NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance should be read in conjunction with NG196.

1 Recommendations

1.1 Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with 1 or more of the following risk factors:

- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40%
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 years or older
- age 65 years or older with 1 of the following: diabetes mellitus, coronary artery disease or hypertension.

1.2 Decide whether to start treatment with dabigatran etexilate after an informed discussion with the person about its risks and benefits compared with warfarin, apixaban, edoxaban and rivaroxaban. For people taking warfarin, consider the potential risks and benefits of switching to dabigatran etexilate taking into account their level of international normalised ratio (INR) control.

2 The technology

2.1 Dabigatran etexilate (Pradaxa, Boehringer Ingelheim; hereafter referred to as dabigatran) is an orally administered anticoagulant that inhibits the thrombin enzyme. Dabigatran has a UK marketing authorisation for the 'prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with 1 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 with 1 of the following: diabetes mellitus, coronary artery disease, or hypertension'.

2.2 The summary of product characteristics states that the recommended daily dose of dabigatran is 300 mg taken as one 150-mg capsule twice daily. Therapy is continued long term. For patients aged 75 to 80 years, a dose of 220 mg taken as one 110-mg capsule twice daily can be considered at the discretion of the physician for individual patients whose thromboembolic risk is low and bleeding risk is high. Patients aged 80 years or older should be treated with a daily dose of 220 mg taken as one 110-mg capsule twice daily because of the increased risk of bleeding in this population.

2.3 Dabigatran is contraindicated in people with severe renal impairment, active clinically significant bleeding, organic lesions at risk of bleeding, impairment of haemostasis, and hepatic impairment or liver disease expected to have an impact on survival. Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole or tacrolimus is also contraindicated. The most common adverse events in people receiving dabigatran are anaemia, abdominal pain, diarrhoea, dyspepsia, gastrointestinal haemorrhage, genitourinary haemorrhage (patients may notice blood in their urine), nausea and nose bleeds. For full details of

adverse reactions and contraindications, see the summary of product characteristics.

2.4 Dabigatran is available as 110 mg and 150 mg capsules and comes in packs of 60 capsules. The manufacturer has stated that the cost to the NHS of a pack of 60 capsules of either dabigatran 110 mg or 150 mg will be £75.60 (excluding VAT). The cost per day per patient based on the recommended dosage will be £2.52 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of dabigatran and a review of this submission by the Evidence Review Group (ERG).

3.1 The manufacturer's submission included 3 trials that directly compared dabigatran with dose-adjusted warfarin: RE-LY, PETRO and 1160.49. The PETRO and 1160.49 trials were both dose-finding studies with safety data collection as the primary objective. The main evidence for clinical effectiveness presented in the manufacturer's submission was based on the RE-LY randomised controlled trial.

3.2 RE-LY was a non-inferiority trial in which 2 blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) were compared with open-label warfarin (with a target international normalised ratio [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 1 additional risk factor for stroke. The RE-LY trial included people with documented atrial fibrillation and at least 1 of the following additional risk factors: history of stroke, transient ischaemic attack, or systemic embolism; left ventricular ejection fraction of less than 40%; symptomatic heart failure; age 75 years or older; age 65 years or older with diabetes mellitus, documented coronary artery disease or hypertension. People were excluded from the RE-LY trial if they had a severe, disabling stroke in the previous 6 months or any stroke within the previous 14 days, conditions associated with increased risk of bleeding, or a contraindication to warfarin treatment.

3.3 The RE-LY study took place in 44 countries including the UK and a total of 18,113 people were randomised across the 3 treatment arms in a 1:1:1 ratio. People recruited into the study were randomised within 14 days of the screening visit and were randomly allocated to dabigatran 110 mg twice daily (n=6,015), dabigatran 150 mg twice daily (n=6,076) or warfarin (n=6,022). Minimum follow-up was 1 year, and median follow-up was 23.7 months. The mean age of people in the study was 71.5 years and 63.6% were male. Risk of stroke at baseline was classified according to $CHADS_2$ score, which is used to estimate the risk of stroke in people with atrial fibrillation to determine whether they need anticoagulation treatment. The score was calculated by giving 1 point each for the presence of

congestive heart failure, hypertension or diabetes mellitus, and age 75 years or older. Two points were given if people had already had an ischaemic stroke or transient ischaemic attack.

3.4 The primary outcome in the study was incidence of all types of stroke (including haemorrhagic stroke) or systemic embolism. To show non-inferiority in the RE-LY trial, the upper limits of the confidence interval (CI) of the hazard ratio (HR) for dabigatran versus warfarin had to be less than the margin specified. Two margins were used in the manufacturer's submission, 1.46 and 1.38, of which 1.38 was specified as the preferred margin of non-inferiority by the US Food and Drug Administration (FDA).

