NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Dabigatran for the prevention of stroke and systemic embolism in atrial fibrillation

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to….

- provide justification for reducing the dabigatran treatment dose from 150 mg to 110 mg at 80 years of age
- comment on the impact of being unable to utilise P-glycoprotein inhibitors on the use of dabigatran and the management of atrial fibrillation
- provide a justification for choosing the mixed treatment comparison (MTC) (SAS) for the base case instead of the results from the MTC (WinBUGs)
- provide a comparison of the different hazard ratios from the MTC (SAS), MTC (WinBUGS) analyses and the direct pairwise results and justify any discrepancies
- justify the exclusion of trials with zero event arms from the MTC
- provide a revised model with the ability to choose any of the included treatments (dabigatran or warfarin) as either a first-line or a second-line treatment option
- provide base-case cost-effectiveness results comparing dabigatran 110 mg and 150 mg when used as either first-line treatment or as a second-line treatment following warfarin
- analyse and provide base-case cost-effectiveness comparing the results of the following treatment sequences:

  dabigatran → warfarin → aspirin → no treatment

  and warfarin → aspirin → no treatment.

Indicative licensed indication

In April 2011 dabigatran (Pradaxa, Boehringer Ingelheim) received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the 'prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

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

The summary of product characteristics (SPC) provided by the manufacturer states that the use of dabigatran is contraindicated in people with severe renal impairment, active clinically significant bleeding, organic lesion at risk of bleeding, or impairment of haemostasis. The draft SPC also states that concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus is contraindicated.

Key issues for consideration

- Does the Committee consider the results from the phase III RE-LY trial to be robust?
- Is the RE-LY trial generalisable to a UK setting?
- What is the therapeutic value of the 110 mg twice daily dose of dabigatran versus the 150 mg twice daily dose?
- Are there any important subgroups for whom dabigatran is more clinically effective? The ERG commented that dabigatran has shown greater benefit

in people who achieve poor warfarin control than in those who are well controlled with warfarin.

- The ERG undertook additional work and presented an alternative base -case analysis, which increased the ICER for dabigatran 150 mg twice daily compared with warfarin from £6,261 to £24,173. Does the Committee agree with the ERG's assumptions underpinning this analysis or support those of the manufacturer?
  - The cost of anticoagulation monitoring is a key driver in the model. Does the Committee agree with the ERG that the average cost of monitoring is overestimated in the manufacturer's model? What are the most appropriate anticoagulation monitoring costs to include?
  - Is the patient cohort used by the ERG more representative of the atrial fibrillation patient population in the UK than the patient cohort from the RE-LY trial?
  - Has the manufacturer underestimated the cost of dyspepsia associated with dabigatran by including costs for the first treatment cycle only, rather than throughout treatment?
  - Is the manufacturer correct in its assumption that disability due to stroke is treatment-dependent, or should it be considered to be independent of treatment, as in the ERG's analysis?
  - Is disutility associated with dabigatran treatment underestimated in the manufacturer's model?
- Does the Committee consider there to be any patient subgroups for which treatment with dabigatran is more or less cost effective? For example, additional work carried out by the ERG suggests that dabigatran is more cost effective in patients with higher baseline $CHADS_2$ scores.
- In addition, the ERG has suggested that the beneficial effects of dabigatran are most pronounced in patients with poor INR control. Does the Committee agree with the ERG's analyses that suggest that dabigatran is not cost effective for patients who can maintain adequate INR levels?

- Is the Committee satisfied that the manufacturer has investigated the full set of relevant sequences of treatment with dabigatran in its economic modelling?
- Is separate consideration required for the two doses of dabigatran? The manufacturer's cost-effectiveness analysis and the ERG's additional work both estimate that the lower 110 mg twice daily dose of dabigatran is associated with higher costs and fewer QALYs than the higher 150 mg twice daily dabigatran dose.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People with atrial fibrillation (AF) who are at moderate to high risk of stroke or systemic embolism. The definition of moderate to high risk is that used in the RE-LY trial which required people with AF to have one additional risk factor for stroke from a pre-defined list.
Intervention	Dabigatran etexilate.
Comparators	The manufacturer's submission presented a primary analysis comparing dabigatran with warfarin. Aspirin monotherapy and clopidogrel plus aspirin were considered in secondary analyses in people who are unable or unwilling to receive warfarin but are eligible for dabigatran.
Outcomes	• stroke • non-central nervous system embolism • myocardial infarction • mortality • adverse effects of treatment including haemorrhage • health-related quality of life.
Economic evaluation	The economic evaluation performed was a cost–utility analysis, and the results are expressed in terms of incremental cost per QALY gained. Various time horizons are presented with lifetime being that of the primary analysis. Costs are considered from the NHS and Personal Social Services perspective.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG noted that the NICE scope for 'Dabigatran for the prevention of stroke and systemic embolism in atrial fibrillation' specifies the target population as people with atrial fibrillation who are at moderate to high risk of stroke or systemic embolism. The ERG further noted that the definition of moderate/high risk of stroke or systemic embolism used in the manufacturer's submission differs slightly to the definition of moderate and high risk adopted in NICE clinical guideline 36. The ERG commented that the population in the manufacturer's submission seemed to be at higher risk of stroke because the definition of 'moderate' included those aged 75 years and over with no additional risk factors, whereas NICE clinical guideline 36 defines moderate as people aged 65 years and over with no additional risk factors. The ERG commented that the inclusion of people aged over 65 years with atrial fibrillation but with no other risk factors for stroke would have been useful, and that the inclusion of this potentially large subgroup would reflect NICE clinical guideline 36 more closely and reduce the overall risk level of the population.

1.2.2 Intervention

The intervention specified in the manufacturer's decision problem is dabigatran etexilate 110 mg or 150 mg twice daily. Three regimens were explored in the submission: 110 mg twice daily, 150 mg twice daily and 150 mg twice daily followed by 110 mg twice daily once the patient reached the age of 80. The ERG sought clarification from the manufacturer on the reasons for the reduction in dose at the age of 80. The manufacturer stated that the regimens incorporating dose reduction at the age of 80 were implemented based on interim feedback from the European Medicines Agency and the posology reflected in the Canadian approval of dabigatran. The ERG noted that the licence granted in the USA does not include an age-related dose reduction in its posology. However, the ERG's clinical advisers considered the dose reduction in people at the age of 80 to be a reasonable

precaution, based upon the known increased risk of bleeding with warfarin, and the pharmacology of dabigatran with decreased renal function, and that this reflects clinical practice.

