.5 Results of the MTC

The RR (95% CI) for dabigatran versus warfarin, aspirin monotherapy and clopidogrel plus aspirin are given in Table 12; results for comparisons with placebo are also given in the MS (P113/4). The main submission, did not present results from the MTC for the comparison between dabigatran 150 mg and dabigatran 110 mg. Results for this comparison were reported in a technical report submitted by the manufacturer.[15] Compared with dabigatran 110 mg treatments to prevent stroke in patients with AF, from the technical report, dabigatran 150 mg resulted in non-significant reductions in the incidence of all stroke (RR 0.71; 95 % CI 0.32 to 1.28), ischaemic stroke (RR 0.69; 95 % CI 0.43 to 1.15), SE (RR 0.86; 95 % CI 0.30 to 2.43), mortality (RR 0.98; 95 % CI 0.69 to 1.45) and haemorrhagic stroke (RR 0.43; 95 % CI 0.00 to 5.67); results for further outcomes were also presented. Results for the comparison between dabigatran 150 mg and 110 mg for ischaemic stroke, all-cause mortality and MI from the manufacturer's response to the points of clarification are presented in Section 4.4.6.

Table 12: Relative risks (95% CI) for dabigatran versus dose-adjusted VKA, aspirin monotherapy and aspirin plus clopidogrel from the MTC

	Dabigatran 110 mg vs. adjusted dose VKA	Dabigatran 150 mg vs. adjusted dose VKA	Dabigatran sequence vs. adjusted dose VKA	Dabigatran 110 mg vs. aspirin monotherapy	Dabigatran 150 mg vs. aspirin monotherapy	Dabigatran sequence vs. aspirin monotherapy	Dabigatran 110 mg vs. clopidogrel plus aspirin	Dabigatran 150 mg vs. clopidogrel plus aspirin	Dabigatran sequence vs. clopidogrel plus aspirin
All stroke	0.92 (0.66 to 1.28)	**0.65* (0.45 to 0.94)**	**0.65* (0.45 to 0.94)**	**0.52* (0.28 to 0.96)**	**0.37* (0.20 to 0.69)**	**0.37* (0.20 to 0.69**	0.55 (0.30 to 1.00)	**0.39* (0.21 to 0.72)**	**0.39* (0.21 to 0.73)**
Ischaemic stroke	1.12 (0.86 to 1.45)	0.77 (0.58 to 1.03)	0.80 (0.60 to 1.06)	0.69 (0.40 to 1.20)	**0.48* (0.27 to 0.84)**	**0.49* (0.28 to 0.87)**	**0.54* (0.33 to 0.87)**	**0.37* (0.23 to 0.61)**	**0.39* (0.23 to 0.63)**
Haemorrhagic stroke	0.32 (0.01 to 15.46)	0.27 (0.00 to 16.67)	0.23 (0.00 to 19.30)	No data			Unreliable estimates		
Fatal or disabling stroke	0.92 (0.68 to 1.26)	**0.67* (0.48 to 0.95)**	**0.67* (0.48 to 0.95)**	**0.57* (0.36 to 0.91)**	**0.42* (0.26 to 0.68)**	**0.42* (0.26 to 0.68)**	0.63 (0.36 to 1.11)	**0.46* (0.26 to 0.82)**	**0.46* (0.26 to 0.83)**
SE	0.86 (0.41 to 1.79)	0.73 (0.34 to 1.59)	0.74 (0.34 to 1.61)	0.48 (0.15 to 1.52)	0.41 (0.13 to 1.33)	0.42 (0.13 to 1.35)	**0.24* (0.08 to 0.70)**	**0.21* (0.07 to 0.61)**	**0.21* (0.07 to 0.62)**
Mortality	0.92 (0.79 to 1.06)	0.89 (0.77 to 1.03)	0.89 (0.77 to 1.03)	0.85 (0.66– 1.10)	0.83 (0.64 to 1.07)	0.82 (0.64 to 1.06)	0.91 (0.68 to 1.21)	0.88 (0.66 to 1.18)	0.88 (0.66 to 1.17)
TIA	0.76 (0.54– 1.08)	0.89 (0.64 to 1.24)	0.82 (0.58 to 1.15)	**0.49* (0.25 to 0.97)**	0.57 (0.29 to 1.12)	0.53 (0.27 to 1.04)	No data		
ICH	**0.33* (0.15 to 0.72)**	0.53 (0.27 to 1.03)	**0.43* (0.21 to 0.88)**	0.65 (0.16 to 2.60)	1.04 (0.28 to 3.90)	0.85 (0.22 to 3.28)	0.62 (0.17 to 2.23)	1.00 (0.30 to 3.32)	0.82 (0.24 to 2.80)
ECH	0.96 (0.75 to 1.22)	1.09 (0.86 to 1.37)	1.05 (0.83 to 1.33)	0.84 (0.34 to 2.09)	0.96 (0.39 to 2.37)	0.92 (0.37 to 2.28)	0.87 (0.52 to 1.44)	0.99 (0.60 to 1.63)	0.95 (0.57 to 1.57)
Minor bleeding	**0.81* (0.74 to 0.89)**	0.92 (0.84 to 1.00)	**0.88* (0.81 to 0.97)**	1.30 (0.66 to 2.54)	1.47 (0.75 to 2.86)	1.41 (0.72 to 2.76)	**0.68* (0.56 to 0.83)**	**0.77* (0.63 to 0.94)**	**0.74* (0.61 to 0.91)**
Acute MI	1.31 (0.92 to 1.86)	1.28 (0.90 to 1.83)	1.30 (0.92 to 1.85)	0.93 (0.50 to 1.72)	0.91 (0.49 to 1.69)	0.92 (0.49 to 1.71)	0.89 (0.45 to 1.73)	0.87 (0.44 to 1.70)	0.88 (0.45 to 1.72)
Vascular mortality	0.92 (0.77 to 1.09)	0.86 (0.72 to 1.03)	**0.83* (0.69 to 0.99)**	0.90 (0.63 to 1.29)	0.85 (0.59– 1.21)	0.82 (0.57 to 1.17)	0.81 (0.57 to 1.14)	0.76 (0.54 to 1.07)	0.73 (0.51 to 1.03)
Any bleeding	0.81 (0.76 to 0.86)	**0.91* (0.86 to 0.97)**	**0.88* (0.83 to 0.94)**	1.10 (0.82 to 1.48)	1.24 (0.92 to 1.66)	1.20 (0.89 to 1.61)	**0.69* (0.60 to 0.79)**	**0.78* (0.68 to 0.89)**	**0.75* (0.66 to 0.86)**

***** Statistically significant in favour of dabigatran

ECH: extra-cranial haemorrhage; ICH: intracranial haemorrhage; MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack; VKA: vitamin K antagonist

4.4.6 Direct pairwise comparisons versus results of the MTC

The results from the MTC can be compared directly with those reported from the RE-LY trial (assuming HRs from the RE-LY trial are broadly equivalent to the RRs from the MTC (Table 13).

Table 13: Results for dabigatran versus dose-adjusted VKA from the MTC and dose-adjusted warfarin from the RE-LY trial

	Results from the MTC RR (95% CI)		**Results from the RE-LY trial** HR (95% CI)	
	Dabigatran 110 mg	**Dabigatran 150 mg**	**Dabigatran 110 mg**	**Dabigatran 150 mg**
Ischaemic stroke	1.12 (0.86 to 1.45)	0.77 (0.58 to 1.03)	1.13 (0.89 – 1.42)	**0.75* (0.58 – 0.97)**
Haemorrhagic stroke	0.32 (0.01 to 15.46)	0.27 (0.00 to 16.67)	**0.31* (0.17 – 0.56)**	**0.26* (0.14 – 0.49)**
All-cause mortality	0.92 (0.79 to 1.06)	0.89 (0.77 to 1.03)	0.91 (0.80 – 1.03)	0.88 (0.77 – 1.00)
ICH	**0.33* (0.15 to 0.72)**	0.53 (0.27 to 1.03)	**0.30* (0.19 – 0.45)**	**0.41* (0.28 – 0.61)**
Acute MI	1.31 (0.92 to 1.86)	1.28 (0.90 to 1.83)	1.29 (0.96 – 1.75)	1.27 (0.94 – 1.71)
Vascular mortality	0.92 (0.77 to 1.09)	0.86 (0.72 to 1.03)	0.90 (0.77 – 1.06)	**0.85* (0.72 – 0.99)**

***** Statistically significant in favour of dabigatran
ICH: intracranial haemorrhage; MI: myocardial infarction; RR: relative risk; HR: hazard ratio; CI: confidence interval

Results from the direct and indirect analyses for both dabigatran doses compared to warfarin, were very similar. The wider confidence intervals for the indirect estimates generated from the MTC are a reflection of the broader range of inputs into this analysis, and increase the generalisability of the results compared with those from single trials. The very wide confidence intervals reported for haemorrhagic stroke are most likely due to the lack of data for this outcome. [redacted] (out of [redacted] trials reported haemorrhagic stroke, [redacted] of which was excluded from the analysis due to zero cell counts.

As a validity check of the MTC, the manufacturer was asked to provide tables of HR and 95% CI for all direct and indirect pairwise comparisons. In their response the manufacturer presented results for three effectiveness outcomes (ischaemic stroke, all-cause mortality and acute MI) for the comparisons between dabigatran and warfarin, aspirin and clopidogrel plus aspirin, using both SAS and WinBUGS (Tables 14 to 19; Figures in bold in upper part of matrix are the direct pairwise results; figures in lower part of the matrix are the results of the indirect comparisons; results in the grey shaded boxes are those of the direct comparison of dabigatran and warfarin from the

RE-LY trial. Care should be taken in reading these tables as the direction of the comparison is not always correct, for example the apparent mis-match between the direct and indirect results for of ischaemic stroke for the comparison between warfarin and clopidogrel plus aspirin (2.17 versus 0.48 (Tables 14 and 15)) is due to one being the inverse of the other).

Table 14: SAS analyses for ischaemic stroke; RR (from the MTC) and HR (from the direct comparisons with 95% CI)

	Dabigatran 150 mg	**Dabigatran 110 mg**	**Warfarin**	**Aspirin**	**Clopidogrel plus aspirin**
Dabigatran 150 mg	*	**1.50 (1.17 to 1.92)**	**0.75 (0.58 to 0.97)**	Not applicable	Not applicable
Dabigatran 110 mg	1.45 (1.09 to 1.92)	*	**1.13 (0.89 to 1.42)**	Not applicable	Not applicable
Warfarin	0.77 (0.58 to 1.03)	1.12 (0.86 to 1.45)	*	**0.30 (0.13 to 0.63)**	**2.17 (1.51 to 3.13)**
Aspirin	0.48 (0.27 to 0.84)	0.69 (0.40 to 1.20)	0.62 (0.38 to 1.01)	*	**0.68 (0.57 to 0.80)**
Clopidogrel plus aspirin	0.37 (0.23 to 0.61)	0.54 (0.33 to 0.87)	0.48 (0.32 to 0.73)	0.78 (0.41 to 1.48)	*

Table 15: WinBUGs analyses for ischaemic stroke; RR (from the MTC) and HR (from the direct comparisons with 95% CI)

	Dabigatran 150 mg	**Dabigatran 110 mg**	**Warfarin**	**Aspirin**	**Clopidogrel plus aspirin**
Dabigatran 150 mg	*	**1.50 (1.17 to 1.92)**	**0.75 (0.58 to 0.97)**	Not applicable	Not applicable
Dabigatran 110 mg	1.45 (0.77 to 4.08)	*	**1.13 (0.89 to 1.42)**	Not applicable	Not applicable
Warfarin	0.80 (0.50 to 1.65)	1.15 (0.72 to 4.34)	*	**0.30 (0.13 to 0.63)**	**2.17 (1.51 to 3.13)**
Aspirin	0.49 (0.23 to 1.05)	0.70 (0.34 to 2.14)	0.60 (0.33 to 1.00)	*	**0.68 (0.57 to 0.80)**
Clopidogrel plus aspirin	0.41 (0.21 to 1.35)	0.59 (0.29 to 3.43)	0.51 (0.29 to 1.27)	0.86 (0.39 to 3.00)	*

Table 16: SAS analyses for all-cause mortality; RR (from the MTC) and HR (from the direct comparisons with 95% CI)

	Dabigatran 150 mg	**Dabigatran 110 mg**	**Warfarin**	**Aspirin**	**Clopidogrel plus aspirin**
Dabigatran 150 mg	*	**1.03 (0.90 to 1.17)**	**0.88 (0.77 to 1.00)**	Not applicable	Not applicable
Dabigatran 110 mg	1.03 (0.89 to 1.19)	*	**0.91 (0.80 to 1.03)**	Not applicable	Not applicable
Warfarin	0.89 (0.77 to 1.03)	0.92 (0.79 to 1.06)	*	**0.95 (0.72 to 1.26)**	**1.01 (0.81 to 1.26)**
Aspirin	0.83 (0.64 to 1.07)	0.85 (0.66 to 1.10)	0.93 (0.76 to 1.14)	*	**0.98 (0.89 to 1.08)**
Clopidogrel plus aspirin	0.88 (0.66 to 1.18)	0.91 (0.68 to 1.21)	0.99 (0.77 to 1.27)	1.06 (0.77 to 1.47)	*

Table 17: WinBUGs analyses for all-cause mortality; RR (from the MTC) and HR (from the direct comparisons with 95% CI)

	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	Aspirin	Clopidogrel plus aspirin
Dabigatran 150 mg	*	**1.03 (0.90 to 1.17)**	**0.88 (0.77 to 1.00)**	Not applicable	Not applicable
Dabigatran 110 mg	1.03 (0.75 to 1.44)	*	**0.91 (0.80 to 1.03)**	Not applicable	Not applicable
Warfarin	0.90 (0.69 to 1.22)	0.92 (0.70 to 1.32)	*	**0.95 (0.72 to 1.26)**	**1.01 (0.81 to 1.26)**
Aspirin	0.82 (0.58 to 1.18)	0.85 (0.59 to 1.28)	0.91 (0.71 to 1.16)	*	**0.98 (0.89 to 1.08)**
Clopidogrel plus aspirin	0.90 (0.60 to 1.52)	0.93 (0.60 to 1.59)	1.01 (0.73 to 1.48)	1.10 (0.74 to 1.78)	*

Table 18: SAS analyses for acute MI; RR (from the MTC) and HR (from the direct comparisons with 95% CI)

	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	Aspirin	Clopidogrel plus aspirin
Dabigatran 150 mg	*	**1.02 (0.77 to 1.35)**	**1.27 (0.94 to 1.71)**	Not applicable	Not applicable
Dabigatran 110 mg	1.02 (0.73 to 1.43)	*	**1.29 (0.96 to 1.75)**	Not applicable	Not applicable
Warfarin	1.28 (0.90 to 1.83)	1.31 (0.92 to 1.86)	*	**0.96 (0.44 to 2.11)**	**1.58 (0.94 to 2.67)**
Aspirin	0.91 (0.49 to 1.69)	0.93 (0.50 to 1.72)	0.71 (0.42 to 1.19)	*	**0.78 (0.59 to 1.03)**
Clopidogrel plus aspirin	0.87 (0.44 to 1.70)	0.89 (0.45 to 1.73)	0.68 (0.38 to 1.20)	0.96 (0.44 to 2.08)	*

Table 19: WinBUGs analyses for acute MI; RR (from the MTC) and HR (from the direct comparisons with 95% CI)

	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	Aspirin	Clopidogrel plus aspirin
Dabigatran 150 mg	*	**1.02 (0.77 to 1.35)**	**1.27 (0.94 to 1.71)**	Not applicable	Not applicable
Dabigatran 110 mg	1.02 (0.39 to 2.61)	*	**1.29 (0.96 to 1.75)**	Not applicable	Not applicable
Warfarin	1.31 (0.67 to 3.30)	1.35 (0.62 to 3.18)	*	**0.96 (0.44 to 2.11)**	**1.01 (0.81 to 1.26)**
Aspirin	0.82 (0.34 to 2.10)	0.84 (0.34 to 2.06)	0.63 (0.31 to 1.10)	*	**0.78 (0.59 to 1.03)**
Clopidogrel plus aspirin	0.98 (0.37 to 3.94)	1.01 (0.33 to 3.55)	0.75 (0.32 to 1.86)	1.22 (0.45 to 3.78)	*

These tables further demonstrate the similarity between the direct and indirect results and also between the SAS and WinBUGs results. There is however some question with regard to the source of the direct evidence presented. The direct comparisons included were each informed by a single study:

- Dabigatran 150 mg versus Dabigatran 110 mg RE-LY[4]
- Warfarin versus Dabigatran 150 mg RE-LY[4]
- Warfarin versus Dabigatran 110 mg RE-LY[4]
- Warfarin versus aspirin: the BAFTA study[16]
- Warfarin versus clopidogrel plus aspirin: the ACTIVE-W study[17]

- Aspirin versus clopidogrel plus aspirin: the ACTIVE-A study.[18]

There were no direct comparisons of dabigatran and aspirin or clopidogrel plus aspirin.

From the original MTC network (P105 of the MS), it can be seen that the direct comparisons of warfarin versus clopidogrel plus aspirin, and aspirin versus clopidogrel plus aspirin [redacted]. However, the direct comparison of dose-adjusted VKA with aspirin should be informed by up to [redacted] trials[16, 19-23] The impact of using the results of the BAFTA trial[16] only, rather than a pooled estimate from a meta-analysis of the available trials, is explored in Section 4.5.

4.4.7 Summary of the results of the MTCs

The MTC generated results reflected the results of the direct comparisons, except that the confidence intervals were wider, as would be expected. Dabigatran sequence also showed a benefit over dose-adjusted VKA for ICH, minor bleeding, and vascular mortality, with no significant difference in the incidence of haemorrhagic stroke. The MTC results found that compared with aspirin or aspirin plus clopidogrel the relative treatment effect favoured both doses of dabigatran for most outcomes (some significantly so).

It is worth noting that in the economic section of the submission, the manufacturer defines two 'dabigatran sequences' that fed into the model. As stated in Section 4.4.1.1, although a dabigatran sequence arm was created for the MTC, the results were not utilised in the economic model. The data for the two 'dabigatran sequences' described in the economic section of the MS, are those of the individual subgroups.

4.5 Additional clinical work conducted by the ERG

In order to investigate the impact of including the trials of warfarin versus aspirin that were omitted from the estimate of the direct comparison between warfarin and aspirin reported in Section 4.4.6, we extracted data and undertook a standard frequentist meta-analysis of all trials available for the three outcomes reported in that section (Table 20; Figure 2). One trial that did not state the specific coumarin used,[23] was not included in these meta-analyses and data were not provided for another trial.[21]There

was no significant heterogeneity across the trails for any outcome and the pooled estimates were similar to those from the single BAFTA trial included in Section 4.4.6. The biggest difference was for ischaemic stroke, where the pooled estimate from direct comparisons was closer to that from the MTC than that of the BAFTA trial. Overall, the inclusion of the additional trials' data would not alter the conclusions that would have been drawn using the results of the BAFTA trial alone.

Table 20: The pooled RR of ischaemic stroke, all-cause mortality and acute MI in five trials the compared dose-adjusted warfarin and aspirin compared to the HR from the BAFTA trial

Ischaemic stroke	
Pooled RR (95% CI)	0.52 (0.36 to 0.76)
BAFTA/Mant (2007) HR (95% CI)	0.30 (0.13 to 0.63)
All-cause mortality	
Pooled RR (95% CI)	0.98 (0.82 to 1.18)
BAFTA/Mant (2007) HR (95% CI)	0.95 (0.72 to 1.26)
Acute MI	
Pooled RR (95% CI)	0.88 (0.56 to 1.39)
BAFTA/Mant (2007) HR (95% CI)	0.96 (0.44 to 2.11)

To explore the appropriateness of the choice of the BAFTA trial for the direct comparison of warfarin versus aspirin, the quality of the trials was investigated. The AFASAK[19] and BAFTA[16] trials are of similar methodological quality and were larger and/or better quality than the trials by Rash *et al.*[22] and McBride *et al.*[20] (Table 21); McBride *et al*. also did not use the standard target INR range used in the NHS, 2.0 to 3.0.[20] AFASAK recruited 677 and BAFTA recruited 973 patients; both trials used computerised randomisation, blinded outcome assessors, undertook power calculations, used an ITT analysis for the primary outcomes, a target INR of 2.0 to 3.0 and achieved similar proportions of TTR (Table 21). AFASAK was conducted in Denmark, was restricted to patients with AF and patients were similar at baseline, whereas BAFTA was conducted more recently and in the UK, but patients with atrial flutter were eligible for inclusion and the warfarin group were at higher risk of stroke at baseline. Therefore, although the BAFTA trial was a recent UK based trail, the impact of the inclusion of patients with atrial flutter on the results, and the generalisability of these results to the target UK NHS population, is unclear.