3.5 The reduction in relative risk of stroke or systemic embolism compared with warfarin was 10% for dabigatran 110 mg and 35% for dabigatran 150 mg. Dabigatran 150 mg twice daily was associated with a lower incidence of stroke or systemic embolism compared with warfarin and this was statistically significant (HR 0.65, 95% CI 0.52 to 0.81). A statistically significant beneficial effect of dabigatran 150 mg twice daily was also demonstrated in terms of a reduced incidence 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 150 mg twice daily to be non-inferior to warfarin (HR 0.88, 95% CI 0.77 to 1.00). There were no statistically significant differences between dabigatran 110 mg twice daily and warfarin in the incidence of stroke or systemic embolism, ischaemic stroke or vascular mortality. Both doses of dabigatran were associated with an increased risk of acute myocardial infarction compared with warfarin but this was not statistically significant (HR 1.29, 95% CI 0.96 to 1.75 [110 mg twice daily]; HR 1.27, 95% CI 0.94 to 1.71 [150 mg twice daily]).

3.6 The manufacturer's submission included post hoc subgroup analyses of people older and younger than 80 years of age. In both age groups, there were no statistically significant differences between either dose of dabigatran and warfarin in the incidence of ischaemic stroke, systemic embolism and myocardial infarction. However, the manufacturer did report a statistically significant reduction in the incidence of transient ischaemic attack (HR 0.45, 95% CI 0.23 to 0.89) in people older than 80 years receiving dabigatran 110 mg twice daily, compared with warfarin.

3.7 The manufacturer's submission reported results from pre-planned subgroup analyses of people naive to vitamin K antagonists such as warfarin (defined as treatment for 2 months or less in a person's lifetime) and people who have previously used vitamin K antagonists (defined as treatment for more than 2 months during a person's lifetime). In both groups, dabigatran 150 mg twice daily was associated with a statistically significant reduction in the incidence of stroke or systemic embolism compared with warfarin (HR 0.63, 95% CI 0.46 to 0.87 [vitamin K antagonist-naive group] and HR 0.63, 95% CI 0.49 to 0.89 [vitamin K antagonist-experienced group]). No statistically significant differences were reported for the lower, 110 mg twice daily, dose of dabigatran compared with warfarin.

3.8 For adverse events, the manufacturer reported a statistically significant reduction in the incidence of haemorrhagic stroke for both doses of dabigatran compared with warfarin (HR 0.31, 95% CI 0.17 to 0.56 [dabigatran 110 mg twice daily] and HR 0.26, 95% CI 0.14 to 0.49 [dabigatran 150 mg twice daily]). Both doses of dabigatran were also associated with statistically 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 (including haemorrhagic stroke) than warfarin (HR 0.30, 95% CI 0.19 to 0.45 [dabigatran 110 mg twice daily]; HR 0.41, 95% CI 0.28 to 0.61 [dabigatran 150 mg twice daily]). Treatment with dabigatran 110 mg was also associated with a statistically significant reduction in major bleeding compared with warfarin. In contrast, both doses of dabigatran were associated with a significantly higher rate of gastrointestinal 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 gastrointestinal bleeding (HR 1.47, 95% CI 1.17 to 1.85) and life-threatening gastrointestinal bleeding (HR 1.62, 95% CI 1.17 to 2.26). The manufacturer reported that more people in the dabigatran groups discontinued the study drug (22.0% in the dabigatran 110 mg twice daily group and 22.8% in the dabigatran 150 mg twice daily group), compared with those on warfarin (17.9%). More people in the dabigatran groups also discontinued study medication because of outcome events; however, discontinuations caused by major bleeds were similar for all treatments.

3.9 The manufacturer reported a statistically significant reduction in the incidence of haemorrhagic stroke in the post hoc subgroup analyses of people younger than 80 years compared with warfarin for both doses of dabigatran (HR 0.33, 95% CI 0.16 to 0.65 [dabigatran 110 mg twice daily]; HR 0.21, 95% CI 0.09 to 0.47 [dabigatran 150 mg twice daily]) and in people older than 80 years receiving dabigatran 110 mg twice daily (HR 0.26, 95% CI 0.07 to 0.91). However, the reduction in incidence of haemorrhagic stroke in people older than 80 years for dabigatran 150 mg twice daily compared with warfarin was not statistically significant (HR 0.93, 95% CI 0.81 to 1.07).

3.10 Health-related quality-of-life data were collected in a sub-study of the RE-LY trial (1440 of the 18,113 people enrolled in the RE-LY study completed the EQ-5D questionnaire as part of the quality-of-life sub-study). The manufacturer reported that the sub-study was reasonably representative of the overall RE-LY population with patients having similar demographic and disease characteristics. The manufacturer stated that analysing the EQ-5D data for specific events of interest was not possible and the quality-of-life sub-study was unable to provide utility values for event-driven health states to use in the economic model. However, background utility values could be derived from the quality-of-life sub-study for people being treated with warfarin and dabigatran, the details of which are academic-in-confidence and are not reported here.

3.11 The manufacturer performed a mixed-treatment comparison of dabigatran, aspirin monotherapy and aspirin plus clopidogrel. The treatments considered by the manufacturer to be relevant in this analysis were dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, dose-adjusted warfarin, aspirin, aspirin plus clopidogrel, and placebo. An additional sequential regimen of dabigatran was used in the mixed-treatment comparison. This was intended to reflect the use of dabigatran according to the licensed regimen which is 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 older. Results from the RE-LY trial and the mixed-treatment comparison were very similar for both dabigatran doses compared with dose-adjusted warfarin.