1.2.3 Comparators

Clinical advisers to the ERG agreed with the NICE scope that defined the comparators as warfarin and antiplatelet agents, such as aspirin, in people for whom warfarin is unsuitable. The ERG noted that warfarin was the primary comparator in the manufacturer's submission and that aspirin monotherapy and clopidogrel plus aspirin were considered secondary comparators. The ERG's clinical advisers considered clopidogrel to have a limited role in this indication, in that it would only be considered in those who are intolerant to warfarin and who experience side effects from aspirin. The ERG noted that further treatments (ximelagatran and vitamin K antagonists other than warfarin) were included in the manufacturer's mixed treatment comparison (MTC), although the results of these comparators were not considered in the manufacturer's submission. The ERG considered that 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.

1.2.4 Outcomes

The ERG noted that the outcomes listed in the NICE scope were considered in the manufacturer's submission. However, it also noted that 'all stroke' was only used as a component of composite outcomes. A range of additional outcomes were considered by the manufacturer, as detailed on pages 21 and 22 of the ERG report. Of the additional outcomes considered by the manufacturer, ischaemic stroke, systemic embolism, myocardial infarction (total), transient ischaemic attack (TIA), haemorrhagic stroke, intracranial haemorrhage (ICH), extracranial haemorrhage (ECH), and minor bleed were included in the economic model.

1.2.5 Economic evaluation

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.

1.2.6 Subgroups

The subgroup for consideration,was defined in the scope as people who have not been previously treated with warfarin. Results for patients under and over 80 years of age (post hoc subgroup) and for warfarin-naïve and warfarin-experienced patients were presented in the manufacturer's submission. The ERG noted that the differences at baseline between the under and over 80 years subgroups were not reported in the manufacturer's submission. The ERG noted that a subgroup analysis based on international normalised ratio (INR) control, a measure of the clotting ability of the blood, was not reported in the manufacturer's submission; however the results of such an analysis were presented in a submission to the Food and Drug Administration (FDA) which are detailed in section 4.3.2.1. of the ERG report. See section 2.2 for more details.

1.3 Statements from professional/patient groups and nominated experts

Clinical specialists stated that current standard therapy for people with atrial fibrillation who have the highest risk of stroke is anticoagulation therapy with warfarin. They commented that the only practical alternative for this group is aspirin, which is less effective in preventing stroke. The clinical specialists stated that the principal disadvantage of warfarin is its narrow therapeutic index, numerous interactions with other drugs and diet, and the requirement for regular monitoring by blood test, in order to calculate the INR, with consequent dose adjustment. The clinical specialists stated that it is possible to identify subgroups of people with atrial fibrillation who have different risk of

stroke (for example, using the $CHADS_2$ score – see section 2.1.1) and different risk of bleeding. The experts commented that the introduction of dabigatran would be predominantly in primary care and would reduce the number of people treated in hospital. Because routine monitoring is not required, there should be no additional costs and it is possible that the number of medical and allied workers required to deliver anticoagulation therapy to this group would decrease.

Clinical specialists commented that dabigatran offers the advantage of effective anticoagulation without the need for monitoring, and with considerably less potential for interactions with other drugs and with dietary components. The clinical specialists noted that the lack of monitoring should make it much easier to administer than the current standard therapy using warfarin, and should also make it more acceptable to patients.

Patient experts commented on the potential for dabigatran to offer more effective anticoagulation and greater reduction in stroke for people with suboptimal anticoagulation who demonstrate a suboptimal time in therapeutic range on warfarin. Patient experts stated that dabigatran is likely to offer a specific advantage in people who experience specific side effects on warfarin.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer identified three trials that directly compared dabigatran with dose-adjusted warfarin: RE-LY, PETRO and 1160.49. The PETRO and 1160.49 trials are both phase II dose-finding studies with safety as the primary objective. The main key evidence for the clinical effectiveness of dabigatran in the manufacturer's submission comes from the pivotal RE-LY randomised controlled trial. A mixed treatment comparison was also provided.

2.1.1 RE-LY trial

The RE-LY trial was designed as a non-inferiority trial in which two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) were compared with open-label warfarin (target INR of 2.0 to 3.0) for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation and at least one additional risk factor for stroke. Randomisation took place within 14 days of the screening visit and people were randomly allocated to one of the three treatment groups with equal probability (1:1:1 allocation ratio). The study took place in 44 countries including the UK and a total of 18,113 people were enrolled across the three treatment arms (dabigatran 110 mg twice daily, n = 6,015; dabigatran 150 mg twice daily, n = 6,076; warfarin, n = 6,022). Minimum follow-up was 1 year, and median follow-up was 23.7 months. The mean age of study participants was 71.5 years and 63.6% were male. The eligibility criteria are detailed on page 55 (table 22) of the manufacturer's submission.

Two margins were used to assess non-inferiority of the RE-LY trial in the manufacturer's submission: 1.46 and 1.38. To show non-inferiority, the upper bound of the confidence interval of the hazard for dabigatran versus warfarin had to be less than the margin specified. Once non-inferiority was established for the primary outcome, further analyses investigated superiority of dabigatran over warfarin.

The manufacturer's submission reported that there were no large differences between the treatment groups in terms of baseline demographic and disease characteristics; see page 63 (table 26) of the manufacturer's submission for a detailed breakdown. Types of atrial fibrillation (persistent, paroxysmal and permanent) were equally distributed among patients.

Risk of stroke at baseline was classified according to $CHADS_2$ score (a clinical prediction rule for the risk of stroke in people with AF whereby each risk [congestive heart failure, hypertension, age, diabetes mellitus and prior

stroke or TIA] is given a score and the total is then translated into a percentage risk of stroke).

Four analyses were defined in the manufacturer's submission for the efficacy analysis: the randomised/intention-to-treat (ITT) set, the safety set, the treated set, and the per-protocol set (PPS). The primary non-inferiority analysis of the RE-LY trial reported in the manufacturer's submission was conducted on the ITT population.

A large number of subgroup analyses were conducted on the primary outcome (16 planned and a further 16 additional post hoc analyses; see pages 73 and 74 of the manufacturer's submission). The results of seven pre-planned analyses were reported in the manufacturer's submission for the primary endpoint, including subgroups broken down by age, sex, BMI and region (see pages 88 to 89 of the manufacturer's submission). Results for a wider range of outcomes were reported for two patient subgroups: 1) post hoc subgroup analyses for patients older and younger than 80 years of age and 2) pre-planned analyses of people naïve to vitamin K antagonists (VKA) (defined as treatment for 2 months or less in a person's lifetime) and people experienced in the use of VKAs (defined as treatment for more than 2 months during a person's lifetime).