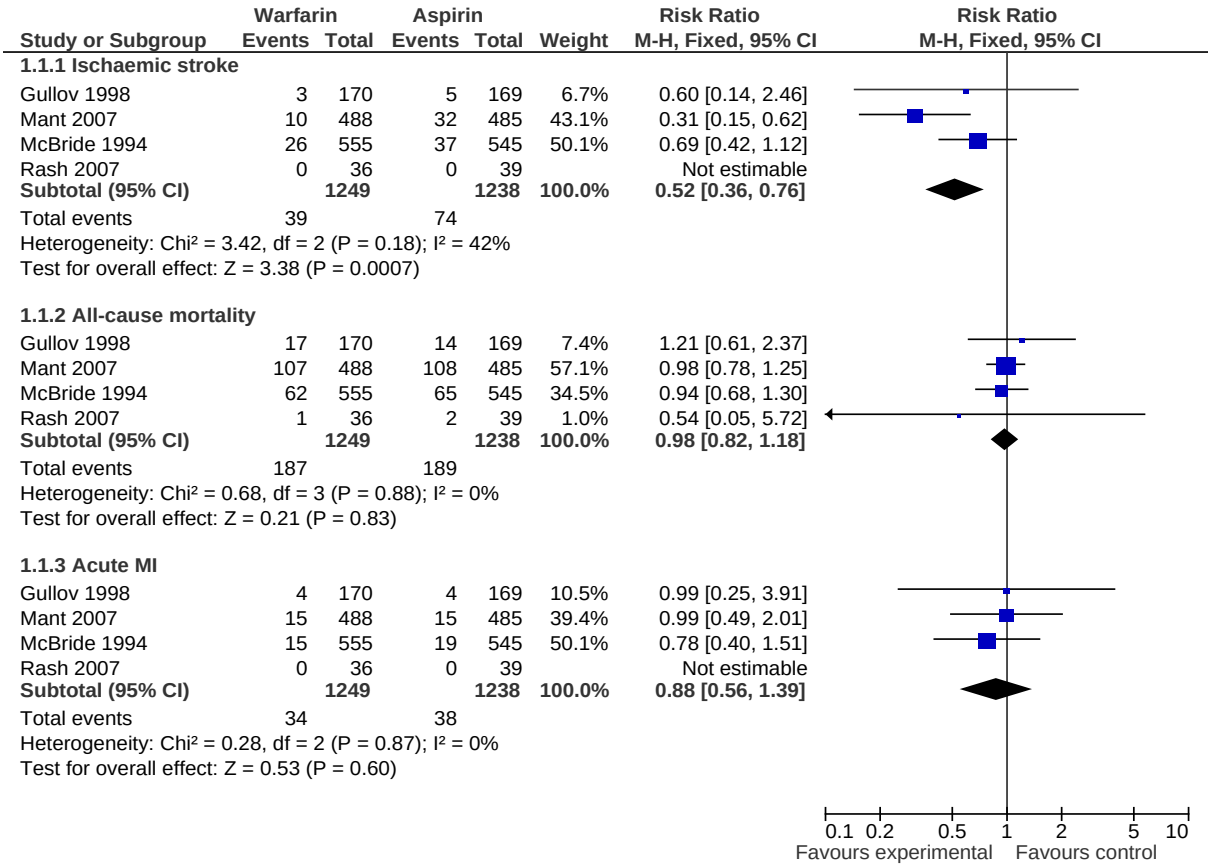


Figure 2: The incidence of ischaemic stroke, all-cause mortality and acute MI in the trials providing data for the comparison between warfarin and aspirin

Table 21: Quality of the four trials providing data for warfarin compared to aspirin

Criterion	**BAFTA/Mant**[16]	**AFASAK/Gullov**[19]	**Rash**[22]	**SPAFI/McBride**[20]
Randomisation method	Yes	Yes	Yes	Yes
Allocation concealment	No	No	Yes	No
Number recruited	973	677	75	715
Similarity at baseline	Higher risk of stroke in warfarin arm	Yes	Yes	Unclear
Blinding - assessors	Yes	Yes	Unclear	Unclear
Blinding – trialists/patients	No	No	No	No
Power calculation	Yes	Yes	Yes	No
ITT analysis	Yes	Yes	Yes	Yes
Dropouts/withdrawals	Yes	Yes	Yes	Yes
Generalisability	Patients with atrial flutter eligible	Yes	Excluded all patients with prior stroke	Yes
Target INR range	2-3	2-3	2-3	1.3-1.8 initially 2.0-4.5 subsequently
% in INR range	67	73	69.2	86

4.6 Clinical effectiveness conclusions

The MS evaluated the effectiveness and safety of dabigatran 110 mg bid and 150 mg bid for the prevention of stroke in patients with AF. The systematic reviews conducted by the manufacturer were generally well-conducted, and no relevant trials appear to have been missed. When compared to the NICE submission, the MS:

- Included aspirin as a comparator, but not in the context of a treatment for patients in whom warfarin was inappropriate
- Reported the outcome of all-stroke only as part of composite outcomes
- Relied primarily upon a trial in which the population had a higher risk of stroke than that specified in the NICE scope (RE-LY[4]).

Overall, the evidence shows that dabigatran 150 mg bid is efficacious in preventing ischaemic stroke and vascular death, without significant concomitant increases in the incidence of haemorrhagic stroke or major bleeding. However, the incidence of GI bleeds is increased with dabigatran 150 mg bid compared to dose-adjusted warfarin. In addition, there seems to be some benefit in a dose reduction in the elderly in terms of haemorrhagic outcomes, and the beneficial effects of dabigatran seem to be most pronounced in those with poor INR control.

5 COST EFFECTIVENESS

5.1 Overview of the manufacturer's economic evaluation

The manufacturer's initial economic submission to NICE included (references in brackets refer to the MS):

- A description of the systematic search strategy used to retrieve existing cost effectiveness studies from published literature with full details in Appendix 10 (P328-332). A file including a full list of studies excluded at the second pass is also attached (P332)
- A detailed series of appendices including full details of other search strategies conducted by the manufacturer. Appendix 12 describes the systematic review for measurement and valuation of health effects (P333). Systematic review of INR monitoring resource-use in Appendix 13 (P334). Systematic review of stroke resource use and costs in Appendix 13 (P336 to 338). Systematic review of the costs of major bleedings in Appendix 13 (P339)
- Details of the OXVASC study sponsored by the manufacturer to assess the cost of stroke in patients with AF are included in Appendix 13 (P340)
- A summary of the '*de novo*' economic evaluation conducted by the manufacturer describing the patient population, model structure, technology, clinical variables, assumptions, health-related quality of life (HRQoL) , costs and finally the base-case results and sensitivity analysis (P150-283, Figure 18–43 , Tables 67–148)
- Electronic copies of two Excel models used in the economic evaluation.

Following the points of clarification raised by the ERG, a number of addenda were submitted by the manufacturer. These included:

1. Revised electronic copies of the Excel models
2. Revised incremental analysis for all treatments in the single-dose model as an approach to enable comparisons between dabigatran 150 mg and 110 mg
3. Original Kaplan-Meier curves for treatment discontinuation as well as probabilities for discontinuation at 30 days, 90 days, 1 year and 2 years
4. Additional justification for using a Weibull distribution for treatment discontinuation of first-line treatments rather than alternative distributions

5. Additional sensitivity analysis for the cost-effectiveness results using alternative survival distributions as well as using the Kaplan-Meier curves followed by constant discontinuation after 2 years
6. Additional sensitivity analysis using the relative rather the absolute effect of discontinuation for aspirin compared to warfarin from the Mant *et al*. (2007) paper[16]
7. Additional justification from the manufacturer on a range of issues identified by the ERG, including: meaning and model implications to the expression "treatment discontinuation"; justification of modelling acute myocardial infarction as an acute event with only one-off costs and disutility and with no consequences beyond 3 months; the exclusion of pulmonary embolism from the economic model; why only one event can occur in each 3-month cycle.

This section of the ERG report focuses on the economic evaluation submitted by the manufacturer. The economic evaluation is subject to a critical review based on the manufacturer's report and by examination of the electronic model. The critical review is conducted with the aid of a checklist designed to assess the quality of economic evaluations and a narrative highlighting the key assumptions, possible limitations and any remaining uncertainties.[24] These issues are subsequently explored with additional analyses undertaken by both the manufacturer during the clarification stage, which are found in Section 5.1, and the further analyses by the ERG in Section 6.

The economic evaluation conducted by the manufacturer combines clinical, economic and outcome data to determine the cost-effectiveness of dabigatran in patients with AF. The primary comparator for dabigatran is warfarin. Aspirin and aspirin plus clopidogrel are the secondary comparators. Aspirin plus clopidogrel is a treatment regimen unlicensed for the indication described in NICE's scope. The population used in the evaluation reflects the patients participating in the RE-LY trial: adult patients diagnosed with non-valvular AF, at risk of stroke or systemic embolism (SE), and eligible for anticoagulation treatment. The manufacturer presented two economic models: a single dose and sequence dose model. In the sequence dose model, the patient cohort was divided by age and modelled separately. Patients aged under 80 years old were started with dabigatran 150 mg, and once they reached 80 years of age in the model they were switched to dabigatran 110 mg. Conversely, patients age 80

years or older at baseline were initiated and kept on dabigatran 110 mg. In the single dose model, the intervention is independent of age. Consequently, starting the patient cohort on a specific dose of dabigatran implies that the alternative dose of dabigatran will not be considered.

The model evaluates clinical events, HRQoL expressed in terms of QALYs, life-years accrued and costs over the lifetime of the patients. The event risk for all treatment strategies is applied to a baseline risk of events representing the risk of patients treated with warfarin from the RE-LY trial. Therefore the risk for various events is modified into a relative risk, anchored on the warfarin arm of the RE-LY trial. The relative risk for dabigatran 110 mg and dabigatran 150 mg for the various clinical events is obtained from the RE-LY trial. The MTC provides the relative risks for aspirin, aspirin plus clopidogrel, and no treatment; data for the no treatment option came from the placebo trials.

The manufacturer uses a three state transition cohort model with three month cycles over a life time horizon. HRQoL estimates are based on disability status and disutility incurred due to the various clinical events. The utility values used in the economic model are incorporated by applying utility weights from the RE-LY QoL sub-study and published literature in order to estimate QALYs. Total costs are calculated by applying the national payment by results (PbR) tariff where applicable. Where national estimates were not available, systematic reviews were conducted in order to estimate the remaining costs. The manufacturer also sponsored a new study to assess the cost of stroke in patients with AF, as part of the OXVASC study. The study assumes a NHS perspective and costs and benefits are discounted at 3.5% per annum. The MS details what they consider the main assumptions in the economic model on p.177. Table 22 of the ERG report provides a summary of the manufacturer's economic evaluation, with justifications for key aspects and signposts to the relevant sections of the MS.

Table 22: Summary of the manufacturer's economic evaluation (and signposts to MS)

	Approach	**Source / Justification**	**Signpost (location in MS)**
Model	Cost-utility analysis using a Markov model.	Sorensen (2009)[1]	Section 6.2.3 P152
States and events	The model contains 4 states: Independent Disability (DL), Moderate DL, Dependent DL or dead. As cycles progress patients may experience the various clinical events: ischemic stroke (IS), intra cranial haemorrhage (ICS), haemorrhagic stroke (HS), extra cranial bleeds (ECH), systemic embolism (SE), transient ischemic attack (TIA) and acute myocardial infarction (MI). The possible consequences of each event imply an increased disability status or switch to second-line treatment or a discontinuation of treatment.	Sorensen (2009)[1]	Section 6.2.3 and 6.2.4 P152-153
Comparators	Dabigatran (150 mg or 110 mg) was compared to: 1. Warfarin (trial like or real world) as primary comparator 2. Aspirin as secondary comparator 3. Aspirin plus clopidogrel as secondary comparator		Section 6.2.7 P156
Sub groups	The manufacturer presented two economic models: a single dose and sequence dose model. The sequence model targets each dose of dabigatran within a specific patient population: DBG Sequence at least age 80 at baseline initiated on DBG 110 mg, DGS Sequence less than age 80 initiated on DBG 150 mg and switched to DBG 110 mg at age 80.	The manufacturer states that the sequence dose model is presented following the proposed SPC.	Section 6.2.1, P151 Tables 67- 68
Natural History	Based on Markov model. Movements between states were based on the RE-LY trial and the results of the meta-analysis. The model tracks patients by disability level following stroke or ICH, which is important given the large costs and health impact s of disability. The Markov cycle length is three month and only one event per cycle is permitted.	The model concept followed the paper by Sorensen *et al*.[1] The structure was informed by previous publications and expert clinical review.	Section 6.2.3 Figure 18
Treatment effectiveness	Clinical outcomes in the economic model: 1. Risk of various clinical events: IS, SE, HS, ICH, ECH, acute MI, TIA, minor bleed.	RE-LY provides baseline risk for all events based on warfarin and event rates for DBG 110 mg and 150 mg. The MTC provides relative risk of events for aspirin, aspirin plus clopidogrel and no treatment in comparison to DBG 110 mg, 150 mg and DBG sequence.	Section 6.3 P156-179 Table 86
	2. Relative risks used for modelling the effect of INR on the risk of ischemic and haemorrhagic events	RE-LY provides the distribution of patients per INR interval: under 2, between 2 and 3 and above 3. Relative risks for IS (assumed to be the same for SE and TIA) and intracranial bleeding (assumed to be the same for HS) are based on Walter *et al*. (2008).[25] Relative risks for Extra cranial haemorrhage (assumed to be the same for	

	Approach	**Source / Justification**	**Signpost (location in MS)**
		acute MI) are based on Yousef *et al*. (2004).[26]	
	3. Disability and mortality risk following IS	Under DBG treatment sourced from RE-LY Under warfarin, aspirin and no treatment based on Hylek (2003)[27] Aspirin plus clopidogrel is assumed to have the same risk as aspirin alone.	
	4. Disability and mortality risk following ICH and HS	Based on Rosand (2004)[28] Disability and mortality risk assumed equal for warfarin and DBG, and equal for aspirin and no treatment.	
	5. Proportion of gastro intestinal bleed from ECH	Based on RE-LY. ECH stratified between GI and non GI according to DBG treatment status.	
	6. Treatment discontinuation and switched due to non clinical events	Weibull distributions fitted to RE-LY derived Kaplan Meier curves for treatment discontinuation. Aspirin discontinuation sourced from Mant (2007).[16] Discontinuation rates from aspirin plus clopidogrel assumed equal to aspirin alone.	
	7. All cause mortality	UK tables adjusted for $CHADS_2$ score Event risk equations derived using simulation methods adjusting for age and sex.	
Health related QoL	The utility values are categorised in three sets: **1.** Utility associated with general health state and treatment status The results of the questionnaire were pooled across the 3 treatment arms (warfarin, DBG 150 and DBG 110). At baseline the utility values for the three treatments were similar. At three months the utility for DBG patients was statistically significantly lower than for WFN ones. At 12 months the utility difference was no longer statistically significant. The manufacture considered that the utility difference between patients groups at 3 months was too small to be clinically significant. Disutility from treatment was tested in the univariate sensitivity analysis. **2.** Utility associated with post stroke disability status This study does not employ EQ 5D but time trade-off to evaluate quality of life. **3.** Utility associated with clinical events EQ 5D, Minor bleeds were assumed to be associated with zero disutility.	The RE-LY QoL sub study (originated from a protocol amendment which allowed for the administration of the EQ 5D). Results based on Gage *et al*. (1996)[29] Results based on Sullivan (2006)[1]	Section 6.4 P180-212 Tables 92 and 97 Table 87 P187
Resource utilisation and costs	Costs were divided into the following categories: associated with antithrombotic treatment (including INR monitoring), acute event costs and long term follow up costs	The national payment by results - PbR tariff was used to estimate unit costs where applicable. Systematic reviews were carried out to	Section 6.5

	Approach	**Source / Justification**	**Signpost (location in MS)**
	resulting from disability The manufacturer sponsored a part of the OXVASC study in order to estimate costs of stroke in patients with AF	estimate remaining costs with no published public prices.	P213 to 244
Discount rates	Costs and benefits were discounted at 3.5% per annum. Discount rates at 0% and 6% were tested in the sensitivity analysis.	In accordance with the NICE reference case.	Section 6.2.6, P155 Table 70
Sensitivity analysis	Structural, univariate and probabilistic sensitivity analysis was performed.	In accordance with the NICE reference case.	Section 6.6 P244 to 255 Table 114 to 117

AF: Atrial fibrillation; DBG: Dabigatran; ECH: Extracranial haemorrhage; HS: Haemorrhagic stroke; ICH: Intracranial haemorrhage; INR: International normalised ratio; IS: Ischaemic stroke; MI: Myocardial infarction; QoL: Quality of life; SE: Systemic embolism; TIA: Transient ischaemic attack; WFN: Warfarin

5.1.1 Literature search

The manufacturer carried out a comprehensive search of economic evaluation studies evaluating the cost-effectiveness of dabigatran etexilate in patients with AF. No previously published economic evaluations of dabigatran for preventing stroke in AF patients were identified by the manufacturer searches.

Electronic databases (EMBASE, MEDLINE, MEDLINE ® In-process, NHS EED, EconLIT) were examined from 1990 up to the 5th July 2010. The search strategies used for each database are shown in Appendix 10 of the MS. In addition to the literature databases, conference proceedings from International Society on Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting 2008 and 2009, and ISPOR Annual European Congress 2008 and 2009 were hand searched. Table 65 (P147 of the MS) summarises the eligibility criteria used to select possibly relevant studies. The literature search retrieved 1,251 studies. All of these studies were subsequently excluded.

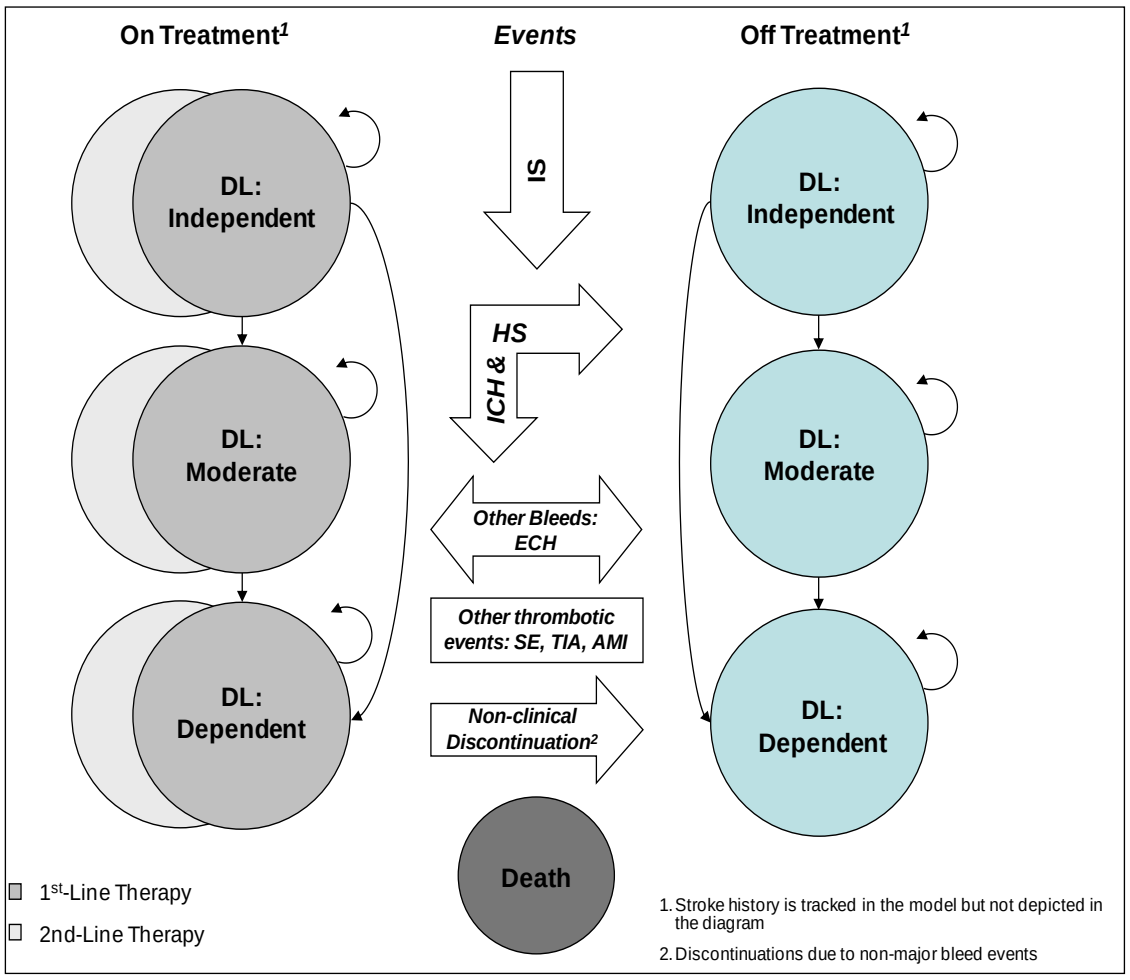
5.1.2 Natural history

A Markov model was employed to follow AF patients through the natural course of the disease. The manufacturer chose a Markov model for three reasons: (1) it allows for the representation and transition between health states relevant to the condition; (2) it is an approach used in the economic evaluation literature for the modelling of AF; and (3) usability and accessibility of Markov models. A simplified model diagram is presented in Figure 3.

The patient cohort enters the model at risk of the various clinical events and on one of the treatments under comparison. The various events considered are: ischaemic stroke, ICH, haemorrhagic stroke, ECH, SE, TIA and acute MI.

As cycles progress, patients may experience the various clinical events. The block arrows represent the possible consequences of each event: vertical for an aggravation of disability status, and horizontal for a switch to second-line or a discontinuation of treatment. The patients are distributed and move between mutually exclusive health states, represented by the circles. The cohort ages over time and is subjected to gender adjusted all-cause mortality risk. Disease-related death is affected by disability level, stroke history and treatment status. ischaemic stroke, haemorrhagic stroke and ICH are the only clinical events that affect the disability status. Disability caused by haemorrhagic stroke and ICH is assessed according to

the modified Rankin scale (mRs). Disability caused by ICH is classified according to the Glasgow outcomes scale.



AMI: Acute myocardial infarction; DL: Disability level; ECH: Extracranial haemorrhage; HS: Haemorrhagic stroke; ICH: Intracranial haemorrhage; IS: Ischaemic stroke; SE: Systemic embolism; TIA: Transient ischaemic attack

Figure 3- Schematic of the model structure developed from Sorensen (2009)[1] (P152 of the MS)

SE, TIA, acute MI, and ECH are assumed to have no effect on disability status. Consequently, these clinical events are also assumed to have no associated ongoing costs and disutilities. The manufacturer states that the model structure was designed to only capture disability from events occurring in the brain.

There are twenty-three possible health states: fourteen permanently active, eight temporary states for patients who have discontinued therapy during one cycle due to ECH, and the final

state, death. (Table 23) describes how the events have been modelled to influence the transition of the patients between health states.

Table 23: Effect of various events on health status (P154 of the MS)

Event	Effect on treatment status	Effect on stroke history	Effect on disability	Additional mortality risk
Ischaemic stroke	If non-fatal, no change	If no previous stroke, switches status from yes to no	Recover to previous disability level or deteriorate to a worse level	Yes
SE	If non-fatal, no change	If no previous stroke, switches status from yes to no	If non-fatal, no change	Yes
Haemorrhagic stroke	If non-fatal, permanent discontinuation	If non-fatal, no change	Recover to previous disability level or deteriorate to a worse level	Yes
ICH	If non-fatal, permanent discontinuation	If non-fatal, no change	Recover to previous disability level or deteriorate to a worse level	Yes
ECH	If non-fatal, no change, temporary or permanent discontinuation	If non-fatal, no change	If non-fatal, no change	Yes
Acute MI	If non-fatal, no change	If non-fatal, no change	If non-fatal, no change	Yes
TIA	No change	If no previous stroke, switches status from yes to no	No change	No
Minor bleed	No change	No change	No change	No
No event	No change, switch to 2nd line or permanent discontinuation	No change	No change	No

ECH: Extracranial haemorrhage; ICH: Intracranial haemorrhage; MI: Myocardial infarction; SE: Systemic embolism; TIA: Transient ischaemic attack

The model estimates costs and outcomes over the lifetime of the patient's cohort (up to 100 years). The outcomes considered are:

- The clinical events included in the model (with the exception of minor bleed)
- Quality of life (as QALYs)
- Life years accrued.