3.12 The manufacturer's economic evaluation was based on a cost–utility analysis designed to compare the costs and outcomes of dabigatran with treatments used in the UK (warfarin, aspirin and aspirin plus clopidogrel). The manufacturer

developed a Markov model that used 3 levels of disability (independent, moderate and severe) and death to define health states. A hypothetical cohort entered the model at risk of specified clinical events and was on 1 of the treatments under comparison. They moved between health states when a clinical event occurred and their disability status changed. The clinical events considered were ischaemic stroke, intracranial haemorrhage, haemorrhagic stroke, extracranial haemorrhage, systemic embolism, transient ischaemic attack and acute myocardial infarction. All clinical outcomes were associated with acute costs and disutility. Further longer-term costs and disutility beyond the acute stage were associated with ischaemic stroke, haemorrhagic stroke and intracranial haemorrhage. The model permitted 1 clinical event per 3-month cycle over a lifetime horizon. The model also allowed for a switch to second-line treatment or a discontinuation of treatment.

3.13 The manufacturer presented 2 economic models: a single-dose model and a sequential regimen model. In the single-dose model, the cohort with atrial fibrillation received either 110 mg twice daily or 150 mg twice daily throughout their treatment. In the sequential regimen model, the cohort was divided by age and modelled separately. The model for people younger than 80 years assumed that treatment began with dabigatran 150 mg twice daily, and switched to dabigatran 110 mg twice daily when the age of 80 years was reached. The model for people aged 80 years or older at baseline assumed a dose of dabigatran 110 mg twice daily throughout. Therefore, the sequential regimen model resulted in 2 sets of outputs: a sequential regimen model for people starting treatment younger than 80 years (incorporating a life-time horizon including the switch to 110 mg twice daily at 80 years) and a sequential regimen model for those starting treatment at 80 years or older.

3.14 The event risk for all treatment strategies was applied to the 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. 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. In the sequential regimen model, the relative risks were derived from the post hoc subgroup analyses of people older and younger than 80 years of age. The relative risks for aspirin, aspirin plus clopidogrel and placebo were obtained from the mixed-treatment comparison.

3.15 The manufacturer's economic evaluation focused on health-related quality of life associated with disability and disutility caused by the various clinical events. The baseline utility value for people with atrial fibrillation in the base-case analyses was taken from the RE-LY quality-of-life sub-study. Utility values associated with clinical events and disability status were derived from published sources.

3.16 The manufacturer's model considered resource costs associated with anti-thrombotic treatment, acute event costs, and long-term follow-up costs resulting from disability. These costs were derived from the national payment by results tariff, systematic reviews and a manufacturer-sponsored study based on the Oxford Vascular study (OXVASC) cohort. The cost of dabigatran was £2.52 (excluding VAT) per day for either the 110 mg twice daily or 150 mg twice daily doses. Treatment with warfarin, aspirin and aspirin plus clopidogrel was assumed to cost £0.04, £0.09, and £0.26 per day, respectively. Treatment with dabigatran was not considered to need any monitoring, but the cost of INR monitoring for warfarin was estimated to be £414.90 per annum. The model assumed an NHS perspective and costs and benefits were discounted at 3.5% per annum.

3.17 The manufacturer reported pairwise cost-effectiveness results for dabigatran compared with warfarin. The incremental cost-effectiveness ratios (ICERs) for the dabigatran sequential regimen in which people started treatment when younger than 80 years and continued for the rest of their lives, and the sequential regimen in which people started treatment when older than 80 years were £7,314 and £7,873 per QALY gained respectively, compared with warfarin. The ICERs for dabigatran 150 mg and 110 mg twice daily compared with warfarin were £6,264 and £18,691 per QALY gained respectively.

3.18 The manufacturer performed structural, univariate and probabilistic sensitivity analyses to reflect uncertainty in the model inputs and assumptions. The structural sensitivity analysis explored the cost effectiveness of dabigatran by varying INR cost (±25%), time horizon (2, 10 and 15 years), and discount rate (0 to 6%). The cost effectiveness of dabigatran was highly sensitive to the time horizon specified. A 2-year time horizon resulted in ICERs of £75,891 and £23,403 per QALY gained, respectively, for the dabigatran sequential regimen in people starting treatment when younger than 80 years and the dabigatran sequential regimen in people starting treatment when older than 80 years, compared with warfarin. For dabigatran 150 mg and 110 mg twice daily, the ICERs

were £75,601 and £108,736 per QALY gained, respectively.