Efficacy results from the RE-LY trial (presented on pages 82 to 90 of manufacturer's submission)

Non-inferiority of dabigatran compared with warfarin was established for the primary outcome of stroke/systemic embolism at both margins investigated (1.46 and 1.38). The relative risk reduction for dabigatran 110 mg and 150 mg compared to warfarin was 10% and 35%, respectively. The p-value for the non-inferiority test, using both margins, was less than 0.0001 for both doses of dabigatran. Dabigatran 150 mg twice daily was associated with a significantly lower incidence of the primary outcome of stroke/systemic embolism compared with warfarin (hazard ratio [HR] = 0.65, 95% CI 0.52 to 0.81); the beneficial effect of dabigatran 150 mg twice daily was also demonstrated in

terms of 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). A reduction in all-cause mortality was also observed and, although it did not reach statistical significance, it showed dabigatran to be non-inferior to warfarin. Dabigatran 110 mg twice daily was not significantly different from warfarin for stroke/systemic embolism, ischaemic stroke or vascular mortality, and failed to show non-inferiority for ischaemic stroke at the lower margin of 1.38. The results for acute myocardial infarction (MI) showed a small but insignificant increased risk with both doses of dabigatran (HR = 1.29, 95 % CI 0.96 to 1.75 [110 mg twice daily]; HR = 1.27, 95 % CI 0.96 to 1.75 [150 mg twice daily]).

In the post hoc subgroup analysis of people aged under 80 years, there were no statistically significant differences between dabigatran and warfarin in the incidence of ischaemic stroke, systemic embolism, TIA or myocardial infarction. The manufacturer did however report a statistically significant reduction in the incidence of TIA (HR = 0.45, 95% CI 0.23 to 0.89) in patients over 80 years of age receiving dabigatran 110 mg bid, compared with warfarin.

In both VKA-naïve and VKA-experienced people, dabigatran 150 mg twice daily was associated with a statistically significant reduction in the incidence of stroke/systemic embolism compared with warfarin (HR = 0.63, 95% CI 0.46 to 0.87 [VKA-naïve patients] and HR = 0.63, 95% CI 0.49 to 0.89 [VKA-experienced patients]). No statistically significant differences were reported for the lower, 110 mg twice daily, dose of dabigatran. The manufacturer also presented results for the secondary endpoint of stroke/systemic embolism/all-cause death by VKA-experience. This showed a statistically significant reduction in the VKA-experienced subgroup for the dabigatran 150 mg twice daily group (HR = 0.77, 95% CI 0.69 to 0.91). No other outcomes were presented in the manufacturer's submission for this subgroup.

Results for treatment effectiveness from the RE-LY trial are presented in table 1, adapted from page 37 of ERG report.

Table 1 Results for treatment effectiveness from the RE-LY trial

	Dabigatran 110 mg versus warfarin [hazard ratio (95% CI)]	Dabigatran 150 mg versus warfarin [hazard ratio (95% CI)]
All patients		
Stroke/systemic embolism	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)
Myocardial infarction	1.29 (0.96 to 1.75)	1.27 (0.96 to 1.75)
Systemic embolism only[a]	Annual rates: 0.13%, 0.11% and 0.18% for dabigatran 110 mg, 150 mg and warfarin, respectively; a hazard ratio was not reported	
Pulmonary embolism[b]	Annual rates: 0.12%, 0.15% and 0.10% for dabigatran 110 mg, 150 mg and warfarin, respectively; a hazard ratio was not reported	
Transient ischaemic attack[c]	Annual rates: 0.62%, 0.72% and 0.84% for dabigatran 110 mg, 150 mg and warfarin, respectively; a hazard ratio was not reported	
Under 80 years		
Ischaemic stroke	[redacted]	0.77 (0.58 to 1.03)
Myocardial infarction	[redacted]	1.26 (0.89 to 1.26)
Systemic embolism only	[redacted]	0.66 (0.30 to 1.47)
Transient ischaemic attack	[redacted]	0.92 (0.66 to 1.29)
Stroke/systemic embolism	Not reported	
Vascular mortality		
All-cause mortality		
Pulmonary embolism		
Over 80 years		
Ischaemic stroke	0.82 (0.51 to 1.33)	[redacted]
Myocardial infarction	1.39 (0.74 to 2.60)	
Systemic embolism only	0.51 (0.13 to 2.06)	
Transient ischaemic attack	**0.45 (0.23 to 0.89)**	
Stroke/systemic embolism	Not reported	
Vascular mortality		
All-cause mortality		
Pulmonary embolism		
VKA naïve		
Stroke/systemic embolism	0.93 (0.70 to 1.24)	**0.63 (0.46 to 0.87)**
Ischaemic stroke	Not reported	
Vascular mortality		
All-cause mortality		
Myocardial infarction		
Systemic embolism only		
Pulmonary embolism		
VKA experienced		
Stroke/systemic embolism	0.87 (0.66 to 1.15)	**0.63 (0.49 to 0.89)**
Ischaemic stroke	Not reported	
Vascular mortality		
All-cause mortality		
Myocardial infarction		
Systemic embolism only		
Pulmonary embolism		

[a] Relative risks for systemic embolism (manufacturer's submission 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).

[b] ERG calculated relative risks for pulmonary embolism: 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 **t**able 31, page 83 of the manufacturer's submission.

[C] ERG calculated relative risks 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).

Adverse events

Information on adverse events from the RE-LY trial is presented on pages 128 to 137 of the manufacturer's submission. The manufacturer reported a statistically significant difference in the incidence of haemorrhagic stroke for both doses of dabigatran compared with warfarin (HR = 0.33, 95% CI 0.16 to 0.65 [dabigatran 110 mg twice daily] and HR = 0.21, 95% CI 0.09 to 0.47 [dabigatran 150 mg twice daily]). The manufacturer also reported a statistically significant reduction in the incidence of haemorrhagic stroke (HR = 0.26, 95% CI 0.07 to 0.91) in people over 80 years of age receiving dabigatran 110 mg twice daily, compared with warfarin. Both doses of dabigatran were associated with significantly fewer life-threatening bleeds compared with warfarin (HR = 0.67, 95% CI 0.54 to 0.82 [dabigatran 110 mg twice daily] and HR = 0.80, 95% CI 0.66 to 0.98 [dabigatran 150 mg twice daily]). Both doses of dabigatran were associated with fewer cases of intracranial haemorrhage than warfarin (HR of intracranial haemorrhage including haemorrhagic stroke = 0.30 (95% CI 0.19 to 0.45) and 0.41 (95% CI 0.28 to 0.61) for dabigatran 110 mg twice daily and 150 mg twice daily doses respectively). Treatment with dabigatran 110 mg was also associated with a significant reduction in major bleeding compared with warfarin. In contrast, both doses of dabigatran were associated with a significantly higher rate of gastrointestinal (GI) bleeding compared with warfarin (HR = 1.35, 95% CI 1.19 to 1.53 [dabigatran 110 mg twice daily] and HR = 1.52, 95% CI 1.35 to 1.72 [dabigatran 150 mg twice daily]). Dabigatran 150 mg twice daily was associated with a significantly higher incidence of major (HR = 1.47, 95% CI 1.17 to 1.85) and life-threatening GI bleeding (HR = 1.62, 95% CI 1.17 to 2.26).