All clinical outcomes are associated with acute costs and disutility. Further longer-term costs and disutility beyond the acute stage are only associated with ischaemic stroke, haemorrhagic stroke and ICH.

The Markov cycle length in the model is three months and only one event per cycle is permitted. The manufacturer provided three reasons for this decision. First, three months should reflect the typical duration of temporary drug discontinuation due to ECH . Second, the likelihood of patients experiencing more than one major event during three months is claimed to be low. Third, disability and mortality due to stroke are suggested to plateau at around three months.

The patient cohort of 10,000 individuals reflects the patients participating in the RE-LY trial. Therefore, the cohort consists of adult patients diagnosed with non-valvular AF, at risk of stroke or SE, and eligible for anticoagulation treatment. To determine the risk of stroke the manufacturer uses the $CHADS_2$ score.[30] Table 24 summarises the $CHADS_2$ scoring system.

Table 24: $CHADS_2$ scoring system[30]

		Points
C	Congestive heart failure	1
H	Hypertension: blood pressure > 140/90 mmHg (or treated hypertension)	1
A	Age ≥ 75 years	1
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA	2

TIA: Transient ischaemic attack

The patient's $CHADS_2$ score reflects risk factors assumed constant during the cohort's lifetime, like congestive heart failure, hypertension and diabetes mellitus. In contrast, age and stroke history change as the model simulates the cohort's lifetime. Once a patient cohort reaches 75 years old, one more point is added to the cohort's $CHADS_2$ score. This reflects the effect of age in the $CHADS_2$ scoring system. Stroke history is updated by adding two more points to the patient's $CHADS_2$ score if an ischaemic stroke, TIA or SE occur. Stroke history is considered to be a binary variable: a patient is with or without stroke history. Therefore, suffering further strokes will not change the risk of future events. Risks for clinical events other than stroke are unchanged by stroke history.

5.1.3 Comparators

The primary comparator for dabigatran was warfarin. Aspirin and aspirin plus clopidogrel were the secondary comparators. Aspirin plus clopidogrel is a treatment regimen unlicensed for the indication described in NICE's scope (prevention of stroke and SE in people with AF). The manufacturer justified the inclusion of aspirin plus clopidogrel, as an experimental regimen due to be appraised by NICE. The no treatment option was considered as an alternative for those who fail aspirin.

5.1.4 Treatment effectiveness within the submission

Treatment sequence

The treatment sequence in the model was determined by whether dabigatran was used as first or second-line treatment (Table 25). If chosen as first-line treatment then comparisons could be made to warfarin, aspirin plus clopidogrel, aspirin or no treatment. Patients starting a sequence with warfarin or dabigatran could be followed by any of the following second-line

treatments: aspirin plus clopidogrel, aspirin or no treatment. When aspirin plus clopidogrel was tested as first-line treatment then only aspirin or no treatment could be used as second-line treatment. If aspirin was chosen as first-line treatment then only 'no treatment' could be considered as second-line.

When dabigatran is second-line, the patient cohort was started on either trial-like or real-world warfarin. A treatment switch would change the patient from warfarin to dabigatran, and the following switch from dabigatran to no treatment. The comparators for dabigatran as second-line were aspirin or no treatment. In this case a switch always resulted in 'no treatment'.

Warfarin was only considered as first-line treatment. The model does not allow patients who fail on dabigatran to use warfarin as a second-line treatment. The model also does not allow dabigatran as first-line treatment to be compared to dabigatran as second-line treatment.

Table 25: Treatment sequences

	Dabigatran as 1st treatment	**Dabigatran as 2nd treatment**
1st Treatment	Dabigatran 150 mg or Dabigatran 110 mg or Dabigatran sequence	Trial-like or Real-world warfarin
2nd Treatment	Aspirin plus clopidogrel Aspirin No treatment	Dabigatran 150 mg or Dabigatran 110 mg or Dabigatran sequence
Comparators	Trial-like warfarin or Real-world warfarin or Real-world prescription behaviour warfarin Aspirin + clopidogrel Aspirin No treatment	Aspirin No treatment

INR control

The RE-LY trial provided the distribution of patients per INR interval: under 2, between 2 and 3 (target range), and above 3. In the economic model, INR affected the risks of clinical events. An INR below 2 increased the risk of ischaemic events (ischaemic stroke, TIA and SE). An INR above 3 increased the risk of haemorrhagic events (ICH, haemorrhagic stroke and ECH).

The study by Walker *et al.* (2008) provided the relative risks used for the base-case analysis for the affect of INR control on ischaemic and haemorrhagic clinical events, with the exception of ECH.[25] The risk of ECH and acute MI used in the model cited Yousef *et al.* (2004), however the source of the data could not be found by the ERG.[26] Table 26

summarises the risk ratios used to adjust the risk for the affected clinical events in the economic model.

Table 26: Relative risks used for modelling the effect of INR on the risk of ischaemic and haemorrhagic events (adapted from economic model)

Clinical event	Risk factor	RR	95% CI	Comments	Source
Ischaemic stroke	INR <2	2.28	1.60-3.26	Assumed the same for SE and TIA	Walker *et al*. (2008)[25]
	INR ≥3	1.56	0.95-2.58		
ICH	INR <2	0.78	0.43-1.45	Assumed the same for HS	
	INR ≥3	2.03	1.12-3.71		
ECH	INR <2	1.108	NS	Assumed the same for acute MI	Yousef *et al*. (2004)[26]
	2< INR <3	0.517	NS		
	INR >3	3.039	NS		

CI: Confidence interval; ECH: Extracranial haemorrhage; ICH: Intracranial haemorrhage; HS: Haemorrhagic stroke: INR: International normalised ratio; MI: myocardial infarction; NS: Not stated in economic model; RR: Relative risk; SE: Systemic embolism; TIA: Transient ischaemic attack.

Risk for clinical events and treatment effects

The event risk for all treatment strategies was applied to a baseline risk of events in patients treated with warfarin in the RE-LY trial. Therefore treatment effects were converted into relative risks and applied to the warfarin arm of the RE-LY trial. Table 72 (P160) of the manufacturer submission summarises the baseline (warfarin) risks of treatment-dependent clinical events. Table 74 (P162 of MS) provides the relative risks of the modelled clinical events.

Baseline risk of ischaemic stroke depended on $CHADS_2$ score and reflected the incidence of ischaemic stroke in the warfarin arm of the RE-LY trial. Ischaemic stroke events in patients with $CHADS_2$ score of 3 and 4, and of 5 and 6 were pooled due to sample size limitations. Hence, the risk of ischaemic stroke was assumed to be equal for patients whose $CHADS_2$ score was 3 or 4, and for patients whose $CHADS_2$ score was 5 or 6.

Table 27: Baseline risk of ischaemic stroke (adapted from Table 73, P161, MS)

$CHADS_2$ score	Ischaemic stroke rate per 100 Patient-Years		
0		[redacted]	
1			
2			
3			
4			
5			
6			

The baseline risk of some bleeding events was age-adjusted. The relative risk of ICH was increased once patients reached 80 years old; the relative risk of ECH was decreased for

patients under 70 years old (Table 85, P170 in MS). The data source quoted was a study by Fang *et al.* (2006).[31]

The relative risk for dabigatran 110 mg and dabigatran 150 mg for the various clinical events were obtained from the RE-LY trial. The relative risk for aspirin, aspirin plus clopidogrel, and no treatment (placebo) were obtained from the MTC. As previously reported in the clinical effectiveness section two MTC analyses were performed: one using SAS and the other using WinBUGS. The SAS MTC was chosen for the base-case in the economic evaluation. The MS did not provide good justification for this choice.

Treatment affects the relative risk of ischaemic stroke, haemorrhagic stroke and ICH. For those patients that did have an event, disability and mortality also depended on the treatment. The effect of treatment on mortality and disability rates of ischaemic stroke were obtained from Hylek (2003) (Table 76, P164 of the MS) except for dabigatran which was obtained from the RE-LY trial (Table 77, P165 of the MS).[27]Rates for aspirin plus clopidogrel were assumed to be equal to rates for warfarin treatment.

Mortality and disability rates following haemorrhagic stroke and ICH were obtained from Rosand (2004) (Table 79, P165 of the MS).[28]The manufacturer submission assumes that mortality and disability for dabigatran is equal to those of warfarin. Similarly, mortality and disability for aspirin is assumed equivalent to no treatment. ECH is classified as gastro-intestinal and non-gastro-intestinal, due to gastro-intestinal haemorrhages being more frequent in the dabigatran arm of the RE-LY trial. Rates of both types of ECH are derived from the RE-LY trial.

Mortality rates of SE, acute MI and ECH were assumed to be independent of the treatment administered. Mortality rates for acute MI and ECH were extracted from the RE-LY trial. Mortality rates for SE were estimated by applying the mortality rates due to SE from the 2007 Mortality Statistics to the event rate in the RE-LY trial.[32] All-cause mortality rates were obtained from the 2007 Mortality Statistics with deaths due to the clinical events in the model excluded using cause elimination approaches to avoid double counting.[32]

Treatment Discontinuation

Treatment discontinuation and switches occurred due to both clinical and non-clinical events. Clinical events leading to permanent treatment discontinuation are haemorrhagic stroke and ICH. ECH was assumed to result in permanent discontinuation for 50% of the patients. Nevertheless, following permanent discontinuation caused by ECH, some patients switched to a second-line therapy. The switch rate was set at 70% for dabigatran and aspirin and 78% for warfarin.

Non-clinical events, such as patient choice, could also cause a switch to second-line therapy or permanent discontinuation of treatment. The RE-LY trial provided treatment discontinuation rates from dabigatran and warfarin for up to two years. Consequently, treatment discontinuation rates for the longer time horizon simulated in the model are extrapolated by fitting parametric survival functions (Weibull) to the original Kaplan-Meier curves for treatment discontinuation. Discontinuation rates from aspirin were estimated by applying the absolute discontinuation rates from Mant *et al.* (2007) to the extrapolated warfarin discontinuation.[16] After six years, discontinuation due to non-adherence is assumed to be zero. The sources and the approaches used to source event risks are summarised in Table 28.

Table 28: Sources and approach used for key events

Events in the model	Sources	Approach
Risk of various clinical events: IS, SE, HS, ICH, ECH, acute MI, TIA, minor bleed	RE-LY MTC	The RE-LY provides: Baseline risk for all events based on warfarin. Event rate for dabigatran 110 mg and 150 mg. The MTC provides: Relative risk of events for aspirin, A+C and NT in comparison to DBG 110 mg, dabigatran 150 mg and dabigatran sequence.
Disability and mortality risk following IS, ICH and HS.	ischaemic stroke: Hylek (2003)[25] and RE-LY	Risk with dabigatran sourced from RE-LY trial. Risk with warfarin, aspirin, and NT sourced from Hylek (2003). A+C assumed to have equal risk as aspirin.
	ICH/HS: Rosand (2004)[28]	Disability and mortality risk assumed equal for warfarin and dabigatran, and equal for aspirin and NT.
Proportion of GI bleed from ECH	RE-LY	ECH stratified between GI and non-GI according to dabigatran treatment status.
Treatment discontinuation and switch due to non-clinical events	RE-LY Mant (2007)[16]	Weibull distributions fitted to RE-LY derived Kaplan-Meier curves for treatment discontinuation. Aspirin discontinuation sourced from Mant (2007). Discontinuation rates from A+C assumed equal to aspirin.
All-cause mortality	UK life tables adjusted for $CHADS_2$ score[32]	Event risk equations derived using simulation methods adjusting for age and sex.

A+C: Aspirin plus clopidogrel; bid: twice daily; ECH: Extracranial haemorrhage; GI: Gastrointestinal; HS: Haemorrhagic stroke; ICH: Intracranial haemorrhage; INR: International normalised ratio; IS: Ischaemic stroke; MI: Myocardial infarction; NT: No treatment (placebo); SE: Systemic embolism; TIA: Transient ischaemic attack

5.1.5 Health-related quality of life

The economic evaluation focused on HRQoL associated with disability status and disutility incurred due to the various clinical events. The manufacturer categorised the utility values in three sets, which were subsequently tested separately in the univariate sensitivity analysis. Table 29 summarises the utility values used in the base-case.

- Set 1 comprised the utility associated with general health state and treatment status: (i) baseline utility for AF patients, (ii) disutility associated with warfarin treatment and INR monitoring, and (iii) disutility associated with dabigatran treatment.
- Set 2 comprised the utility associated with the different disability status, namely independent (mRs 0, 1 or 2), moderate (mRs 3 or 4), and dependent (mRs 5 or 6).
- Set 3 included the acute disutility associated with the occurrence of the various clinical events.

Table 29: Summary of utility values used in the base-case (adapted from Table 97, P211 of MS)

Set	Health state	Base-case		Source and elicitation method
		Mean	95% CI	
1	AF patient	[redacted]	[redacted]	RE-LY study, EQ-5D
	Warfarin treatment	Disutility of treatment not considered		
	Dabigatran treatment	Disutility of treatment not considered		
2	Mild stroke: mRS 0-2	0.76	NR	Gage (1996), TTO[29]
	Moderate stroke: mRS 3-4	0.39	NR	
	Major stroke: mRS 5	0.11	NR	
3	Stroke (severity not specified).	-0.139 [du]	-0.118 to -0.160	Sullivan (2006), EQ-5D[33]
	SE.	-0.120 [du]	-0.102 to -0.139	
	TIA	-0.103 [du]	-0.088 to -0.119	
	ICH	-0.181 [du]	-0.155 to -0.209	
	ECH	-0.181 [du]	-0.155 to -0.209	
	Acute MI	-0.125 [du]	-0.106 to -0.144	
	Minor bleed (not specified).	0 [du]	0	Assumption

AF: Atrial fibrillation; du: disutility; ECH: Extracranial haemorrhage; ICH: Intracranial haemorrhage; MI: Myocardial infarction; mRS: modified Rankin scale; NR: not reported by the original study; TIA: Transient ischaemic attack; TTO: time-trade off.

Set 1: Utility associated with general health state and treatment status

The RE-LY QoL sub-study provided baseline utility data for the general health state used in the base-case. The results of the EQ-5D questionnaire at baseline were pooled across the three treatment arms (warfarin, dabigatran 110 mg and dabigatran 150 mg), and the mean used as the utility value for the patient cohort when entering the economic model (mean utility=[redacted]).

The RE-LY QoL sub-study originated from a protocol amendment to the RE-LY trial which allowed for the administration of EQ-5D. However, less than 10% of the RE-LY participants

completed the EQ-5D for the QoL sub-study. Table 87 (P187 of MS) compares the characteristics between the RE-LY QoL sub-study and RE-LY study participants. The manufacturer concluded that the RE-LY QoL sub-study population could be considered representative of the RE-LY study population.

The RE-LY QoL sub-study collected HRQoL data at baseline, three months and twelve months (Table 88, P188 of MS). [redacted]

[redacted] Therefore, for the base-case analysis, neither of the treatments was associated with any disutility. However, disutility from treatment was tested in the univariate sensitivity analysis.

Set 2: Utility associated with post-stroke disability status

The manufacturer undertook a systematic review to source the utility values associated with the various clinical events and disability states used in the economic model. Only two studies were considered appropriate to provide utilities associated with post-stroke disability status: Gage *et al.* (1996) and Dorman *et al.* (2000).[29, 34]

Set 3: Utility associated with clinical events

The systematic review briefly described above failed to identify any single study describing utilities associated with clinical events. The most complete data was found in two studies by Sullivan (2005, 2006).[33, 35]

The data in Sullivan (2006) was used for the base-case analysis, and the data in the 2005's study was used for the univariate sensitivity analysis.[33] These utility values were obtained from a EQ-5D population survey in the United States. Sullivan (2005, 2006) provided disutilities for all clinical events considered in the model except disutility associated with minor bleeds.[33, 35]Minor bleeds was assumed to be associated with zero disutility in the base-case, and with a minor decrement for the sensitivity analysis.

5.1.6 Resources and costs

The model considered the resource costs associated with antithrombotic treatment (including INR monitoring), acute event costs, and long term follow-up costs resulting from disability. Costs were extrapolated beyond the follow up period of the RE-LY trial. Whenever appropriate, costs were inflated to 2010 price using the inflation indices from the Unit Costs of Health and Social Care.[36] The inflation rate for 2009/10 was assumed to be equal to the inflation rate for 2008/09 (Table 113, P244 of MS). The national PbR tariff was used to estimate unit costs, where applicable. Systematic reviews were conducted in order to estimate the remaining costs. The manufacturer sponsored a new study to assess the cost of stroke in patients with AF, based on the OXVASC study.

Treatments costs

Dabigatran was priced at £2.52 per day for both 110 mg and 150 mg doses. Treatment with: warfarin, aspirin, and aspirin plus clopidogrel, were assumed to cost: £0.04, £0.09, and £0.26 per day, respectively (Table 111, P241 MS).

INR monitoring costs

In clinical practice AF patients receiving antithrombotic treatment are referred to anticoagulation clinics in order to control their INR levels. The cost effectiveness analysis conducted by the manufacturer only considered the monitoring costs for warfarin. Dabigatran treatment was appropriately considered not to require any monitoring.

Neither PbR tariffs nor NHS reference costs existed for this service and therefore a systematic review was conducted. A total of 17 records were identified (Table 101, P220 of MS), however only one was considered appropriate for the economic evaluation: the NICE costing report for year 2006/2007.[37] This costing report accompanied the NICE Clinical Guidance 36 for AF. The annual costs for anticoagulation treatment were estimated at £382.9 per patient. This was a weighted average that assumes that 25% of services were delivered in secondary care and 75% in primary care, assuming that the average patient requires 20 clinic appointments per year. Table 30 summarises the calculation of anticoagulation unit cost carried out in the NICE costing report.[37]This cost was inflated to 2010 prices in the economic model to (£414.9). In the univariate sensitivity analysis (Table 148, p.280 of MS), the INR monitoring costs were varied ±25%.

Table 30- calculation of anticoagulation unit cost (adapted from NICE costing report)[37]

	Cost element	Unit costs (2004/2005)	Cost per year (2004/05)
Primary Care Anticoagulation cost per patient = £322/year	Reagent costs	£3/test	£6,000
	Nursing staff	£20.1/hour	£10,059
	Administration staff	£5/hour	£2,500
	Overheads	£8,969/year	£8,969
	Stationary	£2/clinic	£333
	Hospital accreditation	£150/year	£150
	National Quality Control Scheme	£150/year	£150
	Software maintenance and support	£147/year	£147
	Warfarin costs 4.5mg/day	£38.9/year	£3,888
Secondary cost Cost per patient = 565.8/year	New appointment	£35	£35 (1 visit)
	Follow-up appointment	£28	£532 (19 visits)
Total cost (2004/05)	75% primary care	25% secondary care	£382.9

Assumptions of primary care calculations: (a) 4 tests per hour; (b) 20 tests per patient per year; (c) 3 hours per clinic

Unit costs of events based on PbR tariff

Unit costs for TIA, acute MI, and ECH (gastro-intestinal and non-gastro-intestinal) were calculated based on PbR tariffs and weighted by activity (Table 100, P217 of the MS). The average unit cost per event was the weighted average between costs of admission and costs of excess bed days. A unit cost for SE was not available from the PbR tariff. The systematic review also failed to produce a unit cost for this event. Hence, data from the RE-LY study was used to define the costs involved with SE. The cost of non-fatal SE was based on the cost of computer tomography scan and the cost of lower limb and upper limb arterial surgery. The cost of fatal SE was based on the cost of an autopsy.

Unit costs of events based on OXVASC study

The manufacturer did not use the PbR tariffs for calculating the cost of stroke. Four reasons were stated to justify this decision. First, codes for these events referred to a range of outcomes not always appropriate for the purpose of the assessment. Second, the cost categories of stroke failed to correspond with the mRs scale used in the model. Third, stroke in AF patients may be more expensive than in non-AF ones; the PbR tariff did not distinguish between the two. Hence the true cost of stroke may be underestimated. Fourth, long term rehabilitation costs were not included in these tariffs. The average cost of ischaemic stroke was estimated from the OXVASC study by severity of disability as defined by mRs (Table 104, P233 of the MS):

- Fatal - £3,036
- Independent - £3,382

- Moderate Disability - £17,694
- Totally Dependent - £24,214

The sample sizes for estimating the costs of haemorrhagic stroke and ICH were considered to be too low to enable appropriate analysis (Table 105, P234 of MS). As the systematic review failed to provide the required data, the manufacturer assumed that the costs for haemorrhagic stroke and ICH were the same as for ischaemic stroke. Follow-up post-stroke costs were also estimated from the OXVASC study and included in the model. These were considered the acute costs of a stroke event and are added to the disability costs above in the first cycle following the event.

Other costs

Dyspepsia was the only adverse event cost considered for Dabigatran in the MS. Treatment for this event was considered in the model at a price of £3.31 per patient and was applied in the first cycle. Besides the costs of the event no additional costs were assumed for discontinuation or for treatment switch. Discontinuation without an event was assumed to accrue one GP visit and was valued at £36.51. Table 31 summarises the costs used in the base-case analysis.

5.1.7 Discounting

The manufacturer's model applied a discount rate of 3.5% per annum to expected costs and health effects, in line with the NICE reference case.

5.1.8 Sensitivity analyses

Structural, univariate and probabilistic sensitivity analysis (PSA) were performed by the manufacturer.

Structural sensitivity analysis

The manufacturer presented two economic models: a single dose and sequence dose model. In the sequence dose model, the patient cohort was divided by age and modelled separately. Patients aged under 80 years old were started with dabigatran 150 mg, and once 80 they were switched to dabigatran 110 mg. Conversely, patients 80 years or older at baseline were initiated and kept on dabigatran 110 mg. Therefore, the sequence dose model resulted in two

sets of outputs: sequence model < 80 and sequence model ≥80. In the single dose model, the intervention was independent of age. Consequently, starting the patient cohort on a specific dose of dabigatran implies that the alternative dose of dabigatran will not be considered.