3.19 In the univariate sensitivity analysis, the cost effectiveness of the dabigatran sequential regimen in people starting treatment when younger than 80 years was most sensitive to risk of ischaemic stroke. Setting the relative risk for ischaemic stroke to the 95% upper confidence limits increased the base-case ICER compared with warfarin from £7,314 to £17,100 per QALY gained. The cost effectiveness of the dabigatran sequential regimen in people starting treatment when older than 80 years was most sensitive to risk of ischaemic stroke and high baseline $CHADS_2$ scores. Setting the relative risks for ischaemic stroke to the 95% upper confidence limits increased the base-case ICER for the dabigatran sequential regimen in people older than 80 years compared with warfarin from £7,873 to £46,509 per QALY gained. The ICER for the dabigatran sequential regimen in people starting treatment when older than 80 years compared with warfarin increased from the base-case estimate of £7,873 to £21,129 per QALY gained for a group with a $CHADS_2$ score of 5. The ICER for dabigatran 150 mg twice daily compared with warfarin was robust to the parameters and ranges tested by the manufacturer, and the highest ICER was £10,234 per QALY gained. 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 intracranial haemorrhage.

3.20 In the probabilistic sensitivity analysis, the ICERs for the dabigatran sequential regimens in people starting treatment when younger than 80 years and in people starting treatment when older than 80 years compared with warfarin were £7,811 and £11,912 per QALY gained respectively. The probabilistic ICERs for dabigatran 150 mg and 110 mg twice daily compared with warfarin were £7,940 and £15,867 per QALY gained respectively.

3.21 The ERG noted that the manufacturer's submission included 2 generally well-conducted systematic reviews: the first was of dabigatran trials in the relevant indication, and the second was of all potentially relevant pharmacological interventions for the prevention of stroke in people with atrial fibrillation. 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 highlighted the limitations of non-inferiority trials, such as establishing the non-inferiority margin and the population on which to base analyses. Overall, the ERG felt that adequate

measures were taken by the manufacturer to reduce the impact of potential bias associated with non-inferiority trials.

3.22 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 or 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 or systemic embolism compared with warfarin in people with good INR control (HR 0.68, 95% CI 0.50 to 0.92 for time in therapeutic INR range 65% or above; HR 0.70, 95% CI 0.51 to 0.96 for time in therapeutic INR range 68% or above). The ERG also highlighted that an analysis in the submission produced for the FDA showed a greater benefit of dabigatran in people with poor INR control than in those whose INR was well controlled (the threshold being the centre-level median of 67%). The FDA report concluded that, although the results showed efficacy of dabigatran in people who had INR control above the centre-level median, the results did not show superiority over warfarin. The submission further subdivided people by INR control (less than 58.5%, 58.5% or above, 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 with good INR control with warfarin, little or no additional benefit in terms of effectiveness would be gained with dabigatran.

3.23 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 definition of moderate or high risk of stroke or systemic embolism in the manufacturer's submission differed slightly to the definition in NICE's original guideline on atrial fibrillation (now replaced by NICE's guideline on atrial fibrillation). The ERG commented that the population in the manufacturer's submission seemed to be at higher risk of stroke because the definition of moderate risk included those aged 75 years and over with no additional risk factors, whereas NICE's previous guideline on atrial fibrillation defined moderate risk as people aged 65 years and over with no additional risk factors. The ERG commented that including the potentially large subgroup of people over 65 years with atrial fibrillation but with no other risk factors for stroke would have been useful, and would reflect NICE's previous guideline on atrial fibrillation more closely and reduce the overall risk level of the population. The clinical specialists advising the ERG noted that 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.

3.24 The ERG commented that the general approach taken by the manufacturer to estimate lifetime cost effectiveness was appropriate and met the requirements of the NICE reference case. 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 excluding pulmonary embolism is potentially an optimistic approach in favour of dabigatran because dabigatran is associated with higher rates of pulmonary embolism than warfarin.

3.25 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.

3.26 The ERG highlighted that acute myocardial infarction and systemic embolism were assumed by the manufacturer to be associated with acute costs and disutility, but not with 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 myocardial infarction and systemic embolism on the cost effectiveness of dabigatran is uncertain. The ERG commented that dabigatran was 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.

3.27 The 2 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 starting treatment with dabigatran and subsequently switching to warfarin would be a reasonable treatment sequence, but 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 about the high variability of monitoring costs in practice. This heterogeneity was not considered in the manufacturer's submission. The ERG commented that uncertainty around the monitoring costs was also inadequately modelled in the manufacturer's submission.

3.28 The ERG carried out exploratory cost-effectiveness analyses by subgroups according to INR control with warfarin. The ICER for dabigatran 150 mg twice daily compared with warfarin in people with perfect INR control (that is, in target INR range 100% of the time for the entire duration of treatment) was £60,895 per QALY gained. Dabigatran 110 mg twice daily was dominated by warfarin because it was associated with greater costs but lower health benefits. The group of people with poor INR control was also evaluated by the ERG. The ICER for dabigatran 150 mg twice daily compared with warfarin for people with an INR below 2 was £740 per QALY gained. For people with an INR above 3, warfarin was dominated by dabigatran 150 mg twice daily. The ERG did not include pairwise cost-effectiveness results for dabigatran in the sequential regimen compared with warfarin. The ERG concluded that INR control is a key parameter in the economic evaluation.

3.29 The ERG used 3 approaches to calculate the variable costs of INR monitoring, which it considered had been overestimated in the manufacturer's model. The alternative costs used by the ERG were £279.36, £241.54 and £115.14, instead of £414.90 as assumed by the manufacturer. Adjusting the model to test each individual cost assumption increased the ICER for dabigatran 150 mg twice daily compared with warfarin to £10,528, £11,720 and £15,701 per QALY gained respectively.