Adverse events in people aged under 80 years were similar to those reported for the whole RE-LY trial population. In people aged over 80 years, there was no statistically significant difference between treatment with dabigatran 150 mg twice daily and warfarin and the incidence of intracranial haemorrhage or minor bleeds. However, a significant reduction in haemorrhagic stroke and

intracranial haemorrhage was evident for treatment with dabigatran 110 mg twice daily compared to dose-adjusted warfarin. In contrast, treatment with dabigatran was associated with significantly more extracranial haemorrhages than warfarin treatment.

The manufacturer reported that more people in the dabigatran groups permanently discontinued study medication compared with those on warfarin. More subjects in the dabigatran groups also discontinued study medication permanently due to outcome events; however discontinuations due to major bleeds were similar across all treatments (annual rates of 22.0%, 22.8% and 17.9% for dabigatran 110 mg twice daily, 150 mg twice daily and warfarin, respectively).

Health-related quality of life

Health-related quality of life data were collected in a sub-study of the RE-LY trial. Although 18,113 people were enrolled in the RE-LY study, the manufacturer stated that 1440 patients completed the EQ-5D as part of the quality of life (QoL) sub-study. However, the manufacturer reported that the sub-study was reasonably representative of the overall RE-LY population (data presented in table 87 of the manufacturer's submission). The manufacturer stated that it was not possible to analyse the EQ-5D data with respect to specific events of interest and the QoL sub-study was unable to provide utility values for use in the economic model with respect to the event-driven health states. However, background utility values could be derived from the QoL sub-study for people being treated with warfarin and dabigatran.

The RE-LY QoL sub-study originated from a protocol amendment to the RE-LY trial, which allowed for the administration of EQ-5D. [redacted]

[redacted]

Table 2 EQ-5D values for QoL sub-study

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

Abbreviations: CI, confidence interval; SD, standard deviation
* Confidence intervals calculated for the purposes of this analysis

2.1.2 Meta-analyses and mixed treatment comparison

The manufacturer stated that because of differences in duration and study objective, it would not be appropriate to meta-analyse the results from the large phase III RE-LY study with the two phase II studies, PETRO and 1160.49 (both 12 week duration; 502 and 174 people randomised, respectively).

To facilitate the comparison of dabigatran with aspirin monotherapy and aspirin plus clopidogrel, the manufacturer performed a mixed treatment comparison incorporating a network meta-analysis. The search strategy and selection criteria are described in section 5.7 of the manufacturer's submission and discussed on pages 23 and 24 of the ERG report. All analyses were performed using PROC GLIMMIX in SAS, which, according to the manufacturer, offers an alternative to the traditional WinBUGS software

approach. The manufacturer also presented analyses using WinBUGS in response to a clarification request from the ERG.

The treatments considered by the manufacturer to be relevant in this analysis were dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, adjusted-dose warfarin, aspririn, clopidogrel plus aspirin, and placebo. An additional 'sequence' dabigatran treatment was used in the MTC. This was intended to reflect the use of dabigatran 150 mg twice daily in people up to the age of 80 years, and then 110 mg twice daily in those aged 80 years and over. The outcomes assessed in the MTC were: 'all stroke'; ischaemic stroke; haemorrhagic stroke; fatal or disabling stroke; systemic embolism; pulmonary embolism; all-cause mortality; TIA; intracranial haemorrhage; extracranial haemorrhage; minor bleeds; acute MI; cardiovascular mortality; and 'all bleeding'.

Results from the RE-LY trial and the MTC were very similar for both dabigatran doses compared with dose-adjusted warfarin (see table 13 on page 51 of the ERG report). The results are presented on pages 113 and 114 of the manufacturer's submission and have been adapted below in table 3.

Table 3 Relative risks (95% CI) for dabigatran versus dose-adjusted warfarin, aspirin monotherapy and aspirin plus clopidogrel from the mixed treatment comparison

	Dabigatran 110 vs. adjusted dose VKA	Dabigatran 150 vs. adjusted dose VKA	Dabigatran sequence vs. adjusted dose VKA	Dabigatran 110 vs. aspirin monotherapy	Dabigatran 150 vs. aspirin monotherapy	Dabigatran sequence vs. aspirin monotherapy	Dabigatran 110 vs. clopidogrel plus aspirin	Dabigatran 150 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)**

Abbreviations: ECH, extracranial haemorrhage; ICH, intracranial haemorrhage; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack.
Asterisk denotes statistical significance

2.2 Evidence Review Group comments

The ERG noted that the manufacturer's submission 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 people with AF. The ERG found no relevant studies that were not discussed in the manufacturer's submission.

The ERG commented that the RE-LY trial was of good quality and that the manufacturer appropriately concentrated on the results from this trial. The ERG also commented that, although the open-label nature of the warfarin arm in the RE-LY 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 were considered by the ERG to be less prone to subjective judgements. In addition, the ERG highlighted that the outcome assessors were blinded, reducing the risk of detection bias. Therefore the ERG did not consider the study design to be a major threat to study quality.

The ERG highlighted the limitations of non-inferiority trials including the establishment of the non-inferiority margin and the population on which to base analyses, which can result in the introduction of bias. Referring to the two margins used to assess non-inferiority in the RE-LY trial, the ERG noted that the derivation of the upper-bound confidence interval of 1.46 was not reported in the manufacturer's submission; 1.38 was specified as the preferred margin of non-inferiority of the FDA. The ERG noted that the primary non-inferiority analyses of the RE-LY trial reported in the manufacturer's submission were conducted on the intention-to-treat (ITT) population. To minimise the possibility of bias, the ERG highlighted that analyses of non-inferiority trials ideally use both the ITT and per-protocol populations, and that the trial is considered positive if both analyses support non-inferiority. The ERG highlighted that details of a secondary analysis using the per-protocol population were included in the clinical study report for the RE-LY study.

Although the results of the analysis were not reported, the clinical study report stated that they supported those of the ITT analysis. Overall, the ERG felt that adequate measures were taken by the manufacturer to reduce the impact of potential biases associated with non-inferiority trials.