Table 31: Summary of all costs included in the base-case analysis (adapted from economic model)

Cost category	Item	Cost (£)	SE[1]	Source
Drug	Aspirin	0.09/day	-	MIMS 2010[38]
	Aspirin + clopidogrel	0.26/day	-	
	Warfarin	0.04/day	-	
	Dabigatran 110 mg bid	2.52/day	-	MS
	Dabigatran 150 mg bid	2.52/day	-	
Warfarin monitoring	INR monitoring per patient (20 visits/ year)	414.90/year	-	NICE costing report[37]
Clinical Events	Fatal IS	[redacted]	[redacted]	UK Cost of Stroke study based on OXVASC
	IS, Independent			
	IS, Moderate Disability			
	IS, Totally Dependent			
	SE, Fatal	2,373.00	475.00	NHS reference costs 2008/09[39]
	SE, Non-fatal	400.00	80.00	
	TIA	[redacted]	[redacted]	UK Cost of Stroke study based on OXVASC
	ICH, Fatal			
	ICH, Independent			
	ICH, Moderate Disability			
	ICH, Totally Dependent			
	HS, Fatal			
	HS, Independent			
	HS, Moderate Disability			
	HS, Totally Dependent			
	ECH, Fatal	1,852.00	370.00	NHS reference costs 2008/09[39]
	ECH, Non-fatal, Non-GI	2,109.00	422.00	
	ECH, Non-fatal, GI	1,594.00	319.00	
	Minor Bleed	84.00	17.00	NICE Costing report[37]
	Acute MI, Fatal	2,956.00	591.00	NHS reference costs 2008/09[39]
	Acute MI, Non-fatal	2,956.00	591.00	
	Discontinuation of treatment with event	0.00	-	Assumption
	Treatment switch	0.00	-	Assumption
	Death from unrelated causes	0.00	-	Assumption
Follow-up Costs	Independent without stroke history	0.00	0.00	Assumption
	Independent with stroke history	[redacted]	[redacted]	UK Cost of Stroke study based on OXVASC
	Moderate			
	Dependent			
Other Costs	Dyspepsia treatment (Dabigatran only – first 3 months of treatment)	3.31	-	MIMS 2010[38]
	Discontinuation without event, Aspirin	36.51	-	Curtis, 2009[36]
	Discontinuation without event, Aspirin+Clopidogrel	36.51	-	
	Discontinuation without event-Dabigatran	36.51	-	
	Discontinuation without event-Warfarin	36.51	-	

bid: twice daily; ECH: Extracranial haemorrhage; HS: Haemorrhagic stroke; ICH: Intracranial haemorrhage; IS: Ischaemic stroke; INR: International normalised ratio; MI: Myocardial infarction; TIA: Transient ischaemic attack

Three warfarin scenarios were presented: trial-like warfarin, real-world warfarin and real-world prescription behaviour warfarin (Table 5.32). The scenarios differ on the proportion of patients under, within and over INR target range. Data for trial-like warfarin was extracted from the RE-LY trial. Data for real-world warfarin was based on other published evidence extracted from Kalra (2000) and adjusted using either data from Walker (2008) for the weighted warfarin approach or data from Jones (2005) for the time out of INR approach.[25, 40,

[41] Data for real-world prescription behaviour was extracted from Dewilde (2006) and applied to the real-world data.[41]

Table 32: Warfarin scenarios considered in the model (from economic model in MS)

	Proportion of patients by INR interval		
	RE-LY Warfarin	**Real-world Warfarin**	**Real-world prescription behaviour**
INR <2	22%	26%	13%
2< INR <3	64%	61%	30%
INR >3	13%	13%	6%
% aspirin	0%	0%	35%
% untreated	0%	0%	16%

The model simulates the lifetime of a patient cohort from the RE-LY trial. The RE-LY had a maximum duration of follow-up of two years. The structural sensitivity analysis thus explores the cost-effectiveness of dabigatran over alternative time periods.

The RE-LY trial provides the majority of efficacy data for the economic model. The model was tested using the data from the RE-LY trial as part of an MTC carried out in SAS. Discount rates were varied from 0% to 6% for both health and cost outcomes. Table 5.33 summarises the scenarios explored in the structural sensitivity analysis.

Table 33: Structural sensitivity analysis (adapted from Table 114 P246 and Table 148 P280 in MS)

	Alternative scenario	**ICER or ICER range (min-max)** [1]
Base-case		**£6,264**
Single dose model	Sequence dose model < 80	£7,314
	Sequence dose model > 80	£7,873 (dabigatran 110 mg)
Trial-like warfarin	Real-world adjusted-dose warfarin (Weighted Warfarin Approach)	£5,872
	Real-world adjusted-dose warfarin (Time out of INR Approach)	£5,327
	Real -world prescribing behaviour	£3,925
INR cost	+/- 25%	£2,997 - £9,531
Time horizon – life-time	2, 10 and 15 years	£75,601 - £8,111
RE-LY clinical data	MTC (SAS) clinical data	£6,874
Vary discount rate for costs and health outcomes	0%, 6%	£4,137 - £8,146

[1] The ICER refers to the base-case of dabigatran 150 mg bid as first-line treatment compared to warfarin. [a] ICERs for these scenarios were not included in the submissions results.
ICER: Incremental cost effectiveness ratio; INR: International normalised ratio; Min: Minimum; Max: Maximum

Generally the model was robust to these alternative scenarios. However, the cost-effectiveness of dabigatran 150 mg is highly sensitive to the time horizon simulated. A time horizon of 2 years results in an ICER of dabigatran 150 mg compared to warfarin of £75,601 per additional QALY.

A similar sensitivity analysis was undertaken for dabigatran 110 mg (Table 148, P280 of MS). The base-case ICER of dabigatran 110 mg compared to warfarin is £18,691 per additional QALY. The ICER of dabigatran 110 mg compared to warfarin increased when (1) INR monitoring costs were decreased by 25%, (2) time horizon was shortened (£108,736 per additional QALY for a time horizon of 2 years), and (3) using the MTC data. The ICER decreased when (1) alternative warfarin control scenarios were used, and (2) INR monitoring costs were increased.

Univariate sensitivity analysis

The parameters tested in the univariate sensitivity analysis are summarised in Table 34 and reported in full in the MS (P246 to 248). The manufacturer tested different patient cohorts. Age at model entry was varied by +/- five years. The proportion of males was varied from 0% to 100%. The impact of baseline risk of ischaemic stroke was explored by $CHADS_2$ score and stroke history.

Table 34: Univariate sensitivity analysis for dabigatran 150 mg bid single dose model (adapted from Tables 115, 116 and 117 from MS) – Base-case ICER= £6,264/QALY

	Analysis	ICER or ICER range (min-max) [1]
Base-case		**£6,264**
Characteristics of patient cohort	Varying age at baseline +/- 5 years	£4,852-£8,281
	Varying proportion of males 0 - 100%	£5,375-6,760
	Changing the proportion of patients on each $CHADS_2$ score to 100%	£5,125-£6,770
	Changing stroke history at baseline to 0% and to 100% for $CHADS_2$ score 2, 3, and 4.	£5,740-£7,693
Utilities	Changing utilities set 1, 2 and 3 (as per Table 97 P211 of MS)	£6,593-£6,335
Costs	Varying the costs of ICH, HS, IS and follow-up by +/- 50%	£4,853-£7,675
	Changing the costs of SE, minor bleed and acute MI by +/- 100%	£6,075-£6,453
	Changing the cost of dyspepsia treatment	£6,662
	[redacted]	[redacted]
Relative risks of events	Changing the relative risk of IS, SE, TIA, ICH, HS, ECH and acute MI of DBG to its upper and lower CI	£4,250-£10,234
	Changing the relative risk of HS for aspirin, A+C and NT, and the relative risk of ICH for NT +/- 20%	£6,324
	Varying % of ECH which is gastro-intestinal 0-100%	£6,246-£6,303
	Changing mortality risk following SE, acute MI and ECH to zero.	£6,220
Discontinuation and switch	Changing discontinuation following ECG 0-100%	£6,114-£6,418
	Varying treatment switch to 2nd line +/- 10%	£6,2778-£6,239
	Changing withdrawal to 0.	£5,582
Post-event disability	Changing to -5% to mild/moderate and +5% to totally dependent/dead.	£5,668

bid: twice daily; DBG: dabigatran; MI: myocardial infarction; HS: haemorrhagic stroke; ICH: intra-cranial bleed; IS: ischaemic stroke; TIA: transient ischaemic attack; ECH: extra-cranial haemorrhage; SE: systemic embolism; CI: confidence interval; A+C: aspirin plus clopidogrel; NT: no treatment.
1 – ICER of dabigatran 150 mg bid in comparison to warfarin.

The utility parameters were tested as sets. In set 1, three changes were tested simultaneously: baseline utility, disutility associated with dabigatran treatment, and disutility associated with warfarin treatment. Baseline utility was changed from 0.81 to 0.751 (sourced from Berg *et al.*, 2010).[42] Disutility associated with one year of warfarin treatment was changed from zero

to 0.013, as per Gage *et al.* (1996).[29]Disutility associated with dabigatran treatment was obtained from the RE-LY QoL sub-study. [redacted]

Costs of the major events were varied by 50%, namely ischaemic stroke, ICH and haemorrhagic stroke. The costs of SE, minor bleed and SMI were varied by 100%. The costs of ECH were not tested in the univariate sensitivity analysis.

The univariate sensitivity analysis tested the effect of changing the relative risk of the various clinical events to their upper and lower confidence interval. This was carried out separately for each clinical event.

The effect of discontinuation rates and therapy switch was tested by setting discontinuation due to ECH to 0% and to 100%, varying switch to second-line treatment by 10%, and setting withdrawal to zero.

The ICER of dabigatran 150 mg compared to warfarin appears to be robust to the parameters and ranges tested by the manufacturer. The base-case ICER result was £6,264 per QALY, whereas the results from the univariate sensitivity analysis ranged from dominant to a maximum of £10,234 per QALY. The value of £4,852 per QALY was obtained when age of the patient cohort was set at 66 years old, rather than 71 years old as in the base-case.

A similar univariate sensitivity analysis was undertaken for dabigatran 110 mg. The cost-effectiveness of dabigatran 110 mg in relation to warfarin was highly sensitive to high $CHADS_2$ scores, the acquisition cost of dabigatran, risk of ischaemic stroke and risk of ICH (Table 146, P273 of MS).

The ICER of dabigatran 110 mg in comparison to warfarin increased from £18,691 to £61,552 per QALY for a patient cohort with $CHADS_2$=5. If $CHADS_2$ score is set to 4 for all the cohort, the ICER of dabigatran 110 mg in comparison to warfarin increases to £37,652 per QALY. These results suggest that dabigatran 110 mg may not be cost effective for patients at high risk of stroke. Such interpretation is supported by the results obtained when setting the relative risk of ischaemic stroke for patients treated with dabigatran 110 mg equal

to its 95% upper confidence limit. In this case, the ICER for dabigatran 110 mg in comparison to warfarin increased to £47,352 per QALY. Setting the relative risk of intracranial haemorrhage equal to its 95% upper confidence limit resulted in an ICER for dabigatran 110 mg in comparison to warfarin of £28,259 per QALY from £18,691 per QALY in the base-case.

Probabilistic sensitivity analysis (PSA)

PSA was undertaken for an extensive list of parameters (for full list and associated distributions see Table 118 to Table 128, P250-255 of MS). The sources of uncertainty considered in the PSA were (i) the baseline risk and relative risk of the various clinical events, (ii) utilities, and (iii) the acute and long-term costs due to the occurrence of clinical events.

The manufacturer does not present a full simultaneous probabilistic analysis of the different interventions. Pairwise comparisons are presented instead, in which dabigatran 110 mg or 150 mg are compared to a single alternative, namely warfarin, aspirin or aspirin plus clopidogrel. Cost-effectiveness acceptability curves (CEACs) are presented for each intervention compared with each alternative.

Table 5.35 summarises the results of the PSA performed by the manufacturer. The results suggest that dabigatran 150 mg is likely to be cost-effective. The probability that dabigatran 150 mg is cost-effective compared to warfarin is 93% or 98% for willingness to pay threshold of £20,000 per QALY and £30,000 per QALY, respectively. The probability that dabigatran 110 mg is cost-effective in comparison to warfarin is lower, varying between 67% and 84% depending on willingness to pay.

Table 35: Probability of cost-effectiveness at different willingness to pay thresholds (adapted from Table 147, P275 of MS)

Intervention	Comparator	£20,000 per QALY	£30,000 per QALY
Dabigatran 150 mg	Aspirin	100%	100%
	Warfarin	93%	98%
	Aspirin+Clopidogrel	100%	100%
Dabigatran 110 mg	Aspirin	97%	99%
	Warfarin	67%	84%
	Aspirin+Clopidogrel	98%	100%

5.1.9 Model validation

According to the MS, the economic model was validated in three distinct levels:

- Revision and approval by key opinion leaders
- Validation of the mathematical relations and numerical inputs used by a modeller not involved in the construction of the model
- Substantiation of face validity.

Face validity was verified resorting to two model outputs: life expectancy and ischaemic stroke rates. Life expectancy of the base-case cohort was compared with the estimated for the UK population at 71 years old and with the figure reported by Currie (2006).[43]The model predicts life expectancies around nine to ten years, higher than Currie's (2006) estimates but lower than the UK population life expectancy, even taking into account the higher mortality rate for ischaemic stroke. Ischaemic stroke rates predicted in the model were considered to be consistent with the results reported by Rietbrook (2008) for an AF population based on a review of the UK General Practice Research Database.[44]Hence, the manufacturer concludes that these results provide some assurance for the model validity.

The ERG was unable to validate all aspects of the manufacturer's model. The results of the model were run using a visual basic macro. In calculating the results the model ran a Markov trace for each $CHADS_2$ score and by stroke history, but then cleared the results of each trace before calculating the next. This made it difficult to see how changes in the model affected different patient groups. It also made the model very slow to run. To calculate a single PSA result required 10 hours computation time.

5.1.10 Results included in the manufacturer's submission

The manufacturer presented the following results:

- Comparison of clinical outcomes between RE-LY trial data and model results (Table 129, P256 of MS)
- Life years, disaggregated costs and QALYs obtained in each model (Tables 130 to 132 P261-263 of MS)
- Pairwise incremental analysis for dabigatran 110 mg and dabigatran 150 mg in each relevant model (Tables 137 to 144, P269-271).

The manufacturer concluded that dabigatran 150 mg and dabigatran 110 mg are cost-effective alternatives to warfarin and aspirin.

Results: Costs and health outcomes

Table 36 summarises the total costs, life years and QALYs obtained for each intervention, for the single dose and sequence dose model. Interventions have been sorted in ascending order of costs to facilitate interpretation.

Aspirin is the intervention associated with lowest costs in the single dose model and in the sequence dose model under 80. In these models, warfarin has higher costs but also greater health benefits, both in terms of life years and QALYs gained. In the sequence model over 80, warfarin is the least costly intervention. The combination aspirin plus clopidogrel results not only in higher costs but also less health benefits compared to aspirin, for both the single dose and sequence dose models. Dabigatran is associated with both increased costs and health benefits compared to warfarin and aspirin. Dabigatran 110 mg results in higher costs than dabigatran 150 mg, yet is associated with lower health benefits.

Table 36: Total costs, life years and QALYs for each intervention (adapted from Tables 130-132, P261-263 of the MS)

Model	Intervention	Costs	Life Years	QALYs
Single dose	Aspirin	£15,080	9.40	7.08
	Warfarin	£15,583	9.55	7.28
	Aspirin plus clopidogrel	£16,070	9.40	7.06
	Dabigatran 150 mg	£16,923	9.74	7.50
	Dabigatran 110 mg	£18,835	9.71	7.48
Sequence dose < 80	Aspirin	£16,732	10.09	7.59
	Warfarin	£17,083	10.26	7.82
	Aspirin plus clopidogrel	£17,574	10.08	7.56
	Dabigatran 150 mg → 110 mg	£18,856	10.48	8.06
Sequence dose > 80	Warfarin	£9,098	5.27	4.01
	Aspirin	£9,227	5.23	3.92
	Aspirin plus clopidogrel	£9,479	5.19	3.89
	Dabigatran 110 mg	£9,929	5.38	4.11

Note: interventions in ascending order of costs.

Base-case incremental analysis

The original MS does not provide a full incremental analysis of all treatments under evaluation. The original MS presents incremental analysis for dabigatran 150 mg and 110 mg separately. The ERG requested a full incremental analysis of all treatments under evaluation. The manufacturer provided an analysis for dabigatran 150 mg, dabigatran 110 mg and the sequence dose.

Table 37: Incremental analysis for all treatments (adapted from Table 4, P10 of PfC)

Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Aspirin	£15,080	7.082	Baseline		
Warfarin	£15,583	7.283	£503	0.201	£2,502
Aspirin plus clopidogrel	£16,070	7.061	£487	-0.222	Dominated
Dabigatran 150 mg	£16,923	7.497	£1,340	0.214	£6,261
Sequence model < 80	£17,767	7.449	£844	-0.048	Dominated
Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated

Note: Including the sequence model under 80 in this analysis involved setting the initial conditions in the sequence model to those in the single-dose model (i.e. age at model entry, % male, $CHADS_2$ and previous stroke distribution).

Aspirin is associated with the lowest costs, hence it is considered to be the baseline. Warfarin is associated with greater costs and health benefits than aspirin. The ICER for warfarin compared to aspirin is £2,502 per QALY (Table 37). The combination of aspirin plus clopidogrel is associated with higher costs and less health benefits than warfarin. Therefore this intervention is dominated by warfarin. Dabigatran 150 mg results in higher costs but also greater health benefits than warfarin. The ICER of dabigatran 150 mg compared to warfarin is £6,261 per QALY. Dabigatran 110 mg is associated with greater costs and lower health benefits than dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg. The manufacturer considers that both dabigatran 110 mg and the sequence model under 80 are cost-effective compared to the treatments available in current practice, because both are associated with increased health benefits and costs compared to warfarin.

In the original manufacturer submission, PSA base-case results were presented for dabigatran 150 mg, dabigatran 110 mg and the sequence dose model. Table 38 summarises the results. The PSA base-case analysis takes into account the uncertainty surrounding the input parameters. The inclusion of uncertainty into the model results in similar conclusions to the deterministic analysis.

Table 38: Incremental analysis for the base-case PSA of the single model (adapted from Tables 137-138, P269 MS)

Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Aspirin	£15,279	7.029	Baseline		
Aspirin plus clopidogrel	£15,315	7.014	£36	-0.015	Dominated
Warfarin	£15,566	7.267	£287	0.253	£1,206
Dabigatran 150 mg	£17,092	7.459	£1,526	0.192	£7,940
Dabigatran 110 mg	£18,210	7.434	£1,118	-0.025	Dominated

The probabilistic ICER for warfarin is lower than in the deterministic analysis, reducing from £2,502 to £1,206 per QALY. However, the probabilistic ICER for dabigatran 150 mg is higher than in the deterministic analysis, increasing from £6,261 to £7,940 per QALY. As in the deterministic analysis, dabigatran 110 mg results in higher costs and less health benefits

than dabigatran 150 mg. However, dabigatran 110 mg is associated with more health benefits than warfarin. These results supported the manufacturer's conclusion that dabigatran 150 mg and dabigatran 110 mg are cost-effective alternatives to warfarin, aspirin and to the combination aspirin plus clopidogrel.

5.2 Critique of approach used

The ERG compared the MS to the NICE reference case using the NICE reference case checklist (Table 39). In addition, the methods used by the manufacturer were verified using a detailed checklist for quality assessment.[24]

Table 39: NICE reference case checklist

Attribute	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Defining the decision problem	The scope developed by the institute	Yes	
Comparator(s)	Alternative therapies including those routinely used in NHS	Yes	The main comparator is dose-adjusted warfarin. Secondary analysis compares DBG with both aspirin monotherapy and aspirin plus clopidogrel. Clopidogrel is not licensed for the indication described in the NICE Scope. Clinical experts contacted by the ERG confirmed that the MS included all the relevant comparators with the exception of a device only used for a minority of patients.
Perspective -costs	NHS and PSS	Yes	
Perspective - benefits	All health effects on individuals	Yes	
Type of economic evaluation	Cost-effectiveness analysis	Yes	Markov cohort simulation model.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Lifetime.
Synthesis of evidence on outcomes	Based on systematic review	Yes	Systematic reviews conducted for economic evaluations on the decision problem, relevant costs and health benefits.
Measure of health effects	QALYs	Yes	
Source of data for measurement of HRQoL	Reported directly by patients and/or carers (EQ-5D?)	Yes/No	Baseline HRQoL data and acute utility decrements were obtained EQ-5D. HRQoL associated with different disability status was obtained via TTO.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes/No	Baseline HRQoL data valued by EQ-5D. Utility decrements from published studies based on valuation from the US population. HRQoL associated with different disability status valued by a sample of stroke patients using TTO.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis		Yes	Structural, univariate and probabilistic sensitivity analysis (PSA) were performed.

DBG: Dabigatran; HRQoL: Health-related quality of life; PSS: Personal social services; QALYs: Quality adjusted life years; TTO: Time-trade off

5.2.1 Literature search

In the literature search undertaken by the ERG we found one cost-effectiveness study comparing warfarin to dabigatran for preventing stroke in AF patients which was published after the MS had been sent to the ERG. Below we summarise the methods and results and compare to the MS.[2]

Freeman *et al.* recently published 'Cost-Effectiveness of Dabigatran Compared with Warfarin for Stroke Prevention in Atrial Fibrillation'.[2] This cost-utility analysis from the US perspective found that dabigatran 150 mg was more costly compared to warfarin ($168,398 vs. $143,193) and more effective (10.84 vs. 10.28 QALYs). The ICER of dabigatran 150 mg compared to warfarin was reported to be $45,372 per QALY.

Several differences between this study and the MS explain the differences in results. The most influential difference between the analyses was the acquisition cost of dabigatran. Freeman *et al*. calculate the price of dabigatran 150 mg to be £6.30 per day. The MS uses £2.52 per day. The difference in price makes dabigatran seem less cost-effective than if the published analysis had the same price.

In the published analysis the frequency of INR monitoring was estimated to by 14 visits per year. In the manufacturer's model they assume there are 20 visits per year. This difference also results in a more conservative estimate of cost-effectiveness by the authors.

Freeman *et al*. report the cost-effectiveness of treating patients 65 years or older with a $CHADS_2$ score of 1 or equivalent. This reflects the less severe population in AF with lower risk of ischaemic stroke events. The manufacturer analysed a population of combined severity where severe patients with a higher baseline risk of ischaemic stroke events influence the result toward being more cost-effective.

Some of the other differences in the published study are optimistic towards dabigatran. The published model used a 2 week cycle length compared to a 3 month cycle length modelled by the manufacturer. We would expect the shorter cycle length to increase the number of events that may occur and improve the cost-effectiveness of dabigatran since there are more events for dabigatran to prevent.

The authors assume dabigatran treatment is associated with a higher utility than warfarin. This does not appear to be supported by the trial data which reports a lower utility for dabigatran than warfarin at 3 months and at one year.

Treatment effects are not directly comparable since the published analysis used only the RE-LY trial while the MS used the results of a MTC. However, the treatment effects seem to be relatively close although hemorrhagic strokes were considered differently and could not be compared. The published model also includes recurrent or combined events, which are not included in the MS. However, there is not enough detail in the manuscript to understand how this was undertaken or make an assessment of the direction of effect.

Given the higher acquisition cost, the lower costs of monitoring for warfarin and the less severe population modelled by Freeman *et al*. it is not surprising that dabigatran 150 mg appears less cost-effective in the published analysis although they also appear more optimistic about the treatment-related quality of life of dabigatran.