3.30 The ERG considered that the disutility of dabigatran captured by the RE-LY quality-of-life 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 but it did not change the overall conclusions about the cost effectiveness of this intervention.

3.31 The ERG commented that treatment with dabigatran was associated with an increased incidence of dyspepsia compared with warfarin treatment, but that the

model assumed that the cost of dyspepsia was 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. This caused the ICER for dabigatran 150 mg twice daily compared with warfarin to increase slightly from £6,262 per QALY to £6,659 per QALY gained.

3.32 The ERG highlighted that disability and mortality risk after stroke is considered to be treatment dependent in the manufacturer's model. Therefore, the ERG explored the model assuming that disability caused by 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.

3.33 The ERG presented analyses using an alternative set of assumptions to those provided by the manufacturer. The ERG's alternative base case assumed:

- A patient cohort representing people with atrial fibrillation in the UK, using the data reported by Gallagher et al. (2008).
- The variable (per patient) costs of anticoagulant monitoring are £115.14.
- People have 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 during the first 12 months of treatment as used in the RE-LY quality-of-life sub-study (the details are academic-in-confidence).

3.34 By introducing these assumptions, the ICER for dabigatran 150 mg twice daily compared with warfarin increased from £6,264 to £24,173 per QALY gained in the ERG's alternative base-case analysis.

Manufacturer's additional analyses

3.35 Additional analyses were provided by the manufacturer in response to NICE's request for further clarification on the cost effectiveness of dabigatran presented

in the appraisal consultation document. The manufacturer submitted a revised cost-effectiveness analysis of the sequential regimen model comparing dabigatran with warfarin using relative risks from the whole RE-LY trial population rather than from the post hoc subgroup analysis, as requested by the Committee. Given the uncertainty about costs of warfarin prescription and monitoring because of wide variations in local practice, it also conducted sensitivity analyses that varied the annual cost of INR monitoring (£115.14, £241.54, £279.36 and £414.90) and explored the ERG's preferred assumptions (see section 3.33).

3.36 The manufacturer highlighted that its new base-case analysis included INR costs of £241.54. The manufacturer selected this cost based on the conclusions of the first Appraisal Committee meeting, which stated that the real cost of INR monitoring was likely to lie between the ERG's lower estimate of £115.14 and the manufacturer's upper estimate of £414.90. Assuming an INR monitoring cost of £241.54, the manufacturer's revised base-case ICERs were £14,518 per QALY gained for the dabigatran sequential regimen in people starting treatment when younger than 80 years and £18,269 per QALY gained for the sequential regimen in people starting treatment at 80 years and older, compared with warfarin.

3.37 In response to the Committee's request to include a patient cohort that better reflected people with atrial fibrillation in the UK, the manufacturer highlighted that data from Gallagher et al. (2008) were not easily adapted to the model and that many of the patients included in the Gallagher analysis would not be covered by the marketing authorisation for dabigatran. To address the Committee's request the manufacturer performed an analysis of the General Practice Research Database to derive data required for the model. Applying these data increased the ICERs to £17,373 and £19,680 per QALY gained for the dabigatran sequential regimen in people starting treatment when younger than 80 years and at 80 years and older respectively, compared with warfarin. The manufacturer stated that applying the ERG's preferred assumptions relating to dyspepsia management costs, disability and mortality risks, and disutility associated with dabigatran (see section 3.33) individually had minimal effect on the base-case ICER. Combining an INR monitoring cost of £241.54 with the ERG's preferred assumptions resulted in ICERs of £17,660 and £18,392 per QALY gained for the sequential regimen in people starting treatment when younger than 80 years and people starting treatment at 80 years and older respectively, compared with warfarin.

3.38 The manufacturer also responded to the Committee's request in the appraisal consultation document for further comment and consideration of the cost effectiveness of dabigatran in the subgroup of people whose condition is already well controlled on warfarin. The manufacturer highlighted that the INR control analyses submitted to the FDA (see section 3.22) were stratified by time in therapeutic range only in the warfarin arm and should therefore be interpreted with caution. The manufacturer stated that analyses presented in a study by Wallentin et al. (2010), which was stratified on treatment centre time in therapeutic range (a method that maintains randomisation within a centre), would be more relevant if such an analysis were to be carried out. The manufacturer highlighted that the ERG's initial analysis of good INR control (see section 3.28) assumed a time in therapeutic range of 100%, which is unlikely to be achieved in clinical practice for most patients. The manufacturer further explained that for both the full sequential regimen in people starting treatment younger than 80 years and the over 80 cohort, INR would need to be within target range an average of approximately 83% to 85% of the time for the ICERs to be above £30,000 per QALY gained compared with warfarin.