The ERG commented that the results of the RE-LY trial showed both doses of dabigatran to be non-inferior to dose-adjusted warfarin in the prevention of stroke/systemic embolism. The ERG noted that a submission from the manufacturer to the FDA indicated that dabigatran 150 mg twice daily reduced the risk of stroke/systemic embolism compared with warfarin in people who achieved INR control (HR = 0.68, 95% CI 0.50 to 0.92 [time in therapeutic INR range (TTR) 65% or above]; HR = 0.70, 95% CI 0.51 to 0.96 [TTR 68% or above]). However the ERG commented that lower levels of control were not reported in the manufacturer's submission to the FDA. The ERG also highlighted that an analysis in the medical review produced for the FDA showed a greater benefit of dabigatran in those who achieved poor warfarin control than those who were well controlled (the threshold being the centre-level median of 67%). The report concluded that, although the results showed efficacy of dabigatran in people who achieved INR control above the centre-level median, they did not show superiority over warfarin. The medical review further subdivided people by INR control (less than 58.5%, 58.5% or above, and less than 66.8%, 66.8% or above and less than 74.2%). This demonstrated that the greatest benefit of dabigatran was in the lowest quartile of INR control and that, in people achieving good INR control with warfarin, little or no additional benefit in terms of effectiveness would be gained with dabigatran. The results are presented in table 10 on page 39 of ERG report).

A key uncertainty highlighted by the ERG was the generalisability of the results to people with atrial fibrillation in the NHS. The ERG commented that the population in the RE-LY trial had a higher risk of stroke than that specified in the NICE scope. Furthermore, according to clinical specialists advising the ERG, the threshold for treatment with warfarin seems to be decreasing,

therefore decreasing the risk of stroke in the eligible atrial fibrillation population, making the population in the RE-LY trial less representative of clinical practice over time.

The ERG noted that the software chosen to run the MTC had some limitations. The MTC presented in the manufacturer's submission was conducted using PROC GLIMMIX in SAS. One of the limitations of the SAS MTC noted by the ERG was the exclusion of trials with zero event arms. In response to a request by the ERG to justify the exclusion of these trials, the manufacturer cited issues with stability of the MTC model. The ERG commented that the decision to exclude such treatments from the analyses seemed reasonable given the manufacturer's choice to use SAS (see pages 45 and 46 of the ERG report).

Additional work conducted by the ERG:

The ERG investigated the impact of including the trials of dose-adjusted warfarin versus aspirin that were omitted from the estimate of the direct comparison between warfarin and aspirin in the manufacturer's MTC (see section 4.4.6 of the ERG report). The ERG extracted data and undertook a meta-analysis of all trials available for ischaemic stroke, all-cause mortality and acute MI (see table 20, page 55 of ERG report) and found that the pooled estimates were similar to those from the single BAFTA trial included in the MTC. The biggest difference was for ischaemic stroke, but overall the inclusion of data from the additional trials would not alter the conclusions that would have been drawn using the results of the BAFTA trial alone.

2.3 Statements from professional/patient groups and nominated experts

Clinical specialists commented that the results of the RE-LY study demonstrated that dabigatran 110mg twice daily was associated with similar rates of stroke compared to warfarin, and lower rates of major haemorrhage. Clinical specialists also noted that dabigatran 150mg twice daily was

associated with lower rates of stroke compared to warfarin, and similar rates of major haemorrhage. Clinical specialists stated that both doses of dabigatran were associated with lower rates of intracranial haemorrhage, slightly increased risk of MI, and an increase in gastrointestinal side effects in comparison with warfarin.

Clinical specialists commented on the frequency of withdrawal from anticoagulation therapy being significantly higher in the both dabigatran treatment arms (110 mg twice daily and 150 mg twice daily) compared with the treatment arm on warfarin in the RE-LY study. Clinical specialists also commented on aspects of the RE-LY study which may affect its generalisability. For example, clinical specialists noted that the time spent in therapeutic range (TTR) of people in the warfarin arm averaged 64%; whereas, the average TTR reported from UK centres in the study was 72%. In addition, clinical specialists commented that half of people recruited to the RE-LY study were on long-term warfarin therapy at the time of randomisation, and therefore might be expected to have a lower rate of bleeding events compared to warfarin naive patients.

Clinical specialists stated that the potential for accumulation of dabigatran in people with renal impairment is a disadvantage that is not present with current therapy with warfarin or aspirin. In addition, in the RE-LY trial there was a greater drop-out rate among people taking dabigatran which may be related to the higher incidence of dyspeptic symptoms in those groups. This may make dabigatran unsuitable for some people. Experts stated that people who have medication compliance problems might not be identified during dabigatran treatment because there is no monitoring.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

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 and aspirin plus clopidogrel).

The manufacturer developed a Markov model which uses three levels of disability (independent, moderate, severe) and death to define health states. People enter the model at risk of various clinical events and on one of the treatments under comparison, and they transition between health states when a clinical event occurs and their disability status changes. The clinical events considered are ischaemic stroke, ICH, haemorrhagic stroke, ECH, systemic embolism, TIA and acute MI. All clinical outcomes are associated with acute costs and disutility. Further longer-term costs and disutility beyond the acute stage are associated with ischaemic stroke, haemorrhagic stroke and ICH. The model also allows for a switch to second-line treatment or a discontinuation of treatment.

The model contains 23 possible health states; 14 permanently active, 8 temporary states for people who have discontinued therapy during one cycle due to ECH, and the final state, death. A schematic representation of the model structure is presented on page 152 of the manufacturer's submission.

The patient cohort reflected the people 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 subgroup. The final results were obtained by averaging the results of each subgroup, weighted by $CHADS_2$ distribution. No results were provided by the manufacturer for individual subgroups.

The RE-LY trial provided the distribution of people per INR interval (under 2, between 2 and 3, and above 3) In the economic model, an INR below 2

increased the risk of ischaemic events (stroke, TIA and systemic embolism), and an INR above 3 increased the risk of haemorrhagic events (intracranial haemorrhage, haemorrhagic stroke and extracranial haemorrhage).

The model has a cycle length of 3 months and 1 event per cycle is permitted over a life time horizon. The model assumes a NHS perspective and costs and benefits are discounted at 3.5% per annum.

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. People aged under 80 years were started with dabigatran 150 mg twice daily, and at 80 years they were switched to dabigatran 110 mg twice daily. Conversely, people 80 years or older at baseline were initiated and kept on dabigatran 110 mg twice daily. Therefore, the sequence dose model resulted in two sets of outputs: sequence model under 80 and sequence model 80 or older. In the single dose model, the intervention was independent of age.

The treatment sequence in the model was determined by whether dabigatran is used as first- or second-line treatment. Where dabigatran was chosen as a first-line treatment, comparisons were made with warfarin, aspirin plus clopidogrel, aspirin or no treatment. When dabigatran was modelled as second line, the comparators were aspirin or no treatment, and people commenced treatment on warfarin.