5.2.2 Natural history

A Markov model was employed to model the natural course of the disease. The ERG considers the Markov model to be the appropriate choice. AF sufferers experience a chronic condition which increases their risk from several clinical events, such as stroke. The manufacturer's model captures the long-term consequences of the clinical event and the acute consequences of the event itself.

The natural course of AF is modelled according to the disability states which may be experienced by patients suffering from this condition. Each disability state is associated with specific utilities and costs.

The model includes most of the relevant clinical events in AF. PE, however, was not included in the model. The manufacturer justified this decision in part by stating that PE was a rare event that occurred at similar rates across the treatment arms. SE, however, was included in the model whilst presenting similar rates as PE (Table 40). Further justification given for the exclusion of PE from the model were: 1. that PE had similar costs and outcomes to SE, and variation in rates of SE showed little impact of on overall cost-effectiveness, and 2. stroke and SE are arterial events and PE is a venous event. The exclusion of PE from the model is

potentially an optimistic approach, in favour of dabigatran by the manufacturer. It is expected the addition of PE to the model will increase the ICER comparing dabigatran to warfarin as the rates of PE are higher (on average) for dabigatran.

Table 40: PE and SE rates from RE-LY (P82 and P83 MS)

Outcome	Dabigatran 110 mg		Dabigatran 150 mg		Warfarin	
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate
PE	14	0.12%	18	0.15%	12	0.10%
SE	15	0.13%	13	0.11%	21	0.18%

In the model only ischaemic stroke, ICH and haemorrhagic stroke have been associated with long-term consequences. The remaining clinical events were modelled as acute events with no effect to the patient beyond the three month cycle in which it occurred.

The manufacturer states that they did not include the long-term effect of SE because the model structure was designed to capture only clinical events occurring in the brain. Expert clinical opinion informed the ERG that SE can be associated with long term consequences. For example, SE can result in leg amputation, and therefore a change in long term disability status. However, in the case of SE, this assumption is expected to be conservative due to its lower rate (on average) in dabigatran patients.

The ERG requested clarification from the manufacturer on their modelling of acute MI as an acute event. The manufacturer justified this assumption by arguing that 1) clinical expert opinion suggests that the majority of patients who suffer acute MI recover fully within three months; 2) acute MI has limited impact on HRQoL using Schweikert *et al.* (2009)[45]; and 3) similar rates of acute MI between treatment arms in the RE-LY trial.

Expert clinical opinion informed the ERG that acute MI is likely to have long term impact. The ERGs interpretation of Schweikert *et al.* is that acute MI is associated with significant reductions in HRQoL compared with the general population. Furthermore, the hazard ratios for acute MI for dabigatran 150 mg and dabigatran 110 mg in relation to warfarin are 1.27 (0.94-1.71) and 1.29 (0.96 – 1.75), respectively. Although these results are not statistically significant, the hazard ratios imply higher absolute acute MI rates (on average) with dabigatran. Therefore, failing to include the ongoing costs and disutilities associated with MI may result in bias favouring dabigatran.

The Markov cycle length in the model is three months and only one event per cycle is permitted. Events, such as ischaemic stroke, can occur more often than once every three months. Therefore, the model could have been designed to either simulate more than one event per cycle, or to have a shorter cycle length. However, this assumption is considered to be conservative by the ERG.

The patient cohort simulated in the economic model reflects the patients participating in the RE-LY trial, stratified according to $CHADS_2$ score and stroke history. The RE-LY trial was a multi-centre international clinical trial. Therefore, the characteristics of the patient cohort may not necessarily reflect the characteristics of the UK patients suffering from AF. For example, the proportion of males in the patient cohort is 63.6%, whereas in the UK this proportion has been reported to be 55.1% (Gallagher *et al*. 2008).[46] Furthermore, the average age of the patient cohort in the model is 71 years old, whereas data from Gallagher *et al.* suggests that the average age of the AF patient in the UK is significantly higher.

Using the RE-LY trial for the source of the patient cohort is a reasonable choice given that the results of the trial pertain to this population. However, an alternative scenario that would address the potential generalisability of this to a real world UK clinical setting would have been to simulate a more representative UK patient cohort, perhaps using the results of the study by Gallagher *et al*. This issue is explored further in Section 6.

The economic model simulates each $CHADS_2$ score sub-group separately, and calculates results for each sub-group. The final results are an average of the results for each $CHADS_2$ score sub-group, weighted by $CHADS_2$ distribution. $CHADS_2$ score determines the risk of stroke of the patients simulated by the economic model. Age and stroke history affect the $CHADS_2$ score and therefore the risk of stroke. Stroke history is a binary variable. A patient who has suffered several strokes is considered to be at the same risk of a further stroke as a patient who has only suffered one stroke. This simplification may be reasonable considering the complexity of the disease.

The programming of the model made it difficult to assess the structure of the model. The Markov traces for each $CHADS_2$ score sub-group are cleared after running the simulation. This made it difficult to assess parameter changes in each sub-group. In addition, the model is very slow to run. The PSA, for example, takes 10 hours.

Patients suffering from AF constitute a heterogeneous population, which is reflected by the distribution of $CHADS_2$ scores. The risk for ischaemic stroke of an AF patient with a $CHADS_2$ score of zero is much lower than the risk of an AF patient with $CHADS_2$ score of 5 or 6. Therefore it is expected that dabigatran will have differing cost-effectiveness across these groups. Furthermore, since this information is known to the prescriber, treatment selection can be based on $CHADS_2$ score. Hence it is appropriate to evaluate the cost-effectiveness of dabigatran in each of the $CHADS_2$ scores sub-populations. The MS considers the AF patient population to be heterogeneous, but assumes that all patients will be treated the same. Combining the treatment decision across heterogeneous groups may be an over simplification of the decision problem and does not allow the potential impact of clinical heterogeneity on cost-effectiveness to be considered. This issue is explored further in Section 6 to determine whether there are patient sub-groups for which treatment with dabigatran is more or less cost-effective.

5.2.3 Comparators

The ERG agrees with the comparators considered in the economic model. Expert clinical opinion confirmed that the current first-line anticoagulation treatment for AF is warfarin. In case of contra-indication to warfarin, aspirin is the treatment of choice. Aspirin plus clopidogrel is an intervention seen rarely in clinical practice in this indication, yet it is sometimes used and hence its inclusion is appropriate.

Although all of the important treatments were included as comparators the full set of relevant sequences of treatment (i.e. as part of 1st or 2nd line treatment decisions) was not fully investigated by the manufacturer. The ERG considers that the manufacturer should have also explored the full range of potentially relevant sequences of treatments. This issue is discussed more completely in the treatment sequence section below.

5.2.4 Treatment effectiveness within the submission (includes baseline event rates and adverse events)

Treatment Sequence

The economic model allows the evaluation of a restricted number of treatment sequences. The model structurally assumes that once a patient has been prescribed dabigatran, the second-line treatment will be aspirin plus clopidogrel, aspirin or 'no treatment'. Once a patient

stops treatment on one of the aspirin regimens, the only alternative is to have 'no treatment'. The model assumes that warfarin and dabigatran are mutually exclusive alternatives. This means that the full treatment sequence for AF patients cannot be tested. If dabigatran is approved for first-line treatment of non-valvular AF patients, our clinical advisors suggested that warfarin may continue to be used by those who are intolerant to dabigatran. This suggests the need to include warfarin in the treatment sequence when dabigatran is first-line. This is important when considering which costs dabigatran could off-set. If warfarin is still used then the total costs of warfarin clinics will not be completely off-set. This is discussed further in the cost section.

A more flexible treatment sequence would also allow dabigatran to be evaluated as second-line treatment for those who fail on warfarin compared to using dabigatran as first-line treatment. This issue is further discussed in the following section on INR control. A request was made within the points for clarification for the manufacturer to provide a revised model which allowed the user to set any treatment sequence. The manufacturer found the request impractical given the complexity of the model and the time constraints. The manufacturer argued that discontinuation from one anticoagulant is associated with contra-indication to any anticoagulant. Therefore, if a patient discontinues dabigatran, warfarin is contra-indicated by assumption. In practice, discontinuation from anticoagulant treatment can be based on either a clinical reason, for example, due to major haemorrhage in which case the assumption is correct, or based on patient preference or other adverse events. Consequently, a patient may be switched from dabigatran to warfarin or vice versa. However, the ERG are unable to evaluate the potential cost-effectiveness implications of incorporating this sequence given the restrictions related to the model structure.

INR control

The effectiveness, costs and use of warfarin are highly dependent on INR control. Maintaining INR within target range has been shown to significantly reduce the risk of ischaemic events.[47]Therefore, the manufacturer took the correct approach of including the proportion of patients per INR interval as one of the model parameters. The manufacturer's base-case scenario assumes INR control from the RE-LY trial.

As discussed in the previous section, the model structure does not allow all treatment sequences to be tested. However it is important to determine whether dabigatran is more cost-

effective as a first-line treatment or for those who fail on warfarin. The most common reason for failure with warfarin is lack of INR control. As a second best test of comparing treatment sequences the ERG considered the cost-effectiveness of dabigatran in patients with different levels of INR. This approach also addresses issues of clinical heterogeneity in the AF population due to INR control and the potential implications for cost-effectiveness. This analysis can investigate whether dabigatran is cost-effective for patients regardless of their INR response or whether the cost-effectiveness of dabigatran is potentially dependent upon the degree of control achieved for INR.

Patients able to consistently maintain INR within target may expect greater health benefits than patients whose INR is outside target range. At the same time, patients who are able to consistently maintain INR within target range also require less frequent monitoring. Consequently, patients with controlled INR have better outcomes and lower costs than patients with uncontrolled INR. Heterogeneity in INR control was not considered in the MS although information from the Center for Drug Evaluation and Research report described above (Section 4.3.2.1) suggests there is no statistically significant benefit to dabigatran over warfarin in patients above median control of >67% TTR. Additional exploration is needed to evaluate the cost-effectiveness of dabigatran stratified by INR range. The ERG undertook this additional analysis in Section 6.

Risk for clinical events and outcomes

The warfarin arm of the RE-LY trial provides the baseline risk for the various clinical events. Relative risks for each intervention are calculated from different sources and applied to the baseline risk for the each clinical event.

The manufacturer obtained values for risks of disability and mortality following clinical events from different sources. The reasons behind sourcing some values from the literature, rather than from the RE-LY trial, remain unclear. Disability and mortality risk for patients treated with warfarin, aspirin and 'no treatment' following ischaemic stroke were obtained from the study by Hylek *et al.* (2003).[27] Relative risks of disability and mortality for dabigatran in relation to warfarin were obtained from the RE-LY trial. No justification was given for using Hylek *et al.* (2003) as the baseline risk rather than the RE-LY trial as was done for event risks. No justification was provided for the assumption that the combination aspirin plus clopidogrel presents the same disability and mortality risk as warfarin.

No statistically significant difference between warfarin and dabigatran for mortality and disability post-ischaemic stroke was observed in the RE-LY trial (Table 41).

Table 41: Disability after stroke per treatment (RR (95% CI); adapted from Table 77, P165 MS)

	Dabigatran 110 mg	Dabigatran 150 mg
Sequence Model		
Independent	[redacted]	[redacted]
Moderate Disability		
Mortality		
Single model		
Independent	[redacted]	[redacted]
Moderate Disability		
Mortality		

To derive the probability of each disability state by treatment following ischaemic stroke the point estimates of the above relative rates were applied to the baseline risk for warfarin from Hylek *et al.* (2003).[27] The probability of disability by treatment was tested in the PSA.

Disability and mortality risk due to haemorrhagic stroke and ICH were derived from Rosand *et al.* (2004).[28] No justification was provided for not using the RE-LY trial for this data, nor was the RE-LY trial data tested in a scenario analysis. The disability and mortality risks post haemorrhagic or intracranial haemorrhage were assumed equal for warfarin and dabigatran. No rationale was given for assuming equal disability and mortality due to post haemorrhagic stroke or ICH but different disability and mortality due to ischaemic stroke.

Treatment discontinuation

The MS allows for discontinuation and switch to second-line therapy due to non-clinical events, such as patient choice. The economic model uses discontinuation estimates obtained from fitting a Weibull distribution to the original Kaplan-Meier curves for treatment discontinuation. The original manufacturer submission failed to provide both the original Kaplan-Meier probabilities and Kaplan-Meier curves. The manufacturer submission presents the Weibull parameters for discontinuation of treatment, and neglects goodness of fit statistics and parametric estimates. As a result, the ERG was unable to assess how well the chosen Weibull distributions fit the original discontinuation rates from the trial or whether alternative parametric distributions may have been more appropriate. The ERG asked the manufacturer to provide the original Kaplan-Meier curves and original Kaplan-Meier probabilities of discontinuation at 30 days, 90 days, 1 year and 2 years.

Table 42: Kaplan-Meier Probabilities of discontinuation during RE-LY trial (M. response to Points of Clarification)

	Days	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
All RE-LY	30	4.03%	4.09%	2.46%
	90	6.62%	7.16%	4.20%
	360	12.51%	13.54%	9.25%
	720	17.65%	18.15%	14.89%
RE-LY ≥80	30	7.01%	Not applicable	3.34%
	90	9.19%		5.89%
	360	17.08%		12.70%
	720	25.29%		20.81%
Re-LY <80	30	Not applicable	3.71%	2.29%
	90		6.49%	3.86%
	360		12.29%	8.57%
	720		16.44%	13.73%

Dabigatran is associated with higher likelihood of discontinuation than warfarin throughout the duration of the RE-LY trial (Table 42). The ERG requested that the manufacturer fit alternative distributions to the original Kaplan-Meier curves for treatment discontinuation, and to provide goodness of fit statistics. The results presented by the manufacturer fail to support the choice of the Weibull distribution for the extrapolation. From the manufacturer's response to the points for clarification (Table 5, P11), it is clear that the Weibull distribution does not provide the best fit to the original Kaplan-Meier curves. A lognormal distribution is associated with the best goodness-of-fit. As requested the manufacturer applied the discontinuation estimates obtained from using a lognormal distribution to the economic model. The results suggest that these lognormal estimates may decrease the cost-effectiveness of the interventions (Table 7, P17 of Response to Points for Clarification). The ERG intended to replicate this analysis. However, the manufacturer did not provide the original Kaplan-Meier data, nor the parameters required to replicate the lognormal distribution. In the absence of data, the ERG was unable to simulate the results presented by the manufacturer in the response to the points for clarification.

The key point is that dabigatran is associated with higher discontinuation rates than warfarin in the first two years of the trial. This could suggest that patients tend to tolerate warfarin better than dabigatran. If the magnitude of this difference is incorrectly extrapolated into the future, then the results of the model may be biased.

In the model discontinuation from aspirin was estimated by applying the absolute discontinuation rates sourced from Mant *et al.* (2007).[16]As a result, aspirin was associated with higher discontinuation rates than warfarin, which contradicts the results of Mant *et al.*

(2007).[16] Another option would be to apply the relative discontinuation rate to warfarin treatment from the RE-LY trial. The ERG suggested this to the manufacturer in the points for clarification. In the response to the points for clarification, the manufacturer applied relative discontinuation rates for aspirin based on Mant *et al.* (2007) data. Instead of presenting the results of a complete incremental analysis, the results of a pair-wise comparison between aspirin and dabigatran were presented. As aspirin is part of the treatment sequence for both the dabigatran and the warfarin arm, it would have been more appropriate to present the results of an incremental analysis including all comparators.

The switch to second-line therapy without any events after treatment discontinuation is higher for warfarin than for the other interventions. The value used for warfarin is 78%, whereas for the other treatments, including dabigatran, is 70%. It is unclear the reason behind using a different value for warfarin. Hence it is reasonable to assume the same value for all interventions.

5.2.5 Health-related quality of life

Set 1: Utility associated with general health state and treatment status

For the base-case, baseline utility was sourced from the RE-LY QoL sub-study. At baseline, [redacted] (Table 88, P188 of MS).

[redacted] reviewed the minimal important difference for SF-6D and EQ-5D from 8 longitudinal studies, and reported the average difference as the minimal important difference. This average difference for EQ-5D was 0.074. The range was between -0.011 to 0.14. This wide range reflects the high degree of uncertainty in the estimates and the small number of studies reviewed. [redacted] aimed to determine what magnitude of change is clinically meaningful for a variety of patient-reported outcome measures, in which EQ-5D was not included. It may be reasonable to consider [redacted], however, this paper, in itself, is not adequate to support this view and there is no universally accepted approach for determining the clinical meaning of HRQoL data (Wyrwich *et al.*, 2005).[50] However, Since

discontinuation rates among dabigatran patients were also higher the [redacted]. Although a utility decrement for dabigatran was included in the sensitivity analysis the difference used by the manufacturer was [redacted] rather than the trial reported estimate of [redacted].

Set 2: Utility associated with post-stroke disability status

To determine utility values associated with post-stroke disability status a systematic review was undertaken, only Gage *et al.* (1996) and Dorman *et al.* (2000) were considered appropriate.[29, 34]

The Gage *et al.* (1996) study had the advantage of stratifying the health state descriptions according to the mRs. This allowed the direct application of the utility values to the disability states considered in the economic model. On the other hand, the methodology of this study does not meet the NICE reference case criteria for two major reasons. First, the subjects consisted of 83 American AF patients instead of a representative sample of the UK population. Second, the health states were valuated with the time trade-off method rather than EQ-5D.

The results of Gage *et al.* (1996) study are associated with a considerable degree of uncertainty. For mild stroke, for example, the average utility was 0.76. However, around half the subjects rated mild stroke with at least 0.95 and others rating it worse than death. Similarly, the range of quality of life scored for moderate stroke is reported in the study to be from worse than death to near normal health. The approach taken to incorporate uncertainty is discussed in Section 5.2.7.

Set 3: Utility associated with clinical events

The utility values composing set 3 were sourced from the study by Sullivan *et al.* (2006), and tested using the values quoted in the study by Sullivan *et al.* (2005).[33, 35] Both studies reported utility values for the US population based on EQ-5D. Despite failing to match the requirements of the NICE reference case perfectly, the ERG considers these estimates to be adequate for the economic analysis in the absence of equivalent estimates using UK valuations.

5.2.6 Resources and costs

The acquisition cost of dabigatran 110 mg and 150 mg, and the cost of anticoagulation monitoring are the key drivers of the model in terms of resources and costs. The acquisition cost of dabigatran will not be discussed by the ERG report since this is considered to be a fixed value.

Anticoagulation Monitoring

Costs associated with warfarin treatment are mainly due to INR monitoring. Patients on warfarin must undergo regular INR monitoring and subsequent dose adjustment to ensure that their INR is within the target range between 2 and 3. Patients treated with dabigatran do not require INR monitoring.

INR monitoring costs can be divided into fixed and variable costs. Fixed costs are independent of the number of patients requiring anticoagulation monitoring, e.g. hospital accreditation. Variable costs depend on the number of patients monitored. The introduction of dabigatran will decrease variable per patient costs of anticoagulation monitoring since fewer patients will be receiving such monitoring. The fixed costs of anticoagulation clinics may not be completely avoided since warfarin will still be used in indications for which dabigatran is not licensed, and for patients that are unable to tolerate dabigatran. Fixed costs, such as hospital accreditation, will only be eliminated if anticoagulation clinics are shut down and clinicians diverted to other activities.

In the MS the cost of annual anticoagulation monitoring was derived from the NICE costing report that accompanies NICE clinical guideline number 36 for AF, summarised in Table 30, P74. The cost calculated in this report includes fixed costs, such as hospital accreditation and variable costs, such as reagents, and warfarin costs. As mentioned above the fixed costs of anticoagulation clinics will not be eliminated with the introduction of dabigatran, therefore, the fixed costs of anticoagulation clinics should be included in the dabigatran arm of the model, or simply not included in the model at all. The annual cost of anticoagulation monitoring was further overestimated by £22.74 since the cost of warfarin as per economic model (£16.16) was subtracted from the total cost of monitoring rather than the cost used in the NICE costing report (£38.90).

Sourcing and inflating the anticoagulation monitoring cost from the NICE costing report is reasonable if no more current costs are available. The costs used by the manufacture came from a 2006 report that used 2004/2005 NHS reference costs then inflated the costs to 2005/2006 prices. At the date of the MS, the NHS reference costs for 2009 were already published. Instead of inflating old cost the manufacturer could have replaced the reference costs with those from 2009. For example, the NICE costing report quotes an average value of £35 for first appointment unit cost for anticoagulation services in secondary care and £28 for follow-up. The average costs in the reference cost in NHS foundation trusts for 2008/2009 for this service were £29.58 for first appointment and £21.89 for follow-up.[39] Consequently, the anticoagulation unit costs for 2004/2005, inflated to 2009/2010, may not be the best available estimate of costs for 2009/2010.

In 2005 the Birmingham SMART trial estimated the annual costs of anticoagulation control to be between £73.86 and £123.09, with an average cost of £98.47. This cost was also used by Connock and colleagues to examine the clinical effectiveness and cost-effectiveness of self-testing and self-management of oral anticoagulation treatment compared with clinic based monitoring Connock *et al.,* 2007.[51]

The annual cost usual anticoagulation control of £98.47 inflated to 2009/2010 is £115.14. This is around a quarter of the estimate of £414.90, utilised in the economic model by the manufacturer. This wide range reflects the uncertainty around anticoagulation costs.

The ERG considers that the uncertainty around INR costs was inadequately modelled by the manufacturer. First, in the sensitivity analysis, anticoagulation cost was only tested +/- 25%. Second, anticoagulation costs were not included in the PSA. Third, the manufacturer assumes an average of 20 INR monitoring appointments per patient per year. The number of INR visits depends on the individual patient's INR control. A patient who is able to consistently maintain INR within target range will require less monitoring than a patient whose INR tends to be outside target range.

As the mean estimate of £414.90 may be an over-estimation, the cost-effectiveness results may be biased in favour of dabigatran. Clinical experts for the ERG stated that monitoring costs were highly variable and correlated with treatment effectiveness. Insufficient data was provided by the manufacturer to assess this heterogeneity.

Unit costs of events based on the OXVASC study

The OXVASC study provided unit cost estimates for the events for which the PbR tariff was considered not to be appropriate. PbR tariff prices were used whenever the manufacturer considered it to be applicable (see Table 9, P24).