3.39 The ERG provided a critique and exploratory analysis of the manufacturer's additional analyses. The ERG compared inputs in the revised model with inputs used for the original single-dose and sequential regimen model. It commented that the values for ischaemic stroke disability and mortality rates by treatment used in the revised sequential regimen model were the same as those used in the initial sequential regimen model rather than those from the single-dose model. The ERG commented that correcting for this had the effect of reducing the manufacturer's ICERs slightly. The ERG agreed with the manufacturer that the data presented by Gallagher et al. (2008) are not easily adapted to the model. It commented that the General Practice Research Database data presented by the manufacturer have advantages over the Gallagher study in that they are more recent and therefore more reflective of the current UK atrial fibrillation population, and they refer solely to the people with atrial fibrillation for whom dabigatran is licensed. The ERG compared the results of the incremental analyses presented by the manufacturer with the results obtained by the ERG after including the correct values for ischaemic stroke disability and mortality rates by treatment and including all of the assumptions requested by the Committee. The ERG commented that its results were broadly in line with those presented by the manufacturer. The ERG's estimate of the ICER for the sequential regimen in

people starting treatment when younger than 80 years, including the relative risks from the whole RE-LY trial population, an INR cost of £241.54 and all of the assumptions requested by the Committee, was £18,863 per QALY gained compared with the manufacturer's estimate of £17,660 per QALY gained.

3.40 The ERG acknowledged the manufacturer's view that 100% time in therapeutic range is difficult to achieve in clinical practice. The ERG identified a UK-based study by Jones et al. (2005) that reported that the average time in therapeutic range was 67.9%. The ERG commented that the Jones et al. (2005) study indicated that the people with the best INR control (upper quartile) were within therapeutic range an average of 83.7% of the time, so the ERG performed further exploratory sensitivity analyses testing this value. For the subgroup of patients whose INR is within range 83.7% of the time, the ICER for dabigatran compared with warfarin was £46,989 per QALY gained assuming INR monitoring costs of £241.54 per annum. If the INR costs were increased to £414.90 per annum, the ICER decreased to £31,386 per QALY gained compared with warfarin. The ERG commented that it is unclear how INR monitoring costs vary by time in therapeutic range. The ERG also performed a threshold analysis to estimate the level of time in therapeutic range needed to raise the ICER above £30,000 per QALY gained compared with warfarin, assuming an INR monitoring cost of £241.54 per annum and including all of the ERG's preferred assumptions. The ERG commented that the INR would need to be within the target range an average of 75% to 76% of the time or more for the ICER to be above £30,000 per QALY gained compared with warfarin.

3.41 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dabigatran, having considered evidence on the nature of atrial fibrillation and the value placed on the benefits of dabigatran by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee heard from the clinical specialists and patient experts that the current standard treatment for the prevention of stroke and systemic embolism in people with atrial fibrillation is warfarin, and that because of its lower efficacy, aspirin is used only in people for whom warfarin is unsuitable. The Committee also heard that warfarin, although an effective treatment, is associated with a number of problems. The main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the satisfactory therapeutic range. The Committee heard from the patient experts that stroke is a major concern for people with atrial fibrillation and that stroke severity is usually greater in this group than in people who have strokes from other causes. The patient experts also highlighted that many people taking warfarin are outside their target therapeutic INR range at any 1 time and that warfarin, unlike dabigatran, is associated with a number of inconveniences that make adherence difficult. These include numerous food and drug interactions that can have an impact on people's work, social and family life, and regular monitoring and dose adjustments that can cause disruption and inconvenience. The Committee accepted the limitations of warfarin therapy, and the considerable effect that it may have on the lives of the people who take it, and recognised the potential benefits of dabigatran for people with atrial fibrillation.

4.3 The Committee considered the clinical-effectiveness data from the RE-LY trial comparing dabigatran with warfarin. It noted that this formed most of the clinical-effectiveness evidence in the manufacturer's submission and was the largest published trial in people with atrial fibrillation. The Committee considered that the RE-LY trial was of good quality but noted that a key uncertainty highlighted by the ERG was the generalisability of the results to people diagnosed with atrial fibrillation in the NHS. The Committee noted that the definition of moderate to high risk of stroke in the RE-LY trial was different from the definition used in

NICE's original guideline on atrial fibrillation (now replaced by NICE's guideline on atrial fibrillation) and did not include people aged 65 years and over with no additional risk factors for stroke, resulting in a higher risk profile in the trial than in the general population eligible for anticoagulation prophylaxis. However, the Committee was persuaded by the clinical specialists that the RE-LY trial included a broad range of people that reflected those seen in UK clinical practice and that the results were applicable to a wide range of people with atrial fibrillation. The Committee concluded that the population included in the trial was appropriate and broadly relevant to UK clinical practice.

4.4 The Committee considered the results of the RE-LY trial. It noted that dabigatran 150 mg twice daily was associated with a statistically significantly lower incidence of stroke or systemic embolism, ischaemic stroke and vascular mortality compared with warfarin, but that there were no statistically significant differences in these outcomes between dabigatran 110 mg twice daily and warfarin. It also noted that both doses of dabigatran were associated with an increased risk of acute myocardial infarction compared with warfarin but that this was not statistically significant. The Committee heard from the clinical specialists that this reflected a small absolute difference in the incidence of acute myocardial infarction between the treatment groups, but it was unclear whether this was because of a protective effect of warfarin or a negative effect of dabigatran treatment, and that the effects did not appear to translate into an increased vascular mortality risk. The Committee concluded that dabigatran 150 mg twice daily was more clinically effective than warfarin in reducing the risk of stroke or systemic embolism, ischaemic stroke and vascular mortality and that this represented an important development for people with atrial fibrillation. It also concluded that the lower 110 mg dabigatran twice-daily dose had shown non-inferiority to warfarin.