3.1.1 Clinical evidence

The clinical data populating the economic model can be stratified into five categories: baseline characteristics; baseline risk of treatment dependent clinical events; relative risk of treatment dependent clinical events; other treatment-dependent probabilities; other non-treatment independent probabilities.

The event risk for all treatment strategies was applied to a baseline risk of events in people 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 (page 160) of the manufacturer's submission summarises the baseline risks of treatment-dependent clinical events. Baseline risk for ischaemic stroke in people with $CHADS_2$ scores of 3 and 4 and of 5 and 6 were pooled because of lack of data. The manufacturer stated that this simplifying assumption is unlikely to have a major impact on the model.

The relative risks for the various clinical events while on treatment with dabigatran 110 mg twice daily and 150 mg twice daily were obtained from the RE-LY trial. The relative risks for aspirin, aspirin plus clopidogrel and placebo were obtained from the MTC.

Other treatment-dependent probabilities included in the economic model were mortality and disability following ischaemic stroke (obtained from Hylek [2003] and the RE-LY trial), haemorrhagic stroke and intracranial haemorrhage (obtained from Rosand [2004]). The manufacturer assumed that mortality and disability associated with dabigatran were equal to those of warfarin. Similarly, mortality and disability associated with aspirin were assumed to be equivalent to no treatment.

A summary of the clinical variables included in the economic model is presented in table 86 (pages 172 to 175) of the manufacturer's submission.

3.1.2 Utilities

The manufacturer's economic evaluation focused on health-related quality of life associated with disability 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. The sets were as follows:

Set 1: utility values relating to the general health state and treatment status

- baseline utility for AF patients
- disutility associated with WFN treatment
- disutility associated with dabigatran treatment.

Set 2: utility associated with different disability status

Set 3: acute disutility associated with the occurrence of the various clinical events.

Table 4 summarises the utility values used in the base-case analysis (from table 29, page 72 of the ERG report, or table 97, page 211 of the manufacturer's submission).

Table 4 Summary of utility and disutility values used in the base-case analysis

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]
	Systemic embolism	-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.

For the base-case analyses, baseline utility for the general health state (set 1) was sourced from the RE-LY quality of life (QoL) sub-study. The RE-LY QoL sub-study originated from a protocol amendment to the RE-LY trial which allowed for the administration of EQ-5D. [redacted]

[redacted]

3.1.3 Costs

The model considered resource costs associated with anti-thrombotic treatment (including INR monitoring), acute event 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 in order to estimate the remaining costs. The manufacturer sponsored a new study (OXVASC study) to assess the cost of stroke in patients with atrial fibrillation.

The cost of dabigatran was £2.52 per day both for 110 mg twice daily and 150 mg twice daily doses. Treatment with warfarin, aspirin and aspirin plus clopidogrel were assumed to cost £0.04, £0.09, and £0.26 per day, respectively.

In addition, the cost of INR monitoring was considered for warfarin. Treatment with dabigatran was not considered to require any monitoring. To estimate the cost of this service, the manufacturer conducted a systematic review and derived the value used in the base-case modelling from the NICE costing report that accompanied NICE clinical guideline 36 for atrial fibrillation. The cost of INR monitoring was then inflated to 2010 prices (£414.90).

The details of all costs included in the economic model can be found on pages 213 to 243 of the manufacturer's submission (and are summarised in table 31 of the ERG report).

3.1.4 Results

The original manufacturer's submission presented incremental analyses for dabigatran 110 mg twice daily and dabigatran 150 mg twice daily separately and did not provide a full incremental analysis of all treatments under evaluation. The ERG requested that the manufacturer provide a full incremental analysis of all treatments under evaluation. The incremental results provided by the manufacturer are shown in table 5 below, adapted from table 4 of the manufacturer's clarification response.

Table 5 Incremental analysis for all treatments

Intervention	Cost	QALY	Incremental cost	Incremental 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 under 80	£17,767	7.449	£844	-0.048	Dominated
Dabigatran 110 mg	£18,385	7.433	£1,462	-0.064	Dominated

Aspirin was considered as the baseline as it was associated with the lowest costs. Warfarin was associated with greater costs and health benefits than aspirin, and the incremental cost-effectiveness ratio (ICER) for warfarin compared to aspirin was £2,502 per QALY gained. Aspirin plus clopidogrel was dominated by warfarin because warfarin was less costly and was associated with greater health benefits. Dabigatran 150mg twice daily was more costly but was associated with greater health benefits than warfarin. The ICER for dabigatran 150 mg twice daily compared to warfarin was £6,261 per QALY gained. Dabigatran 110 mg twice daily was dominated by the 150 mg twice daily dose because it was associated with greater costs but lower health benefits. Although dabigatran 110 mg twice daily and the dabigatran sequence under 80 were both dominated by dabigatran 150 mg twice daily,

the manufacturer stated that dabigatran is cost effective in all scenarios compared with the treatments available in current practice. The ICERs for dabigatran 110 mg twice daily, dabigatran sequence under 80 and dabigatran sequence over 80 compared with warfarin were £18,691, £7,314 and £7,873 per QALY gained respectively.

The manufacturer presented probabilistic sensitivity analysis base-case results for dabigatran 150 mg twice daily, dabigatran 110 mg twice daily and the dabigatran sequence dose in its submission to assess the uncertainty surrounding the input parameters. Table 6 summarises the results. The inclusion of uncertainty into the model increased the ICER for dabigatran 150 mg twice daily compared with warfarin to £7,940 from £6,261 per QALY gained in the manufacturer's deterministic analysis.

Table 6 Incremental analysis for the base-case probabilistic sensitivity analysis of the single model (adapted from tables 137 and 138, page 269 of the manufacturer's submission)

Intervention	Cost	QALY	Inc. cost	Inc. QALY	ICER
Aspirin → NT	£15,279	7.029	Baseline		
A+C → aspirin → NT	£15,315	7.014	£36	-0.015	Dominated
Warfarin → aspirin → NT	£15,566	7.267	£287	0.253	£1,206
DBG150 → aspirin → NT	£17,092	7.459	£1,526	0.192	£7,940
DBG110 → aspirin → NT	£18,210	7.434	£1,118	-0.025	Dominated
DBG: dabigatran; A+C: aspirin plus clopidogrel; NT: no treatment					

The manufacturer performed structural, univariate and probabilistic sensitivity analysis. Three warfarin scenarios were presented for the structural sensitivity analysis: 'trial-like warfarin', 'real-world warfarin' and 'real-world prescribing-behaviour warfarin'. Trial-like warfarin data were taken from the RE-LY trial, while the two alternative scenarios were based on various published sources (see pages 244 and 245 of manufacturer's submission). The structural sensitivity analysis also explored the cost effectiveness of dabigatran by varying INR cost (+/-25%), time horizon (2, 10 and 15 years), and discount rate (0–6%). The cost effectiveness of dabigatran 150 mg twice daily was

highly sensitive to the time horizon specified, with a 2-year time horizon resulting in an ICER of £75,601 per QALY gained compared with warfarin. Structural sensitivity analysis was similarly carried out for dabigatran 110 mg twice daily. The results are summarised in table 7.