[redacted]

The manufacturer considered the PbR tariff not appropriate for ischaemic stroke, ICH, haemorrhagic stroke and TIA. Nevertheless, the costs defined in the PbR tariff could be used for comparison (Table 43). It is difficult to compare the costs used in the economic model from the OXVASC and the costs from the PbR tariff for 2010/2011.[52] Nevertheless, a comparison between average costs suggests that the costs used in the economic model are considerably higher than the costs of the PbR tariff (Table 43). An alternative source of data for comparison is the study by Connock *et al.* (2007).[51]

Table 43: Comparison between Economic model costs sourced from OSXVASC and PbR tariff costs

Study	Item	Cost
OXVASC (2009/10)	Fatal IS/ICH/HS	[redacted]
	Independent IS/ICH/HS	
	Moderate Disability IS/ICH/HS	
	Totally Dependent IS/ICH/HS	
	TIA	
	Average cost	
PbR tariff 2010/2011	AA04Z - Intracranial procedures except trauma with non-transient stroke or CVA, nervous system infections or encephalopathy category 4	£11,033
	AA10Z - Intracranial procedures except trauma with non-transient stroke or CVA, nervous system infections or encephalopathy category 3	£11,035
	AA16Z - Intracranial procedures except trauma with non-transient stroke or CVA, nervous system infections or encephalopathy category 1 or 2	£3,061
	AA22Z - Non-transient stroke or CVA, nervous system infections or encephalopathy	£3,759
	AA23Z - Haemorrhagic cerebrovascular disorders	£4,411
	AA29Z – TIA	£671
	Average cost	**£5,662**

CVA: Cerebrovascular accident; HS: Haemorrhagic stroke; ICH: Intracranial haemorrhage; IS: Ischaemic stroke; Transient ischaemic attack

The unit costs used in the economic model by Connock *et al.* (2007) are considerably different from the unit costs used in the MS.[51] Fatal stroke costs in Connock *et al.* are more than double the fatal costs used in the MS. Conversely, costs of ischaemic stroke are much lower than in the MS. Similarly, costs of haemorrhagic stroke and ICH are much higher in the MS than in the study by Connock *et al.*. A comparison between average costs suggests that the costs used in the economic model are considerably higher than the costs used by Connock *et al*. (Table 44).

Table 44: Comparison of OXVASC unit costs and Connock et al. unit costs (Adapted from economic model in MS and from Table 17, P38 in Connock *et al*., 2007)

Study	Item	Cost
OXVASC (2009/10)	Fatal IS/ICH/HS	[redacted]
	Independent IS/ICH/HS	
	Moderate Disability IS/ICH/HS	
	Totally Dependent IS/ICH/HS	
	TIA	
	Average cost	
Connock *et al*. (2007)[51] **Costs inflated to 2009/10**	Fatal stroke	£10,334.19
	Thrombotic stroke	£1,995.91
	Minor thrombotic stroke	£779.89
	Thrombectomy	£2,540.78
	TIA	£613.86
	Cerebral haemorrhage	£2,520.90
	Rehabilitation for 1st year disability	£1,089.89
	Long-term care of disability	£4,035.08
	Average cost	**£2,988.81**

HS: Haemorrhagic stroke; ICH: Intracranial haemorrhage; IS: Ischaemic stroke; Transient ischaemic attack

The cost-effectiveness of dabigatran may be biased in favour of dabigatran if the costs used by the MS are over-estimations of the true cost of ischaemic and haemorrhagic events.

Other costs

Treatment with dabigatran is associated with increased incidence of dyspepsia, in comparison with warfarin treatment. The model assumes the cost of dyspepsia is £3.31 for 3 months and is only accrued in the first cycle. A more conservative approach would be to assume that costs of dyspepsia continue throughout treatment.

The submission states that the cost of a non-fatal SE was assumed to be £2,372 (average between cost of imaging and surgery), and the cost of fatal SE was assumed to be £400 (based on the cost of the autopsy). In the economic model the costs of fatal embolism is £2,372, and non-fatal SE is £400.

5.2.7 Sensitivity analyses

Structural Sensitivity Analysis

There are four key parameters in what the manufacturer calls the structural sensitivity analysis: 1) warfarin control scenario, 2) cost of INR monitoring, 3) time horizon and 4) mixed treatment comparison (MTC). Results for these scenarios are described in Section 5.1.8. Despite the manufacturer denominating this sensitivity analysis as structural, structure is not tested. Instead, individual input parameters are tested. However, these are important scenarios to be tested.

Univariate Sensitivity Analysis

The MS includes extensive univariate sensitivity analysis. The ERG considers that the univariate sensitivity analyses were generally carried out appropriately. The results were presented in a table (Table 146, P273 of MS).

In the sensitivity analysis, disutility associated with dabigatran treatment is tested with disutility associated with warfarin treatment. Moreover, disutility associated with dabigatran treatment is only considered for a three month period, whereas disutility associated with warfarin is considered for 12 months period. While the ERG agreed that it is pertinent to test both possible sources of disutility in the sensitivity analysis, the manufacturer have minimised the effect of the difference in utility by treatment found in the RE-LY trial by simultaneously considering a separately calculated disutility of warfarin. These disutilities should have been considered separately. However, if they were to be used together then to calculate the disutility of dabigatran must take into account that the disutility estimated from

the RE-LY trial was the difference between dabigatran and warfarin and not the absolute value. Furthermore, the time differential between the disutility from dabigatran and disutility from warfarin may bias the analysis in favour of dabigatran.

Probabilistic Sensitivity Analysis (PSA)

Risks for the various clinical events were included in the PSA. Of the general health state and treatment status utilities only those for the independent AF patient without stroke history were included in the PSA. Both disutility associated with warfarin treatment and disutility associated with dabigatran treatment were not included in the PSA. As the disutility associated with warfarin treatment from Gage *et al.* (1996) is less than half of the value found in the RE-LY sub-study for disutility associated with dabigatran treatment, failing to include these parameters in the PSA may favour the results towards dabigatran.[29] Utility associated with post-stroke disability status were included in the PSA. The study providing these values neglected to report standard errors. Therefore, the manufacturer assumed standard errors based on the standard error obtained for the utility for independent without stroke history from the RE-LY QoL sub-study. Considering the wide interval reported in Gage *et al.* (1996), discussed in Section 5.2.5 (P40), this assumption may not have been the most appropriate approach. The assumed standard errors fail to reflect the uncertainty surrounding the utility values found by the Gage *et al.* (1996) study. Therefore, the PSA will be unable to fully capture the uncertainty surrounding these input parameters.

As with the univariate analysis the range of INR monitoring costs were not sufficiently wide to capture the uncertainty surrounding this very influential cost.

5.2.8 Results

Base-case Analysis

The manufacturer submission includes extensive tables providing the results of pair-wise comparisons between dabigatran 150 mg and 110 mg, and each of the comparator treatments. In addition, Markov traces were given for all interventions and both models.

The manufacturer did not include a full incremental comparison between the interventions and all the comparators. The ERG requested full incremental comparison of the ICERs in which both strengths of dabigatran and all the comparators were included in the points for clarification. The manufacturer provided the comparison of the ICERs for all treatments in

the single dose model as an approximation, as the model structure is unable to compare both strengths of dabigatran.

The manufacturer provided the probability of cost-effectiveness at different willingness to pay thresholds for the pair-wise comparisons, but not for simultaneous comparisons between the different interventions and comparators (Table 147, of P275 of MS). In addition, cost-effectiveness plane and cost-effectiveness acceptability curve for each pair-wise comparison were also presented. Again, the cost-effectiveness acceptability curves for simultaneous comparisons were not presented.

The ERG requested the manufacturer for the results of the cost-effectiveness analysis using simultaneous comparisons between dabigatran (150 mg and 110 mg) and all the comparators. The manufacturer was unable to provide such results due to the structure of the model.

5.2.9 Model validation

The manufacturer submission reported that the model was validated with three different mechanisms: 1) clinical experts, 2) double checking of inputs and 3) substantiation of face validity. The ERG considers that all three levels of validation are appropriate and constitute good practice in economic evaluation.

5.2.10 Summary of uncertainties and issues

There are a number of issues left unanswered by the MS. Most importantly, the cost-effectiveness of dabigatran as second-line treatment compared to dabigatran as first-line treatment. Similarly, it is not clear from the MS whether dabigatran is cost-effective in patients who are controlled on warfarin.

No analysis has been done to assess the generalisability of the RE-LY cohort to a UK clinical setting and no analysis has considered the many heterogeneous groups of patients separately. It is possible that there are sub-groups for which dabigatran is more/less cost-effective and possibly sub-groups in which other treatments would be preferred. It is also uncertain what effect including long-term consequences of acute MI and SE will have on the cost-effectiveness of dabigatran, further exploration is needed. In addition, the disutility of dabigatran captured by the trial has not been fully reflected in the cost-effectiveness analysis and the uncertain treatment dependent disability following stroke needs further support.

The costs of anticoagulation monitoring are very influential in this cost-effectiveness analysis and it is unclear how much of these costs will be off-set by dabigatran. Questions remain about which are the most appropriate anticoagulation monitoring costs to include and the effect of using these different costs.

Finally, due to the multiple sources of uncertainty related to inputs and assumptions employed in the MS it is unclear how combining these uncertainties and alternative scenarios will impact the cost-effectiveness decision.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

Overview

The ERG focussed its exploratory work on the main issues described above. The discussion starts with the treatment sequence considered by the manufacturer. It continues with generalisability to the UK-AF population. The patient cohort used in the manufacturer analysis mirrors the patients participating in the RE-LY trial, which is considerably different than the UK-AF patient population. This analysis should be able to explore the potential impact on cost-effectiveness of dabigatran associated with issues of generalising the RE-LY population to the relevant UK-AF population.

INR monitoring is a key issue in the economic model. The effectiveness, costs and use of warfarin are highly dependent on the individual patient INR. The AF patient population is therefore a heterogeneous population. Heterogeneity is due both to risk of ischaemic events as measured by $CHADS_2$ score and INR control. The ERG undertook extensive exploratory work to determine the cost-effectiveness of dabigatran 150 mg and dabigatran 110 mg on these different patient subgroups.

Warfarin monitoring cost is a major driver of the economic model. The manufacturer analysis assumes that all costs associated with anticoagulation monitoring will be eliminated with the introduction of dabigatran. The ERG considers that only the variable (per patient) costs would be reduced. As warfarin is likely to still be prescribed, anticoagulation monitoring clinics will still be required. Hence, the ERG explores alternative monitoring costs and their effect on the cost-effectiveness of dabigatran.

Acute MI and SE are assumed by the manufacturer to be associated with acute costs and disutility, and not any ongoing or long term consequences. The ERG considers this assumption to be over-simplistic, and analyses the alternative assumptions on the cost-effectiveness of dabigatran.

Disability due to stroke is considered to be treatment-dependent according to the MS. As discussed in Section 5.2, this assumption is unsubstantiated by the evidence provided. The ERG thus explores the model assuming that disability due to stroke is independent of treatment.

Disutility associated with dabigatran treatment is not considered by the manufacturer base-case. However, the results of RE-LY QoL sub-study indicate that dabigatran treatment is associated with some disutility. These results are inputted in the model to explore how the cost-effectiveness of dabigatran is affected.

Finally, the ERG found appropriate to build an alternative base-case. This base-case differs from the manufacturer's base-case in the patient cohort, costs, disutility and disability parameters discussed above. The ERG base-case provides an alternative estimate of the cost-effectiveness of dabigatran 150 mg and 110 mg.

Treatment Sequence

As mentioned in Section 5, the base-case analysis assumes that dabigatran will replace warfarin. Such scenario would imply that dabigatran not only is the treatment of choice for all patient groups, but also that all patients would be willing and able to tolerate possible side-effects from dabigatran. Furthermore, dabigatran is not licensed for all the indications that warfarin is currently licensed for. Hence, it seems unlikely that the approval of dabigatran for use in the NHS will result in the abandonment of warfarin. As evidenced by the dabigatran discontinuation rates in the RE-LY trial, there will be patients who try dabigatran, and subsequently switch treatment to warfarin.

Starting on dabigatran and then switching to warfarin is a reasonable treatment sequence as per clinical expert opinion. Unfortunately the structure of the model fails to allow the full range of relevant treatment sequences to be fully explored. These additional treatment sequences would also enable the model to better reflect potential clinical practice.

In the response to the points for clarification, the manufacturer failed to include these treatment sequences in the economic model. The ERG is thus unable to provide full incremental comparisons for all treatment sequences. As an approximation, the results of both the single dose model and the sequence dose model will be compared and explored.

Generalisability

As discussed in Section 5.2, the patient cohort simulated in the economic model and the AF patients in the UK have different demographics. More specifically, data from Gallagher *et al.* (2008) suggests that UK-AF patients are older than the patient cohort simulated in the model.[46] Table 45 shows the distribution of UK-AF patients across patient groups.
Age, proportion of males, and distribution of $CHADS_2$ score were changed by the ERG to match the characteristics of the UK-AF population, as reported in Gallagher *et al.* (2008).[46] Table 45 summarises the results of the incremental analysis for the different treatment alternatives, for the base-case patient cohort and for the AF-UK patients. The patient cohort for the sequence model is different than the patient cohort in the single model, in terms of age at model entry, proportion of males, and distribution of $CHADS_2$ score. In order to compare the results of both models, the single model patient cohort was used for the sequence model. This made the models more comparable.

The results for UK-AF population scenario suggest that dabigatran 150 mg is more cost-effective than warfarin. In this analysis warfarin is extendedly dominated, i.e. the ICER for warfarin is higher than the ICER for dabigatran 150 mg. Hence the incremental analysis excludes the warfarin alternative, and the ICER for dabigatran 150 mg is calculated in relation to aspirin. Nevertheless, the ICER for dabigatran 150 mg for the UK-AF population scenario is higher than the ICER for the base-case scenario. This analysis also suggests that dabigatran 110 mg and the sequence model are associated with higher costs and lower health benefits than dabigatran 150 mg. Therefore neither are cost-effective alternatives in comparison to dabigatran 150 mg.

Table 45: Incremental analysis for the different treatment alternatives for the base-case patient cohort (adapted from MS p.159) and for AF-UK patients (adapted from Table 1, P1501 of Gallagher *et al*., 2008)[46]

Parameters		**All RE-LY**					**AF UK population**					
Age		71					**Age**	**Proportion**				
							40-65	13.9%				
							65-70	10.8%				
							70-75	17.4%				
							75-80	19.4%				
							80-85	20.1%				
							85-115	18.4%				
							Average age assumed to be 77 years old					
% males		63.6%					55.1%					
CHADS2	0	2.5%					12.6%					
	1	29.4%					30.6%					
	2	35.6%					30.7%					
	3	20.2%					14.9%					
	4	8.9%					8.1%					
	5	2.9%					2.8%					
	6	0.5%					0.4%					
Intervention		**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**ICER**	**Intervention**	**Costs**	**QALY**	**Inc. Cost**	**Inc. QALY**	**ICER**
Aspirin		£15,080	7.082	Baseline			**Aspirin**	£9,651	5.840	Baseline		
Warfarin		£15,583	7.283	£503	0.201	£2,502	**A+C**	£10,346	5.818	£784	-0.02	D
A+C		£16,070	7.061	£487	-0.222	D	**Warfarin**	£10,582	5.905	£1.021	0.065	ED
DBG 150		£16,923	7.497	£1,340	0.214	£6,261	**DBG 150**	£11,847	6.059	£2,286	0.219	£10,455
DBG Sequence		£17,767	7.45	£844	-0.047	D	**DBG 110**	£12,570	6.036	£723	-0.023	D
DBG 110		£18,385	7.433	£1,462	-0.064	D	**DBG Sequence**	£12,864	5.943	£1,017	-0.116	D

A+C: Aspirin plus clopidogrel; AF: Atrial fibrillation; DBG: Dabigatran; ED: extended dominance; D: dominance; ICER: incremental cost-effectiveness ratio; Inc.: Incremental; QALY: Quality-adjusted life-years

Heterogeneity

As discussed in Section 5.2.2 patients suffering from AF constitute a heterogeneous population, which is reflected by the distribution of $CHADS_2$ scores. Since the $CHADS_2$ score is known to the prescriber this information can help guide treatment decisions. The ERG examined the cost-effectiveness of dabigatran 150 mg and dabigatran 110 mg for subpopulations of AF patients according to $CHADS_2$ score and stroke history. The ERG used the manufacturer's base-case when calculating each of these heterogeneous groups. The only difference is that the results were not combined into the single figure presented by the manufacturer to represent the total population. In order to enable a comparison between the two models, age, proportion of males and $CHADS_2$ score in the sequence dose model was equalised to the single dose model input parameters. Table 46 summarises the incremental costs and benefits (in QALYs) of each intervention.

Table 46 demonstrates that dabigatran 150 mg is consistently associated with increased costs and increased health benefits compared with warfarin and that dabigatran 110 mg is

associated with both increased costs and decreased health benefits compared with dabigatran 150 mg.

Table 46: Incremental analysis for dabigatran 110 mg, dabigatran 150 mg, warfarin and aspirin according to $CHADS_2$ score and stroke history for single model base-case patient cohort

$CHADS_2$	Stroke history	Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Patient cohort as per single dose model base-case		Aspirin	£15,080	7.082	Baseline		
		Warfarin	£15,583	7.283	£503	0.201	£2,502
		A+C	£16,070	7.060	£487	-0.223	Dominated
		Dabigatran 150 mg	£16,923	7.497	£1,340	0.214	£6,262
		Sequence < 80	£17,767	7.45	£844	-0.047	Dominated
		Dabigatran 110 mg b	£18,385	7.433	£1,462	-0.064	Dominated
0	No	Aspirin	£9,942	7.596	Baseline		
		A+C	£10,941	7.560	£999	-0.036	Dominated
		Warfarin	£11,178	7.649	£1,237	0.053	£23,340 (ED)
		Dabigatran 150 mg	£12,654	7.853	£2,712	0.257	£10,535
		Sequence < 80	£12,761	7.859	£107	0.006	£17,970
		Dabigatran 110 mg	£15,358	7.842	£597	-0.017	Dominated
1	No	Aspirin	£10,797	7.496	Baseline		
		Warfarin	£11,750	7.591	£953	0.095	£10,032 (ED)
		A+C	£11,800	7.469	£50	-0.122	Dominated
		Dabigatran 150 mg	£13,166	7.8	£2369	0.304	£7,793
		Sequence < 80	£13,939	7.75	£773	-0.05	Dominated
		Dabigatran 110 mg	£14,085	7.774	£919	-0.026	Dominated
2	No	Aspirin	£12,993	7.096	Baseline		
		Warfarin	£13,230	7.316	£237	0.22	£1,077
		A+C	£14,028	7.069	£798	-0.247	Dominated
		Dabigatran 150 mg	£14,482	7.528	£1252	0.212	£5,906
		Sequence < 80	£15,328	7.476	£846	-0.052	Dominated
		Dabigatran 110 mg	£15,960	7.467	£632	-0.009	Dominated
3	No	Warfarin	£13,948	7.222	Baseline		
		Aspirin	£14,102	6.938	£154	-0.284	Dominated
		Dabigatran 150 mg b	£15,028	7.444	£1,080	0.222	£4,865
		A+C	£15,252	6.902	£224	-0.542	Dominated
		Sequence < 80	£15,850	7.405	£822	-0.039	Dominated
		Dabigatran 110 mg	£16,900	7.355	£1,050	-0.05	Dominated
4	No	Warfarin	£15,922	7.031	Baseline		
		Aspirin	£16,626	6.651	£704	-0.38	Dominated
		Dabigatran 150 mg	£16,847	7.270	£925	0.239	£3,870
		A+C	£17,720	6.656	£873	-0.614	Dominated

$CHADS_2$	Stroke history	Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
		Sequence < 80	£17,879	7.211	£1,032	-0.059	Dominated
		D Dabigatran BG 110 mg	£19,370	7.134	£1,491	-0.077	Dominated
2	Yes	Aspirin	£24,136	6.908	Baseline		
		A+C	£24,850	6.914	£714	0.006	£119,000 (ED)
		Warfarin	£25,404	7.054	£1,268	0.146	£8,685
		Dabigatran 150 mg	£27,222	7.259	£1,818	0.205	£8,868
		Sequence < 80	£28,110	7.207	£888	-0.052	Dominated
		Dabigatran 110 mg	£28,488	7.202	£378	-0.005	Dominated
3	Yes	Aspirin	£24,807	6.777	Baseline		
		A+C	£25,570	6.777	£763	0	Dominated
		Warfarin	£25,812	6.975	£1,005	0.198	£5,076
		Dabigatran 150 mg	£27,492	7.188	1,680	0.213	£7,887
		Sequence < 80	£28,380	7.146	£888	-0.042	Dominated
		Dabigatran 110 mg	£29,074	7.107	£694	-0.039	Dominated
4	Yes	Aspirin	£26,554	6.339	Baseline		
		Warfarin	£27,067	6.670	£513	0.331	£1,550
		A+C	£27,340	6.356	£273	-0.314	Dominated
		Dabigatran 150 mg	£28,568	6.89	£1,501	0.22	£6,823
		Sequence < 80	£29,753	6.824	£1,185	-0.066	Dominated
		Dabigatran 110 mg	£30,764	6.766	£1,011	-0.058	Dominated
5 & 6	Yes	Aspirin	£27,692	6.089	Baseline		
		Warfarin	£27,813	6.154	£121	0.065	£1,862
		A+C	£28,574	6.092	£761	-0.062	Dominated
		Dabigatran 150 mg	£29,033	6.752	£1,220	0.598	£2,040
		Sequence < 80	£30,162	6.722	£1,129	-0.03	Dominated
		Dabigatran 110 mg	£31,834	6.579	£1,672	-0.143	Dominated

A+C: Aspirin plus clopidogrel; ED: Extended dominance; Sequence: Dabigatran sequence

The sequence model is associated with increased costs and decreased health benefits when compared with dabigatran 150 mg, with the exception of patients with $CHADS_2$=0 in which case the sequence model has less benefits and less costs.

As expected, warfarin is not a cost-effective option for AF patients whose $CHADS_2$ score is zero or one. According to NICE Guideline 36 (The management of AF),[37] AF patients without moderate or high risk factors should be offered aspirin. Hence, warfarin is unlikely to be the choice for AF patients with $CHADS_2$ of zero or one.

This analysis of heterogeneity only considered the difference in baseline risk for different $CHADS_2$ scores and stroke history. Since treatment effect is not available for each of these sub-groups, this analysis assumes that all patients receive the same treatment benefit as the average patient in the RE-LY trial.

The results of this analysis suggest that dabigatran 150 mg is cost-effective in patients with no prior history of stroke and a $CHADS_2$ score of 0 or 1. The results for the sub-population whose $CHADS_2$ is 0 should be interpreted with caution due to the small proportion of patients in the RE-LY trial with such low risk of stroke. Only 2.5% of patients participating in the RE-LY trial had $CHADS_2$ score of zero. There will be considerable uncertainty around the event rate for these patients due to low statistical power.