4.5 The Committee considered the results of the manufacturer's subgroup analyses. It was aware, however, that the manufacturer's analyses by age had been defined post hoc and it therefore considered that the results should be interpreted with caution. The Committee also considered the results of the manufacturer's pre-planned analyses of people naive to vitamin K antagonists and people who have previously used vitamin K antagonists. It noted that dabigatran 150 mg twice daily was associated with a statistically significant reduction in the incidence of stroke or systemic embolism compared with warfarin in both vitamin K

antagonist-naive and vitamin K antagonist-experienced subgroups, but dabigatran 110 mg twice daily did not show a statistically significant reduction in either group. The Committee concluded that dabigatran 150 mg twice daily showed increased efficacy compared with warfarin in people with atrial fibrillation irrespective of their previous exposure to vitamin K antagonists.

4.6 The Committee discussed the effectiveness of dabigatran compared with warfarin according to INR control. It noted the evidence presented by the ERG that people with good INR control with warfarin may not gain additional clinical benefit by taking dabigatran. However, the clinical specialists emphasised the importance of the significantly lower rates of intracranial haemorrhage and haemorrhagic stroke associated with both doses of dabigatran compared with warfarin in the RE-LY trial, and that this effect is maintained in people with good INR control. The Committee heard that haemorrhagic stroke and intracranial haemorrhage have devastating and life-threatening consequences and concluded that the lower rates associated with dabigatran represent an important advance in the treatment of atrial fibrillation alongside reduction in ischaemic stroke. It concluded that this applied to all patients with atrial fibrillation, including those with good INR control, and that there were also benefits of taking a treatment that didn't need INR monitoring or dietary restriction.

4.7 The Committee considered the additional adverse events reported in the RE-LY trial. It noted that both doses of dabigatran were associated with statistically significant reductions in the incidence of life-threatening bleeds compared with warfarin. However, it also noted that the incidence of gastrointestinal bleeding, in contrast to cerebral haemorrhage, was statistically significantly higher for both doses of dabigatran, and the comment from the manufacturer that this may be the result of a local effect of the orally administered drug on the gastrointestinal mucosa. Dabigatran 150 mg twice daily was associated with a statistically significantly higher incidence of major and life-threatening gastrointestinal bleeding. The Committee noted that even small changes in total gastrointestinal bleeding rates might have a substantial impact on the provision of services and that major gastrointestinal bleeding is associated with a significant mortality risk. The Committee concluded that treatment with dabigatran resulted in more gastrointestinal bleeding than warfarin, but also recognised the particular importance of the effects of dabigatran on reducing the risk of haemorrhagic

stroke and intracranial haemorrhage for people with atrial fibrillation when compared with warfarin.

4.8 The Committee was aware that health-related quality-of-life data were collected in a sub-study of the RE-LY trial. It noted that baseline utility values for people with atrial fibrillation were derived from the sub-study. The Committee agreed that because the sub-study was reasonably representative of the overall RE-LY population, this approach was appropriate.

4.9 The Committee considered the manufacturer's economic model and the critique and exploratory analyses performed by the ERG. The Committee considered the utility values used in the model and noted that it was unclear how the utility values relating to the effect of stroke were derived. However, the Committee agreed with the ERG that the general approach taken by the manufacturer to estimate the lifetime cost effectiveness of dabigatran was appropriate.

4.10 The Committee noted that the manufacturer presented a single-dose model, and a sequential regimen model in which people younger than 80 years began treatment with dabigatran 150 mg twice daily, and at the age of 80 years were switched to dabigatran 110 mg twice daily. As the summary of product characteristics for dabigatran excludes people older than 80 years from treatment with dabigatran 150 mg twice daily because of additional risks in this group, the Committee concluded that the sequence of dabigatran 150 mg twice daily followed by dabigatran 110 mg twice daily once people reach 80 years would be the only regimen appropriate for the assessment of the cost effectiveness of dabigatran relative to warfarin in the whole eligible UK population.

4.11 The Committee heard from the ERG that the relative risks used to inform the manufacturer's original sequential regimen model were derived from people in the younger than 80 years and older than 80 years subgroups of the RE-LY trial that were defined post hoc. It also heard that using relative risks from the whole RE-LY trial population would be more appropriate to determine reliable effectiveness estimates for the dabigatran sequence. Therefore, the Committee asked the manufacturer to submit a re-analysis of the data for discussion at the second Appraisal Committee meeting using the relative risks from the whole RE-LY trial population.