Table 7 Structural sensitivity analysis (from table 33 [page 78] of the ERG report)

	Alternative scenario	ICER or ICER range (min-max) [1]
Base case		£6,264
Single dose model	Sequence dose model under 80	£7,314
	Sequence dose model over 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– lifetime	2, 10 and 15 years	£75,601 - £8,111
RE-LY clinical data	Mixed treatment comparison (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 if dabigatran 150 mg twice daily as first-line treatment compared with warfarin. ICERs for these scenarios were not included in the submission.
ICER: Incremental cost effectiveness ratio; INR: International normalised ratio

The parameters tested in the univariate sensitivity analysis are presented in tables 115 to 117 in the manufacturer's submission (pages 246 to 248). Costs of major events (ischaemic stroke, ICH and haemorrhagic stroke) were varied by 50%, while the costs of systemic embolism, minor bleed and acute MI were varied by 100%. The effect of changing utility parameters, relative risks of events, discontinuation rates and therapy switch were tested separately and for each event. The highest ICER for dabigatran 150 mg twice daily compared with warfarin estimated in the univariate sensitivity analysis was £10,234 per QALY gained (see table 8).

Table 8 Univariate sensitivity analysis for dabigatran 150 mg twice daily single dose model (adapted from tables 115, 116 and 117 from manufacturer's submission). 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 people 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 page 211 of manufacturer's submission)	£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 systemic embolism, minor bleed and acute MI by +/- 100%	£6,075–£6,453
	Changing the cost of dyspepsia treatment	£6,662
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 gastrointestinal 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 second 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

[1] ICER of dabigatran 150 mg twice daily in comparison to warfarin.
DBG: dabigatran; MI: myocardial infarction; HS: haemorrhagic stroke; ICER: incremental cost effectiveness ratio; 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

A similar univariate sensitivity analysis was performed for dabigatran 110 mg twice daily. The cost effectiveness of dabigatran 110 mg twice daily in relation to warfarin was highly sensitive to high baseline $CHADS_2$ scores, risk of ischaemic stroke and risk of ICH (see table 146, page 273 of the manufacturer's submission). The ICER for dabigatran 110 mg twice daily compared with warfarin increased from the base-case estimate of £18,691 to £37,652 for a patient cohort with a $CHADS_2$ score of 4 and to £61,552 for a patient cohort with a $CHADS_2$ score of 5. Setting the relative risks of ischaemic stroke and intracranial haemorrhage for people treated with dabigatran 110 mg twice daily equal to the 95% upper confidence limits increased the base-case ICER for dabigatran 110 mg twice daily compared with warfarin from £18,691 to £47,352 and £28,259 respectively.

3.2 Evidence Review Group comments

The ERG considered the Markov model to be the appropriate choice 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.

The ERG noted that the model included most of the relevant clinical events in atrial fibrillation; however, pulmonary embolism was not included in the model. The ERG commented that the exclusion of pulmonary embolism is potentially an optimistic approach in favour of dabigatran because dabigatran is associated with higher rates of pulmonary embolism.

The ERG noted that, although the manufacturer's submission considered the atrial fibrillation population to be heterogeneous, reflected by the distribution of $CHADS_2$ scores, the manufacturer assumed that all people would be treated the same. The ERG commented that this 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.

The ERG highlighted that acute MI and systemic embolism are assumed by the manufacturer to be associated with acute costs and disutility, and not any ongoing or long-term consequences. The ERG considered this assumption to be over-simplistic and that the effect of including long-term consequences of acute MI and SE on the cost effectiveness of dabigatran is uncertain.

The ERG commented that dabigatran is associated with higher discontinuation rates than warfarin in the first 2 years of the trial, which could suggest that people tend to tolerate warfarin better than dabigatran. The ERG was concerned that the magnitude of this difference may have been incorrectly extrapolated into the future, possibly biasing the results of the model.

The two main weaknesses of the manufacturer's model were considered by the ERG to be related to the sequence of treatments and the cost of anticoagulation monitoring. The ERG commented that the full set of relevant sequences of treatment was not fully investigated by the manufacturer. For example, the ERG considered that commencing treatment with dabigatran and subsequently switching to warfarin would be a reasonable treatment sequence, but that the manufacturer's model assumed that a person could not switch to warfarin if dabigatran was the first treatment. In addition, the ERG stated that the cost of anticoagulation monitoring was a key driver of the model in terms of resources and costs, and that it was likely that the average cost of monitoring had been overestimated in the model, biasing the results in favour of dabigatran. The ERG also highlighted that its clinical advisers were concerned with the high variability of monitoring costs in practice and that people with well-controlled INR will have much lower costs than people with uncontrolled INR. This heterogeneity was not considered in the manufacturer's submission. Moreover, the ERG commented that uncertainty around the monitoring costs was also inadequately modelled in the manufacturer's submission.

3.2.1 Additional work undertaken by the ERG

The ERG undertook exploratory work relating to the treatment sequence considered by the manufacturer, the generalisability to the UK NHS population, INR monitoring, disability due to stroke and disutility associated with dabigatran treatment. As a result, the ERG built an alternative base case which provided an alternative estimate of the cost effectiveness of dabigatran 150 mg twice daily and 110 mg twice daily compared with warfarin.

With regard to generalisability, the ERG commented that the patient cohort simulated in the manufacturer's model and people with atrial fibrillation in the UK have different demographics. The ERG carried out an alternative analysis using the results of a UK study which suggested that the UK atrial fibrillation population has a lower risk of stroke than that of the RE-LY trial, but is older. In this analysis warfarin was extendedly dominated while dabigatran 110 mg twice daily was dominated by dabigatran 150 mg twice daily. The ERG stated that the analysis suggests that dabigatran 150 mg twice daily is more cost effective than warfarin and that treatment with dabigatran 110 mg twice daily is not cost effective compared with dabigatran 150 mg twice daily, regardless of age (see table 45, page 106 of the ERG report).

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 twice daily is more cost effective in people with higher $CHADS_2$ scores (see table 46 and 47, pages 109, 110 and 112, of the ERG report). The ICERs for dabigatran 150mg twice daily ranged from £10,535 per QALY gained for people with a baseline $CHADS_2$ score of 0 and no history of stroke, to £3,870 for people with $CHADS_2$ score 4 and no history of stroke, and to £2,040 for people with a baseline $CHADS_2$ score of 5 and 6 and a history of stroke. Across all $CHADS_2$ scores, dabigatran 110 mg twice daily, either in the single-dose model or the in the sequence model, is associated with higher costs and lower health benefits than dabigatran 150 mg twice daily.