The proportion of patients in the RE-LY trial with $CHADS_2$ score of 5 or 6 was also small (2.9% with $CHADS_2$=5 and 0.5% with $CHADS_2$=6). The manufacturer recognised this issue, and joined together the group with $CHADS_2$=5 and $CHADS_2$=6 for the calculation of the event rate. The results for the sub-population with $CHADS_2$=6 are equal to the results for the sub-population whose $CHADS_2$=5, thus not shown. As with the results for the sub-population of patients whose $CHADS_2$ score is 0, the results of the incremental analysis for the subpopulation of patients whose $CHADS_2$ score is 5 or 6 should be interpreted with caution, due to the low statistical power of the RE-LY trial for these sub-populations.

Note that for patients whose $CHADS_2$ score is 3 or 4 with no stroke history, that warfarin is the baseline and not aspirin. Once again this is not an unexpected result: patients with high risk of stroke should be offered anticoagulation with warfarin, as per NICE guidance. Dabigatran 150 mg can be considered a cost-effective alternative for these patients. Similarly, dabigatran 150 mg and warfarin are cost-effective interventions for patients with stroke history ($CHADS_2$ score of at least 2). A similar analysis was carried out for the sequence model for over 80 years old. In order to enable comparison between single and sequence model over 80, the characteristics of the patient cohort of the sequence model over 80 was inputted into the single model (Table 47). The patient cohort considered was on average 82.9 years old, 57.1% were males, and the $CHADS_2$ score distribution is summarised in Table 71 (P159 of MS).

Table 47: Incremental analysis for dabigatran 110 mg, dabigatran 150 mg, warfarin and aspirin according to $CHADS_2$ score and stroke history for sequence model >80 base-case patient cohort

$CHADS_2$	Stroke history	Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
As per manufacturer's base-case		Aspirin	£7,005	4.296	Baseline		
		A+C	£7,599	4.279	£594	-0.017	Dominated
		Warfarin	£7,809	4.344	£804	4.344	£16,750 (ED)
		Dabigatran 150 mg	£8,840	4.447	£1,835	0.151	£12,152
		Dabigatran 110 mg	£9,389	4.429	£549	-0.018	Dominated
		Sequence > 80	£9,929	4.111	£1,089	-0.336	Dominated
1	No	Aspirin	£4,536	4.469	Baseline		
		A+C	£5,121	4.451	£585	-0.018	Dominated
		Warfarin	£5,656	4.472	£1,120	0.003	£373,333 (ED)
		Sequence > 80	£6,492	4.379	£836	-0.093	Dominated
		Dabigatran 150 mg	£6,748	4.571	£2,212	0.102	£21,686
		Dabigatran 110 mg	£7,022	4.571	£274	0	Dominated
2	No	Aspirin	£4,971	4.427	Baseline		
		A+C	£5,568	4.410	£597	-0.017	Dominated
		Warfarin	£5,932	4.448	£961	0.021	£45,762 (ED)
		Dabigatran 150 mg	£6,981	4.549	£2,010	0.122	£16,475
		Dabigatran 110 mg	£7,369	4.543	£388	-0.006	Dominated
		Sequence>80	£8,096	4.12	£1,115	-0.429	Dominated
3 & 4	No	Aspirin	£6,381	4.244	Baseline		
		Warfarin	£6,819	4.331	£438	0.087	£5,034
		A+C	£7,049	4.223	£230	-0.108	Dominated
		Dabigatran 150 mg	£7,726	4.437	£907	0.106	£8,557
		Dabigatran 110 mg	£8,476	4.408	£750	-0.029	Dominated
		Sequence>80	£9,419	4.024	£1,693	-0.413	Dominated
3 & 4	Yes	Aspirin	£13,375	4.070	Baseline		
		A+C	£13,852	4.061	£477	-0.009	Dominated
		Warfarin	£14,299	4.127	£924	0.057	£16,211 (ED)
		Dabigatran 150 mg	£15,490	4.230	£2,115	0.16	£13,219
		Dabigatran 110 mg	£16,129	4.203	£639	-0.027	Dominated
		Sequence>80	£16,398	3.893	£908	-0.337	Dominated
5 & 6	Yes	Aspirin	£15,042	3.805	Baseline		
		Warfarin	£15,366	3.958	£324	0.153	£2,117.65
		A+C	£15,587	3.794	£221	-0.164	Dominated
		Dabigatran 150 mg	£16,322	4.074	£956	0.116	£8,241.38
		Dabigatran 110 mg	£17,534	4.007	£1,212	-0.067	Dominated
		Sequence> 80	£18,146	3.586	£612	-0.488	Dominated

A+C: Aspirin plus clopidogrel; ED: Extended dominance; Sequence: Dabigatran sequence

Intuitively, dabigatran 110 mg and the sequence model over 80 should provide equal results.

The sequence model over 80 consists of treating patients over 80 years old with dabigatran

110 mg. As the patient cohort used for the single model has the same age, male proportion and $CHADS_2$ score distribution as in the sequence model, the results should correspond with the results of the sequence model over 80.

In reality, the results of dabigatran 110 mg for single and sequence model do not match. This is because the various event rates in the sequence model are different from the event rates in the single model. The event rates of the single model correspond to the pooled event rates of the RE-LY trial. The event rates of the sequence model correspond to the event rates of the RE-LY trial for the sub-set of patient under or over 80 years old. Nevertheless, both approaches indicate that dabigatran 110 mg is associated with increased costs and lower health benefits than dabigatran 150 mg.

Across all $CHADS_2$ scores, dabigatran 110 mg, either in the single model or in the sequence model, is associated with higher costs and lower health benefits than dabigatran 150 mg. Therefore dabigatran 110 mg is dominated by dabigatran 150 mg.

In this analysis dabigatran 150 mg was more cost-effective than warfarin. Warfarin was extendedly dominated for the following subpopulations in the patient cohort aged 82.9 years old: patients with no stroke history, $CHADS_2$=1 or 2; patients with stroke history, $CHADS_2$=3 or 4.

INR Control

As discussed in Section 5.2, the effectiveness, costs and use of warfarin are highly dependent on INR control. Some patients are able to consistently maintain INR within the target range of 2 and 3, whilst other patients struggle. Therefore, it seems reasonable to consider these patients as a separate subpopulation for the economic evaluation. Table 48 summarises the results of the incremental analysis for a patient cohort whose INR is consistently within target range. With the exception of INR, the patient cohort simulated matches the manufacturer's base-case for the single model. Namely, age at model entry is 71 years old, 63.1% males, and $CHADS_2$ score as per Table 71 (P159 of MS).

Table 48: Incremental analysis for the subpopulation able to maintain INR within target range

Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Warfarin if 100% INR within target range	£14,609	7.459	Baseline		
Aspirin	£15,080	7.082	£471	-0.377	Dominated
Aspirin + clopidogrel	£16,070	7.061	£1461	-0.398	Dominated
Dabigatran 150 mg	£16,923	7.497	£1,843	0.038	£60,895
Dabigatran sequence < 80	£17,767	7.450	£844	-0.047	Dominated
Dabigatran 110 mg	£18,385	7.433	£618	-0.017	Dominated

ICER: Incremental cost effectiveness ratio Inc.: Incremental; INR: International normalised ratio; QALY: Quality-adjusted life year

Warfarin is the least costly option for the subpopulation of patients who is able to maintain INR within target range. Aspirin is associated with increased costs but also with increased benefits, and so is dabigatran 150 mg. The ICER for dabigatran 150 mg is £60,895 per QALY. Once again, neither the sequence model nor dabigatran 110 mg are cost-effective.

The ICER of £60,895 per QALY for dabigatran 150 mg is likely to be an underestimate. Patients who are able to maintain INR within range may also require less frequent INR monitoring. Therefore the costs associated with warfarin treatment should be lower compared to the average treatment. As a result, dabigatran 150 mg would be even less cost-effective if this was taken into account.

The sub-population of patients who are unable to keep INR within range was also evaluated. The same incremental analysis was performed for the manufacturer's base-case cohort, in which all patients had INR below 2 or above 3. Table 49 summarises the results.

Table 49: Incremental analysis for patients unable to keep INR within target range

	Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
INR <2 For all patients	Aspirin	£15,080	7.082	Baseline		
	Aspirin + clopidogrel	£16,070	7.061	£990	-0.021	Dominated
	Warfarin	£16,616	7.074	£1,536	-0.008	Dominated
	Dabigatran 150 mg	£16,923	7.497	£307	0.415	£740
	Sequence<80	£17,767	7.449	£844	-0.048	Dominated
	Dabigatran 110 mg	£18,385	7.433	£618	-0.016	Dominated
INR >3 For all patients	Aspirin	£15,080	7.082	Baseline		
	Aspirin + clopidogrel	£16,070	7.061	£990	-0.021	Dominated
	Dabigatran 150 mg	£16,923	7.497	£1,843	0.415	£4,441
	Warfarin	£17,731	6.852	£808	-0.645	Dominated
	Sequence<80	£17,767	7.449	£36	-0.048	Dominated
	Dabigatran 110 mg	£18,385	7.433	£618	-0.064	Dominated

ICER: Incremental cost effectiveness ratio Inc.: Incremental; INR: International normalised ratio; QALY: Quality-adjusted life year

The results suggest that INR control is a key parameter in the economic model. For patients unable to keep INR within target range, warfarin is not a cost-effective option. Dabigatran 150 mg bid and aspirin are the cost-effective interventions for patients unable to keep INR within target range.

This analytical procedure was performed for the patient cohort simulated as base-case for the sequence model over 80 (Table 50). Both the single model and the sequence model over 80 were run with a patient cohort whose age at entry is 82.9 years old, 57.1% males and $CHADS_2$ score as per Table 71 (P159 of MS).

Table 50: Incremental analysis for patients whose INR is within target range and outside target range for the sequence model > 80 base-case patient cohort

	Intervention	Cost	QALY	Inc. Cost	Inc. QALY	ICER
INR between 2 and 3 For all patients	Aspirin	£7,005	4.296	Baseline		
	A+C	£7,599	4.279	£594	-0.017	Dominated
	Warfarin	£7,324	4.413	£319	0.117	£2,726
	Dabigatran 150 mg	£8,840	4.447	£1,516	0.034	£44,588
	Dabigatran 110 mg	£9,389	4.429	£549	-0.018	Dominated
	Sequence > 80	£9,929	4.111	£1,089	-0.336	Dominated
INR <2 For all patients	Aspirin	£7,005	4.296	Baseline		
	A+C	£7,599	4.279	£594	-0.017	Dominated
	Warfarin	£8,239	4.274	£1,234	-0.022	Dominated
	Dabigatran 150 mg	£8,840	4.447	£1,835	0.151	£12,152
	Dabigatran 110 mg	£9,389	4.429	£549	-0.018	Dominated
	Sequence > 80	£9,929	4.111	£1,089	-0.336	Dominated
INR >3 For all patients	Aspirin	£7,005	4.296	Baseline		
	A+C	£7,599	4.279	£594	-0.017	Dominated
	Dabigatran 150 mg	£8,840	4.447	£1,835	0.151	£12,152
	Warfarin	£9,172	4.137	£332	-0.31	Dominated
	Dabigatran 110 mg	£9,389	4.429	£549	-0.018	Dominated
	Sequence > 80	£9,929	4.111	£1,089	-0.336	Dominated

A+C: Aspirin plus clopidogrel; ICER: Incremental cost effectiveness ratio Inc.: Incremental; INR: International normalised ratio; QALY: Quality-adjusted life year; Sequence: Dabigatran sequence

Similar results emerge when an older patient cohort is evaluated. For patients whose INR is consistently within target range, warfarin is more cost-effective than dabigatran 150 mg. For patients whose INR is outside target range, warfarin is not cost-effective. Dabigatran 150 mg is a cost-effective alternative for those patients whose INR is outside range. As before,

dabigatran 110 mg is not a cost-effective alternative for both single and sequence dose models.

Costs of INR monitoring

The monitoring cost used in the model was obtained from the NICE costing report and inflated from 2004/05 to 2009/10 prices (Section 5.1.6). This value includes fixed and variable costs. The ERG took three approaches to calculate the variable costs of INR monitoring. First, using the NICE costing report calculations, the ERG estimated the variable primary care costs to be £165.67 (inflated to 2009/10). Variable costs did not include; overheads, hospital accreditation, national quality control scheme and software maintenance and support. We also removed the cost of warfarin since it is included as part of the treatment cost. The secondary care costs were obtained from the reference costs 2008/2009.[39] Since the secondary care costs were aggregated we did not remove the fixed costs at this point.

For our second approach we removed the fixed costs from secondary care by calculating the proportion of fixed costs in the primary care and subtracting this proportion from the secondary care costs. The ERG considered that it would be reasonable to assume that the proportion of fixed costs for secondary care could be equivalent to the proportion of fixed costs in primary care. Using the NICE costing report, the fixed costs are 33% of the total monitoring costs. If 33% of the reference costs are fixed costs, the relevant secondary costs would be £241.54.

The third approach was to use an alternative estimate for the costs of anticoagulation services, £115.14. This value is based on the calculation by Connock *et al.* (2007) of £98.47 in 2005, updated to 2009/10, discussed in Section 5.2.6.[51] Table 51 summarises the manufacturer's base-case and the three alternatives presented by the ERG. Appendix 1 summarises the calculations.

Table 51: INR monitoring costs

	INR costs	Source	Assumptions	Method
Manufacturer submission	£ 419.9	NICE costing report 2006[37] NHS reference costs for 2004/2005	Dabigatran will totally replace warfarin. Includes both fixed and variable costs in primary and secondary care.	2004/05 reference costs inflated to 2009/10 prices. Removed 2009/10 annual cost of warfarin (£16.16) and not the 2004/05 annual cost of warfarin (£38.9).
ERG Alternative 1	£279.36	NICE costing report 2006[37] NHS reference costs for 2008/09[39]	Dabigatran will not totally replace warfarin. Includes variable costs in primary care and total costs in secondary care.	Replaced 2004/05 reference costs with 2008/09 reference costs and inflated to 2009/10 prices. Removed fixed costs from primary care. Removed 2004/05 annual cost of warfarin.
ERG Alternative 2	£241.54	NICE costing report 2006[37] NHS reference costs for 2008/09[39]	Dabigatran will not totally replace warfarin. Includes solely variable costs in both primary and secondary care.	Used ERG Alternative 1 (£279.36. Calculated the proportion of fixed costs in the primary care – 33%. Removed 33% of secondary care costs.
ERG Alternative 3	£115.14	Connock *et al*. 2007.[51]	INR monitoring costs based on data collected in Birmingham SMART trial.	Annual costs for INR control of £98.47 in 2004/05 inflated to 2009/10.

Table 52 summarises the results of incremental analysis for all treatments using £279.45, £241.54 and £115.14 as the INR monitoring costs. Results are similar to the base-case, although the ICER for dabigatran 150 mg was between £10,528 per QALY and £15,701 per QALY. These results suggest that the cost of INR monitoring is a key driver of the economic model and has important unresolved uncertainty.

Table 52: Incremental analysis for all treatments from the single-dose and sequential models using alternative INR monitoring cost and single dose patient cohort

		Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Patient Cohort **As per Single Model** **Base-case** **71 years old** **63.6% males**	**Base-case**	Aspirin	£15,080	7.082	Baseline		
		Warfarin	£15,583	7.283	£503	0.201	£2,502
		A+C	£16,070	7.061	£487	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.497	£1,340	0.214	£6,262
		Sequence < 80	£17,767	7.45	£844	-0.047	Dominated
		Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated
	Exploratory analysis Monitoring cost = £279.36	Warfarin	£14,670	7.283	Baseline		
		Aspirin	£15,080	7.082	£410	-0.201	Dominated
		A+C	£16,070	7.061	£1,400	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.497	£2,253	0.214	£10,528
		Sequence < 80	£17,767	7.45	£844	-0.047	Dominated
		Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated
	Exploratory analysis Monitoring cost = £241.54	Warfarin	£14,415	7.283	Baseline		
		Aspirin	£15,080	7.082	£665	-0.201	Dominated
		A+C	£16,070	7.061	£1,655	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.497	£2,508	0.214	£11,720
		Sequence < 80	£17,767	7.45	£844	-0.047	Dominated
		Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated
	Exploratory analysis Monitoring cost = £115.14	Warfarin	£13,563	7.283	Baseline		
		Aspirin	£15,080	7.082	£1,517	-0.201	Dominated
		A+C	£16,070	7.061	£2,507	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.497	£3,360	0.214	£15,701
		Sequence < 80	£17,767	7.45	£844	-0.047	Dominated
		Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated

A+C: Aspirin plus clopidogrel; ICER: Incremental cost effectiveness ratio Inc.: Incremental; INR: International normalised ratio; QALY: Quality-adjusted life year; Sequence: Dabigatran sequence

Cost of Fatal Systemic Embolism

The manufacturer submission states that the cost of fatal SE is £400 and the cost of non-fatal embolism is £2,373. In the economic model, the cost of fatal SE is £2,373, and the cost of non-fatal SE is £400. The model was tested using the inputs stated in the manufacturer submission. The cost of SE has very little influence on the cost-effectiveness results. The ICER for dabigatran 150 mg decreased slightly from £6,262 per QALY (manufacturer's base-case) to £6,234 per QALY (exploratory analysis).

Dyspepsia Costs

Treatment with dabigatran is associated with increased incidence of dyspepsia, in comparison with warfarin treatment. The manufacturer base-case analysis assumes that dyspepsia costs are only incurred for the first three months of dabigatran treatment. Increasing the length of dyspepsia treatment would reflect clinical practice more accurately. The ERG tested the model by increasing the length of dyspepsia treatment from three months to the whole duration of dabigatran treatment. The ICER for dabigatran 150 mg increased slightly from £6,262 per QALY to £6,659 per QALY which suggests that this is not a key driver of the model.

Long-term consequences of acute MI and SE

Acute MI and SE are assumed to be associated with only acute costs and disutilities in the MS. Clinical expert advice informed the ERG that acute MI and SE can be associated with long-term consequences. The model structure does not allow for ongoing costs and disutility to be associated with acute MI and SE. In order to test for the effect on dabigatran's cost-effectiveness, the ERG increased the costs and disutility associated with acute MI and SE. The cost-effectiveness of dabigatran 150 mg and warfarin were robust to extreme simultaneous changes in the costs (12x) and disutility (2x) of SE and acute MI.

Disability due to stroke

As discussed in Section 5.2 the MS assumes that disability due to stroke depends on treatment. However, the evidence provided by the manufacturer fails to support such hypothesis. The ERG explored the situation in which treatments did not affect the disability. In this scenario we assumed that all treatments had the same disability as warfarin post stroke. Table 53 summarises the results of making disability risks equal for either strength of dabigatran and warfarin. The ICER for dabigatran 150 mg increases to £8,393 per QALY

from £6,262 per QALY. As before, dabigatran 110 mg and the sequence model are not cost-effective alternatives, because they are associated with increased costs and decreased health benefits when compared with dabigatran 150 mg.

Table 53: Incremental analysis after equalizing disability risks for dabigatran and warfarin

		Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Patient Cohort **As per Single Model** **Base-case** **71 years old** **63.6% males**	**Base-case**	Aspirin	£15,080	7.082	Baseline		
		Warfarin	£15,583	7.283	£503	0.201	£2,502
		A+C	£16,070	7.061	£487	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.497	£1,340	0.214	£6,262
		Sequence < 80	£17,767	7.45	£844	-0.047	Dominated
		Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated
	Exploratory Analysis	Aspirin	£15,080	7.082	Baseline		
		Warfarin	£15,583	7.283	£503	0.201	£2,502
		A+C	£16,070	7.061	£487	-0.222	Dominated
		Dabigatran 150 mg	£17,312	7.489	£1,729	0.206	£8,393
		Dabigatran 110 mg	£17,815	7.458	£503	-0.031	Dominated
		Sequence < 80	£17,827	7.46	£515	-0.029	Dominated
Patient Cohort **As per Sequence Model > 80** **Base-case** **82.9 years old** **57.1% males**	**Base-case**	Aspirin	£7,005	4.296	Baseline		
		A+C	£7,599	4.279	£594	-0.017	Dominated
		Warfarin	£7,809	4.344	£804	0.048	£16,750 (ED)
		Dabigatran 150 mg	£8,840	4.447	£1,835	0.151	£12,152
		Dabigatran 110 mg	£9,389	4.429	£549	-0.018	Dominated
		Sequence > 80	£9,929	4.111	£1,089	-0.336	Dominated
	Exploratory Analysis	Aspirin	£7,005	4.296	Baseline		
		A+C	£7,599	4.279	£594	-0.017	Dominated
		Warfarin	£7,809	4.344	£804	0.048	£16,750 (ED)
		Dabigatran 150 mg	£8,997	4.444	£1,992	0.148	£13,459
		Dabigatran 110 mg	£9,168	4.439	£171	-0.005	Dominated
		Sequence > 80	£9,871	4.132	£874	-0.312	Dominated

A+C: Aspirin plus clopidogrel; ED: Extended dominance; ICER: Incremental cost effectiveness ratio Inc.: Incremental; INR: International normalised ratio; QALY: Quality-adjusted life year; Sequence: Dabigatran sequence

Disutility associated with dabigatran

The results from the RE-LY QoL sub-study [redacted] The disutility associated with dabigatran treatment was tested by the ERG using two approaches. First, the difference in utility, [redacted] reported in the RE-LY QoL sub-study was incorporated into the model. A difference in utility of [redacted] Second, [redacted]

[redacted] Table 54 summarises the results of the incremental analysis for both approaches, applied to the younger cohort of the single model and to the older cohort of the sequence model over 80.