Considering the people able to maintain INR within the target range of 2 and 3 as a separate sub-population for the economic evaluation, the ERG carried out an analysis that suggested that warfarin was the most cost-effective intervention for people who are able to keep INR within target range. In the sub-population able to maintain INR within target range, the ICER for dabigatran 150 mg twice daily compared to warfarin was £60,895 per QALY gained; dabigatran 110 mg twice daily and the sequence model were dominated by warfarin. The sub-population of people who are unable to keep INR within range was also evaluated by the ERG. The ICER for 150 mg twice daily dabigatran compared with warfarin for people with an INR below 2 was £704 per QALY gained. For people with an INR above 3, warfarin was dominated by dabigatran. The ERG concluded that 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 ERG undertook three approaches to calculate the variable costs of INR monitoring, which it considered had been overestimated in the manufacturer's model (see table 51, page 116 of the ERG report). The alternative costs used by the ERG were £279.45, £241.54 and £115.14 instead of £414.90 assumed by the manufacturer. Adjusting the model to test each individual assumption increased the ICER to £15,701 per QALY gained.

The ERG considered that the disutility of dabigatran captured by the RE-LY QoL sub-study had not been fully reflected in the manufacturer's cost-effectiveness analysis. The disutility associated with dabigatran treatment was tested by the ERG using two approaches. Firstly, the difference in utility between dabigatran and warfarin of [redacted], reported in the RE-LY QoL sub-study at 3 months, was incorporated into the model. Secondly, a [redacted] yearly utility decrement was incorporated into the model. Incorporating disutility associated with dabigatran treatment increased the ICER for

dabigatran 150 mg twice daily slightly, however it did not change the overall conclusions regarding the cost effectiveness of this intervention.

The ERG commented that treatment with dabigatran is associated with an increased incidence of dyspepsia, in comparison with warfarin treatment, but that the model assumes that the cost of dyspepsia is only accrued in the first cycle. The ERG considered that a more conservative approach would be to assume that costs of dyspepsia continue throughout treatment. The ICER for dabigatran 150 mg twice daily compared with warfarin increased slightly from £6,262 per QALY to £6,659 per QALY gained.

The ERG highlighted that disability due to stroke is considered to be treatment-dependent in the manufacturer's model. The ERG considered this assumption to be unsubstantiated by the evidence provided. The ERG thus explored the model assuming that disability due to stroke is independent of treatment. The ICER for dabigatran 150 mg twice daily compared with warfarin increased from £6,262 to £8,393 per QALY gained. Dabigatran 110 mg twice daily and the sequence model were associated with increased costs and decreased health benefits when compared with dabigatran 150 mg twice daily.

Finally, the ERG presented an alternative base-case analysis to the one presented by the manufacturer. The ERG alternative base case assumes:

- A patient cohort representative of the atrial fibrillation patient population in the UK, using the data reported by Gallagher et al. (2008).
- The variable (per patient) costs of anticoagulant monitoring are £115.14.
- People suffer from dyspepsia throughout dabigatran treatment, not just in the first 3-months of treatment.
- Disability and mortality risks after stroke are treatment-independent

- Disutility associated with dabigatran is [redacted] during the first 12 months of treatment as per the RE-LY QoL sub-study.

By introducing these assumptions, the ICER for dabigatran 150 mg twice daily compared with warfarin increased to £24,173 from £6,264 per QALY gained in the manufacturer's base-case analysis. The ICER for dabigatran 150 mg twice daily compared with warfarin was further increased using the full SAS-MTC, from £24,173 to £25,694. Assuming that the WinBUGS-MTC is the most appropriate, the ICER for dabigatran 150 mg twice daily compared with warfarin increased to £29,131. Extensive analyses are presented on pages 104 to 122 of the ERG report. A summary of the incremental analysis for the ERG base case is presented in table 10. A summary of the analysis undertaken by the ERG is presented in table 11.

Table 10 Incremental analysis for the ERG base case

Treatment	Cost	QALY	Inc. cost	Inc. QALY	ICER
Warfarin → Aspirin → NT	£8,909	5.907		Baseline	
Aspirin → NT	£9,561	5.840	£652	-0.067	Dominated
A+C → Aspirin → NT	£10,346	5.818	£1,437	-0.089	Dominated
DBG 150 → Aspirin → NT	£12,124	6.040	£3,215	0.133	£24,173
DBG 110 → Aspirin → NT	£12,348	6.035	£224	-0.005	Dominated
Age<80 DBG150 → aspirin → NT Age >80 DBG110 → aspirin → NT	£12,791	5.947	£667	-0.093	Dominated

DBG: dabigatran; A+C: aspirin plus clopidogrel; NT: no treatment; ICER: Incremental cost effectiveness ratio.

Table 11 Summary of analyses undertaken by the ERG

Assumption	Comparator	ICER (/QALY)
Base case	Warfarin	£6,262
UK population [a]	Warfarin	£10,582
INR controlled	Warfarin	£60,895
INR below 2	Aspirin	£740

INR above 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 DBG treatment for 3 months	Warfarin	£6,442
Disutility from DBG 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

[a] Connock M 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
DBG: dabigatran; ICER: Incremental cost effectiveness ratio; INR: International normalised ratio

3.2.2 Equality and diversity

The manufacturer stated that the final scope for this technology appraisal guidance notes that:

> *'*Consideration should be given to the advantage of dabigatran in terms of its lower requirement for therapeutic monitoring.'

This addition to the final scope was a result of the agreement of consultees that dabigatran, due to less therapeutic monitoring required, could potentially improve access to treatment for people for whom therapeutic monitoring is difficult. This correlates with the points raised in the response to section 2.5 of the manufacturer's submission, which outlined that some people currently receive suboptimal care.

4 Authors

Christian Griffiths and Zoe Charles, with input from the Lead Team: Dr Alec Miners, Dr Ann Richardson, Dr John Watkins.

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination and the Centre for Health Economics, University of York:

- Spackman E, Burch J, Faria R et al. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation, March 2011

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Boehringer Ingelheim

II Professional/specialist, patient/carer and other groups:

- AntiCoagulation Europe (ACE)
- Arrhythmia Alliance (Atrial Fibrillation Association affiliated)
- Atrial Fibrillation Association
- British Cardiovascular Society
- Clinical Leaders of Thrombosis (CLOT)
- Heart Rhythm UK
- NHS Salford
- Royal College of Nursing
- Royal College of Pathologists
- British Society for Haematology
- Royal College of Physicians
- South Asian Health Foundation