Table 54: Incremental analysis for the different interventions incorporating disutility associated with dabigatran treatment

		Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Patient Cohort **As per Single Model** **Base-case** **71 years old** **63.6% males**	**Base-case**	Aspirin	£15,080	7.082	Baseline		
		Warfarin	£15,583	7.283	£503	0.201	£2,502
		A+C	£16,070	7.061	£487	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.497	£1,340	0.214	£6,262
		Sequence < 80	£17,767	7.45	£844	-0.047	Dominated
		Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated
	Exploratory analysis Disutility = [redacted]	Warfarin	£15,080	7.082	Baseline		
		Aspirin	£15,583	7.283	£503	0.201	£2,502
		A+C	£16,070	7.061	£487	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.491	£1,340	0.208	£6,442
		Sequence < 80	£17,767	7.443	£844	-0.048	Dominated
		Dabigatran 110 mg	£18,385	7.427	£1,462	-0.064	Dominated
	Exploratory analysis Disutility = [redacted]	Aspirin	£15,080	7.082	Baseline		
		Warfarin	£15,583	7.283	£503	0.201	£2,502
		A+C	£16,070	7.061	£487	-0.222	Dominated
		Dabigatran 150 mg	£16,923	7.483	£1,340	0.2	£6,700
		Sequence < 80	£17,767	7.435	£844	-0.048	Dominated
		Dabigatran 110 mg	£18,385	7.419	£1,462	-0.064	Dominated
Patient Cohort **As per Sequence Model > 80** **Base-case** **82.9 years old** **57.1% males**	**Base-case**	Aspirin	£7,005	4.296	Baseline		
		A+C	£7,599	4.279	£594	-0.017	Dominated
		Warfarin	£7,809	4.344	£804	0.048	£16,750 (ED)
		Dabigatran 150 mg	£8,840	4.447	£1,835	0.151	£12,152
		Dabigatran 110 mg	£9,389	4.429	£549	-0.018	Dominated
		Sequence > 80	£9,929	4.111	£1,089	-0.336	Dominated
	Exploratory analysis Disutility = [redacted]	Aspirin	£7,005	4.296	Baseline		
		A+C	£7,599	4.279	£594	-0.017	Dominated
		Warfarin	£7,809	4.344	£804	0.048	£16,750 (ED)
		Dabigatran 150 mg	£8,840	4.441	£1,835	0.145	£12,655
		Dabigatran 110 mg	£9,389	4.423	£549	-0.018	Dominated
		Sequence > 80	£9,929	4.106	£1,089	-0.335	Dominated
	Exploratory analysis Disutility = [redacted]	Aspirin	£7,005	4.296	Baseline		
		A+C	£7,599	4.279	£594	-0.017	Dominated
		Warfarin	£7,809	4.344	£804	0.048	£16,750 (ED)
		Dabigatran 150 mg	£8,840	4.434	£1,835	0.138	£13,297
		Dabigatran 110 mg	£9,389	4.416	£549	-0.018	Dominated
		Sequence > 80	£9,929	4.1	£1,089	-0.334	Dominated

A+C: Aspirin plus clopidogrel; ED: Extended dominance; ICER: Incremental cost effectiveness ratio Inc.: Incremental; INR: International normalised ratio; QALY: Quality-adjusted life year; Sequence: Dabigatran sequence

Incorporating disutility associated with dabigatran treatment increased the ICER for dabigatran 150 mg slightly, yet it did not change the overall conclusions regarding the cost-effectiveness of this intervention.

Software used to conduct the MTC

As described in Section 4.4.1.2, two software programs with slightly different assumptions were used to conduct MTCs by the manufacturer. In the base-case the manufacturer models the results of the SAS analysis for aspirin, aspirin + clopidogrel and no treatment, using the trial results for warfarin, dabigatran 150 mg, dabigatran 110 mg and sequential treatment. The ERG tested two other options i) full SAS-MTC ii) WINBUGS MTC. The ICER comparing dabigatran 150 mg increased from £6,264 per QALY to i) £6,874 per QALY or ii) £8,357 per QALY using these alternate data inputs.

Treatment discontinuation

As discussed in section 5.2, the manufacturer did not provide sufficient data to replicate the extrapolation of discontinuation using the lognormal distribution. However, they did provide an estimate of the cost-effectiveness of dabigatran 150 mg compared to warfarin using this extrapolation. The ICER of dabigatran 150 mg compared to warfarin increased from £6,264 per QALY to £6,305 per QALY.

The ERG 'alternative' base-case

The ERG presents an alternative base-case to the manufacturer's base-case. This alternative base-case combines elements from the above sensitivity analysis that were considered by the ERG to be plausible alternatives to those employed by the manufacturer and provides an estimate for the cost-effectiveness of dabigatran (150 mg and 110 mg) in relation to warfarin and aspirin. The ERG alternative base-case assumes:

1) A patient cohort representative of the AF patient population in the UK, using the data reported by Gallagher *et al.*, 2008.[46]
2) The variable (per patient) costs of anticoagulant monitoring are £115.14
3) Patients suffer from dyspepsia during dabigatran treatment, not only three months.
4) Disability and mortality risks after stoke are treatment independent
5) Disutility associated with dabigatran is [redacted] during the first 12 months of treatment

Table 55 summarises the incremental analysis for the ERG base-case. The ICER for dabigatran 150 mg is £24,173 per QALY for the ERG alternative base-case scenario. In contrast, the ICER for dabigatran 150 mg in the manufacturer's scenario is £6,264 per QALY. The ICER for dabigatran 150 mg is further increased using the full SAS-MTC, from £24,173 per QALY to £25,694 per QALY. Assuming that the WinBUGS-MTC is the most appropriate, the ICER for dabigatran 150 mg is £29,131 per QALY.

Table 55: Incremental analysis for the ERG base-case

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER
Warfarin	£8,909	5.907	Baseline		
Aspirin	£9,561	5.840	£652	-0.067	Dominated
Aspirin plus clopidogrel	£10,346	5.818	£1,437	-0.089	Dominated
Dabigatran 150 mg	£12,124	6.040	£3,215	0.133	£24,173
Dabigatran 110 mg	£12,348	6.035	£224	-0.005	Dominated
Sequence < 80	£12,791	5.947	£667	-0.093	Dominated

7 IMPACT ON ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The analyses undertaken in Section 6 are summarised in Table 56.

Table 56: Summary of the analyses undertaken in Section 6

Assumption	Comparator	ICER (/QALY)
Base-case	Warfarin	£6,262
UK population [51]	Warfarin	£10,582
INR controlled	Warfarin	£60,895
INR <2	Aspirin	£740
INR >3	Aspirin	£4,441
Cost of INR monitoring = £279.36	Warfarin	£10,528
Cost of INR monitoring = £241.54	Warfarin	£11,720
Cost of INR monitoring = £115.14	Warfarin	£15,701
Dyspepsia costs over treatment	Warfarin	£6,659
Equal disability risk	Warfarin	£8,393
Disutility from dabigatran treatment for 3 months	Warfarin	£6,442
Disutility from dabigatran treatment for 12 months	Warfarin	£6,700
SAS-MTC	Warfarin	£6,874
Winbugs-MTC	Warfarin	£8,357
Lognormal distribution for the extrapolation of discontinuation	Warfarin	£6,305
ERG base-case	Warfarin	£24,173

8 CONCLUSIONS

Based primarily on a single trial (RE-LY[4]), dabigatran 150 mg bid was shown to be non-inferior, and subsequently superior, to dose-adjusted warfarin in the prevention of stroke/SE. Dabigatran 150 mg bid was also shown to be efficacious in preventing ischaemic stroke and vascular death, without significant concomitant increases in the incidence of haemorrhagic stroke or major bleeding. However, the incidence of GI bleeds, including major GI bleeds and life-threatening GI bleed, was increased with dabigatran 150 mg bid compared to dose adjusted warfarin.

Results for those under 80 years of age were similar to those of the whole population, both in terms of effectiveness and safety. However, there seems to be some benefit in a dose reduction in the elderly in terms of haemorrhagic outcomes, with dabigatran 110 mg bid showing a significant reduction in the incidence of haemorrhagic stroke and ICH compared to dose-adjusted warfarin, but not dabigatran 150 mg bid. In addition, although dabigatran is efficacious in patients with good warfarin control, the beneficial effects of dabigatran seem to be most pronounced in those with poor INR control.

The main uncertainty surrounding the evaluation of the clinical evidence is the generalisability of the results to the AF population in the UK NHS. The population in the RE-LY trial, on which the assessment of efficacy and safety relied, had a higher risk of stroke than that specified in the NICE scope. Furthermore, according to clinical experts advising the ERG, the threshold for treatment with warfarin seems to be decreasing, therefore decreasing the risk of stroke in the eligible AF population, making the population in the RE-LY trial less representative of clinical practice over time.

The economic model structure was considered appropriate for the decision problem, and the general approach employed by the manufacturer to estimate lifetime cost-effectiveness was deemed appropriate and met the requirements of the NICE reference case approach. However, the ERG identified a few alternative assumptions to those used in the model. By instituting these assumptions the cost-effectiveness of dabigatran 150 mg bid compared to warfarin ranged from £24,173 to £29, 131 per QALY.

The main uncertainty surrounding the economic evaluation is the cost-effectiveness of dabigatran in the heterogeneous groups of the UK population. In the additional work

undertaken by the ERG we showed that the cost-effectiveness of dabigatran differs by severity and that it is not cost-effective for patients who can maintain adequate INR levels. Since it is unclear from treatment outset which patients will have INR control it may be possible to use warfarin and dabigatran sequentially. The cost-effectiveness of warfarin with second-line dabigatran compared to first-line dabigatran will depend on the risk associated with warfarin until INR control can be decided.

8.1 Implications for research

Further information on the appropriate treatment pathway could be obtained by modelling the cost-effectiveness of dabigatran as second-line therapy compared to dabigatran as first-line. This decision would also be improved with additional information on the differences in costs and effects of dabigatran by severity and INR control, which could also be used in the economic model.

9 REFERENCES

1. Sorensen SV, Dewilde S, Singer DE, Goldhaber SZ, Monz BU, Plumb JM. Cost-effectiveness of warfarin: trial versus "real-world" stroke prevention in atrial fibrillation. *Am Heart J* 2009;157:1064-73.

2. 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;154:1-11.

3. Camm AJ. The RE-LY study: Randomized Evaluation of Long-term anticoagulant therapY: dabigatran vs. warfarin. *Eur Heart J* 2009;30:2554-55.

4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009;361:1139-51.

5. *RELY-ABLE long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed RE-LY trial*. Boehringer Ingelheim Pharmaceuticals; [cited 29/11/10]. Available from: http://clinicaltrials.gov/ct2/show/NCT00808067?term=NCT00808067&rank=1.

6. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant Aspirin compared with Warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study). *Am J Cardiol* 2007;100:1419-26.

7. Nagarakanti R, Ezekowitz MD, Parcham-Azad K, Reilly PA, Nehmiz G, Lionetti DA, et al. *Long-term open label extension of the prevention of embolic and thrombotic events study in patients with atrial fibrillation randomized to dabigatran (PETRO–Ex study)*. In: Scientific Sessions of the American Heart Association. New Orleans; 2008. p. P08-14579 Abstract #4269.

8. *Clinical trial report: Open-label, randomised exploratory dose response study in pharmocodynamics and safety of BIBR 1048 (110mg b.i.d and 150mg b.i.d) for 12 weeks in patients with non-valvular atrial fibrillation in comparison to warfarin*. Tokyo: Nippon Boehringer Ingelheim Company Ltd; 2007.

9. Snapinn SM. Noninferiority trials. *Current Controlled Trials in Cardiovascular Medicine* 2000;1:19-21.

10. *Risk of stroke with AF*. Clinical Exercise Physiology Consortium, VA Palo Alto Medical Center and Stanford University; [cited 2010 January 10th]. Available from: http://www.cardiology.org/tools/risk_of_stroke_AF.html.

11. Lip GY, Nieuwlaat R, R. P, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263-72.

12. *FDA Advisory Committee Briefing Document: Dabigatran Etexilate (DE)*. Ingelheim am Rhein Boehringer Ingelheim GmbH; 2010.

13. Beasley N, Thompson A. *Clinical Review: Pradaxa (dabigatran)*. Silver Spring, MD: FDA Center for Drug Evaluation and Research; 2010.

14. Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. *Arch Intern Med* 2006;166:1269-75.

15. Roskell N. *Systematic review and meta-analyses of treatments used for the prevention of stroke in patients with atrial fibrillation*. Manchester: RTI Health Solutions (for Boehringer Ingelheim GmbH); 2010.

16. Mant J, Hobbs FDR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GYH, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493-503.

17. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903-12.

18. Connolly SJ, Yusuf S, Camm J, Chrolavicius S, Commerford P, Flather M, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066-78.

19. Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation - Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med* 1998;158:1513-21.

20. McBride R, Chesebro JH, Wiebers DO, Holland AE, Linker S, Bardsley WT, et al. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation - Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687-91.

21. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial-fibrillation. *Lancet* 1989;1:175-79.

22. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007;36:151-56.

23. Hellemons BSP, Langenberg M, Lodder J, Vermeer F, Schouten HJA, van Ree JW, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ* 1999;319:958-64.

24. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8:1-179.

25. Walker AM, Bennett D. Epidemiology and outcomes in patients with atrial fibrillation in the United States. *Heart Rhythm* 2008;5:1365-72.

26. Yousef ZR, Tandy SC, Tudor V, Jishi F, Trent RJ, Watson DK, et al. Warfarin for non-rheumatic atrial fibrillation: five year experience in a district general hospital. *Heart* 2004;90:1259-62.

27. Hylek EM, Go AS, Chang YC, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;349:1019-26.

28. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral Hemorrhage. *Arch Intern Med* 2004;164:880-84.

29. 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;156:1829-36.

30. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke - Results from the national registry of Atrial Fibrillation. *Jama-Journal of the American Medical Association* 2001;285:2864-70.

31. Fang MC, Go AS, Hylek EM, Chang Y, Henault LE, Jensvold NG, et al. Age and the risk of warfarin-associated hemorrhage: The anticoagulation and risk factors in atrial fibrillation study. *J Am Geriatr Soc* 2006;54:1231-36.

32. *Historic Interim Life Tables, Great Britain 2005-2007*. Office for National Statistics; [cited 2010 15th December]. Available from: http://www.statistics.gov.uk/statbase/Product.asp?vlnk=14459.

33. 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;24:1021-33.

34. Dorman P, Dennis M, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? *Journal of Neurology Neurosurgery and Psychiatry* 2000;69:487-93.

35. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. *Med Care* 2005;43:736-49.

36. Curtis L. *Unit Costs of Health and Social Care*. Canterbury: Personal Social Services Research Unit, University of Kent; 2009. Available from: http://www.pssru.ac.uk/uc/uc2009contents.htm

37. *Atrial Fibrillation: the management of atrial fibrillation. Costing report: implementing NICE guidance in England*. London: National Institute of Health and Clinical Excellence; 2006. Report No.: NICE Clinical Guideline no. 36. Available from: http://www.nice.org.uk/nicemedia/pdf/CG036costingreport.pdf

38. *MIMS Online*. Haymarket Medical Media; [cited 2010 15th December]. Available from: http://www.mims.co.uk/.

39. *NHS reference costs 2008-2009*. London: Department of Health; 2010. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591

40. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* 2000;320:1236-39.

41. DeWilde S, Carey IM, Emmas C, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. *Heart* 2006;92:1064-70.

42. 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;19:381-90.

43. Currie CJ, Jones M, Goodfellow J, McEwan P, Morgan CL, Emmas C, et al. Evaluation of survival and ischaemic and thromboembolic event rates in patients with non-valvar atrial fibrillation in the general population when treated and untreated with warfarin. *Heart* 2006;92:196-200.

44. Rietbrock S, Plumb JM, Gallagher AM, van Staa TP. How effective are dose-adjusted warfarin and aspirin for the prevention of stroke in patients with chronic atrial fibrillation? An analysis of the UK General Practice Research Database. *Thromb Haemost* 2009;101:527-34.

45. Schweikert B, Hunger M, Meisinger C, Konig HH, Gapp O, Holle R. Quality of life several years after myocardial infarction: comparing the MONICA/KORA registry to the general population dagger. *Eur Heart J* 2009;30:436-43.

46. Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate

patients receive stroke prophylaxis? *Journal of Thrombosis and Haemostasis* 2008;6:1500-06.

47. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. *Ann Intern Med* 1999;131:492-+.

48. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523-32.

49. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007;110:196-202.

50. Wyrwich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL, Symonds T, et al. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res* 2005;14:285-95.

51. Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technol Assess* 2007;11.

52. Department of Health Payment by Results Team. *Payment by Results 2010-11 tariff information spreadsheet*. London: Department of Health; 2010. Available from: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/@sta/@perf/documents/digitalasset/dh_115898.xls

Appendix 1: Calculation of alternative INR monitoring costs

Calculation of alternative monitoring costs

	Item	Cost
Primary Care (PC) Variable Costs	Reagents	£6,000
	Nursing staff	£10,059
	Administration staff	£2,500
	Stationary	£333
	Total	£18,892
	Variable costs per patient (/100)	£188,92
	Weighted PC variable costs per patient (x 75%)	£141.69
	Weighted PC variable costs per patient inflated from 2004/2005 to 2009/2010 (x1.16925)	£165.67
Secondary Care (SC) Costs	Reference cost for anticoagulation services[1]	£22.36
	Annual SC per patient (x20 visits)	£447.20
	Weighted SC per patient (x25%)	£111.80
	Weighted SC costs per patient inflated from 2008/2009 to 2009/2010 (x1.01685)	£113.68
Total monitoring costs (£165.67+£113.68)		**£279.36**

[1] – The reference cost for anticoagulation services is an average of all costs of anticoagulation services, weighted per activity

Calculation of alternative INR monitoring costs

	Item	Cost
Primary Care (PC) Variable Costs	Total PC costs	£32,196
	Warfarin costs 4.5mg/day	£3,888
	Fixed costs (£32,196-£3,888)	£9,416
	Proportion of fixed costs (9,416/(£32,196-£3,888))	33%
	Weighted PC variable costs per patient inflated from 2004/2005 to 2009/2010 (x1.16925)	£165.67
Secondary Care (SC) Costs	Reference cost for anticoagulation services[1]	£22.36
	Annual SC per patient (x20 visits)	£447.20
	SC variable costs per patient (£447.20 - 33% x £447.20)	£298.40
	Weighted SC per patient (x25%)	£74.60
	Weighted SC costs per patient inflated from 2008/2009 to 2009/2010 (x1.01685)	£75.86
Total monitoring costs (£165.67+£75.86)		**£241.54**

Appendix 2: Quality Assessment using the Philips economic modelling checklist

Quality criterion	***Question(s)***	***Response (√, X, or NA)***	***Comments***
S1	Is there a clear statement of the decision problem?	√	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	*X*	The decision problem is to assess whether dabigatran etexilate is cost-effective for the prevention of stroke and SE in AF, within its licensed indication. The model was designed to evaluate the cost-effectiveness of dabigatran as an alternative to warfarin as a primary analysis, and aspirin and the combination of aspirin plus clopidogrel as secondary analysis. The model does not allow the assessment of all treatment sequences appropriate to UK clinical practice, namely using dabigatran as an alternative to warfarin in patients whose INR is outside target range.
	Is the primary decision-maker specified?	√	
S2	Is the perspective of the model stated clearly?	√	
	Are the model inputs consistent with the stated perspective?	√	
	Has the scope of the model been stated and justified?	√	
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	√	
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	√	
	Are the sources of data used to develop the structure of the model specified?	√	
	Are the causal relationships described by the model structure justified appropriately?	√	
S4	Are the structural assumptions transparent and justified?	√	
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	*X*	The manufacturer assumes that acute myocardial is associated solely with acute costs and disutility, and not with any long-term consequences. The clinical experts contacted by the ERG considered this assumption to be unreasonable taking in consideration the natural course of this event. Pulmonary embolism was not included in the model.
S5	Is there a clear definition of the options under evaluation?	√	
	Have all feasible and practical options been evaluated?	√	Clinical experts confirmed that the MS included all the relevant comparators with the exception of a device only used for a minority of patients.

	Is there justification for the exclusion of feasible options?	NA	
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	√	
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	√	
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	√	
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	√	
S9	Is the cycle length defined and justified in terms of the natural history of disease?	√	The cycle length is three months and patients can only experience one event per cycle. In the opinion of clinical experts consulted by the ERG an event can occur more frequently than every three months. The cycle length chosen is likely to bias the results against dabigatran.
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	√	
	Where choices have been made between data sources, are these justified appropriately?	√	
	Has particular attention been paid to identifying data for the important parameters in the model?	√	
	Has the quality of the data been assessed appropriately?	√	
	Where expert opinion has been used, are the methods described and justified?	*X*	Recommendations by clinical experts reflected in the model were not sufficiently justified.
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	*X*	The extrapolation of discontinuation rates beyond the horizon of the RE-LY trial was unclear.
D2a	Is the choice of baseline data described and justified?	√	
	Are transition probabilities calculated appropriately?	√	
	Has a half-cycle correction been applied to both cost and outcome?	√	
	If not, has this omission been justified?	N/A	

D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	√	
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	*X*	The use of Weibull distributions to extrapolate discontinuation rates beyond the duration of the RE-LY trial was not justified.
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	*X*	Alternative extrapolation assumptions were explored at the request of the ERG in the Points for Clarification.
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	√	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	*N/A*	
D2c	Are the costs incorporated into the model justified?	√	
	Has the source for all costs been described?	√	
	Have discount rates been described and justified given the target decision-maker?	√	
D2d	Are the utilities incorporated into the model appropriate?	√	
	Is the source for the utility weights referenced?	√	
	Are the methods of derivation for the utility weights justified?	*N/A*	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	√	
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	√	
	Is the process of data incorporation transparent?	√	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	√	
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	√	

D4	Have the four principal types of uncertainty been addressed?	*X*	Parameter uncertainty was addressed with the PSA. Nevertheless, PSA failed to include the totality of uncertain parameters. Uncertainty around anticoagulation costs was not included in the PSa. In addition, the standard errors assumed for the utility values associated with post-event disutility were implausible taking in consideration the data reported by the original paper. Therefore, the PSA does not reflect the set of parameter uncertainty. As the parameter uncertainty is inadequately simulated by the PSA, decision uncertainty is thus under-estimated. Heterogeneity was not explored by the MS. Heterogeneity in the AF population is due to two main reasons: $CHADS_2$ score, which measures the risk of ischaemic stroke; and INR range in case of warfarin-treated patients. The ability to keep INR within range will affect the risk of haemorrhagic events, ischaemic events and monitoring costs. Such heterogeneity was not evaluated in the MS.
	If not, has the omission of particular forms of uncertainty been justified?	X	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	*X*	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	X	The structural sensitivity analysis did not test all structural assumptions. Structural assumptions such as acute myocardial infarction having no long term consequences were not tested in the structural sensitivity analysis.
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	X	The manufacturer did not run sub-group analysis.
D4d	Are the methods of assessment of parameter uncertainty appropriate?	*X*	As the model only allows to compare one intervention against another one, the output of the PSA was solely cost-effectiveness acceptability curves comparing two interventions. However, dabigatran 150 mg and dabigatran 110 mg should be compared against each other, warfarin, aspirin, and aspirin plus clopidogrel. Therefore, the appropriate method would have been to draw a cost-effectiveness acceptability frontier, which compared all interventions simultaneously.
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	√	
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	*X*	Due to model programming inconsistencies when resetting model inputs the manufacturer was asked to confirm that the model was using the correct parameters. In the response to the points for clarification, the manufacturer provided a corrected model.
	Are any counterintuitive results from the model explained and justified?	*N/A*	
	If the model has been calibrated against independent data, have any differences been explained and justified?	√	
	Have the results of the model been compared with those of previous models and any differences in results explained?	*X*	No comparison was undertaken by the manufacturer.