4.12 At the first Appraisal Committee meeting, the Committee noted that the ERG had highlighted a number of uncertainties relating to assumptions used in the manufacturer's economic model. First, the Committee noted the ERG's view that an analysis based on an older patient cohort with a lower risk of stroke using data reported by Gallagher et al. (2008) would be more representative of people with atrial fibrillation in the UK than the cohort from the RE-LY trial used by the manufacturer. The Committee accepted that there was uncertainty around which cohort most realistically reflected the population of people with atrial fibrillation in the UK.

4.13 Second, the Committee noted that the ERG questioned whether disability and mortality were independent of the treatment received. The Committee heard from the clinical specialists that the manufacturer's assumption that a stroke would be less severe after treatment with dabigatran than warfarin was plausible and that there is evidence that both the incidence and the severity of stroke may vary according to the treatment received. The Committee also noted the ERG's views about disutility of dabigatran and the inclusion of dyspepsia management costs throughout treatment (see sections 3.30 and 3.31). The Committee agreed that including all of these assumptions would be a more conservative approach.

4.14 Third, the Committee noted the ERG's view that the cost of INR monitoring had been overestimated in the manufacturer's model. The Committee heard from the clinical specialists that the introduction of dabigatran would not result in complete closure of anticoagulation services with release of all the funding, and the manufacturer's estimate (£414.90) was likely to be too high. It also heard that INR monitoring costs varied in different settings and could not be quantified precisely. The Committee agreed that exploring the effect of assuming the alternative INR monitoring costs put forward by the ERG (£115.14, £241.54, £279.36), in addition to the cost assumed in the manufacturer's submission, would enable it to make a more accurate judgement about the cost effectiveness of dabigatran.

4.15 Finally, the Committee noted the ERG's comments that the cost effectiveness of dabigatran compared with warfarin varied substantially according to level of INR control in those already being treated with warfarin. In the appraisal consultation document, the manufacturer of dabigatran was therefore asked to provide further analyses addressing the uncertainties outlined in sections 4.11 to 4.15.

4.16 The Committee discussed the manufacturer's revised analyses and the critique and the exploratory analyses performed by the ERG. The Committee noted that the manufacturer's revised analysis included the relative risks from the whole RE-LY trial population rather than from the post hoc subgroup analysis and had explored the effect of varying the cost of INR monitoring as requested. It also noted that the manufacturer's revised analysis incorporated an INR monitoring cost of £241.54 in its base case as opposed to £414.90 in the original submission. The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee accepted the manufacturer's approach, acknowledging that although INR costs may vary widely, this assumption was reasonable.

4.17 The Committee discussed the manufacturer's approach to including the ERG's other preferred assumptions in the revised analysis (see section 3.33). The Committee noted that the Gallagher et al. (2008) data on atrial fibrillation had not been incorporated. However, the Committee accepted the manufacturer's rationale and the supporting views of the ERG for using General Practice Research Database data instead (see section 3.39). The Committee noted that, in its revised analyses, the manufacturer had incorporated the ERG's preferred assumptions about dyspepsia management costs throughout treatment, disability and mortality risks being treatment independent, and disutility associated with dabigatran. It further noted that combining all of these assumptions together with an INR monitoring cost of £241.54 resulted in an ICER for dabigatran of £17,700 per QALY gained for the full sequential regimen in people starting treatment when younger than 80 years and £18,400 per QALY gained in people starting treatment at 80 years and older, compared with warfarin. Finally, the Committee noted that the ERG's analysis, which included all of the requested assumptions, an INR monitoring cost of £241.54, and the corrected values for ischaemic stroke and disability rates (see section 3.39) resulted in an ICER of £18,900 per QALY gained for the sequential regimen in people starting treatment younger than 80 years, compared with warfarin. The Committee concluded that this was broadly in line with the manufacturer's estimate and that the ICERs presented by the manufacturer were robust to the changes requested. The Committee therefore accepted the manufacturer's approach and concluded that the most plausible ICERs for the whole population eligible for dabigatran were within the range normally considered a cost-effective use of NHS resources, being less than

£20,000 per QALY gained.

4.18 The Committee discussed comments from consultees that suggested it may be appropriate to recommend dabigatran for use only in people with atrial fibrillation whose INR is not well controlled on warfarin. The Committee was satisfied that the technology was a cost-effective treatment for the whole patient group. It noted that robust evidence of differential clinical effectiveness and cost effectiveness, with clear justification of the threshold level chosen, would be needed to select out a subgroup, based on INR control, for whom dabigatran would not be recommended.

4.19 The Committee was aware of the need for guidance to apply equally to those already on warfarin and to those newly diagnosed with atrial fibrillation. The Committee noted that, for people newly diagnosed but not already taking an anticoagulant, any stratification of the population according to INR control would mean that all patients would have to try warfarin for at least a few months to assess whether the INR was well controlled and to estimate the time in therapeutic range. The Committee heard from clinical specialists that many of the significant complications of warfarin therapy are experienced in the first months of treatment before the dose is established and stabilised. The Committee accepted therefore that a large number of people having a trial of warfarin at initial diagnosis could be expected to switch to dabigatran. It also accepted that it was not reasonable to expect all patients to try warfarin first, with the associated risks, for the purpose of selecting out a subgroup for whom dabigatran was less cost effective.

4.20 The Committee was also aware of the estimates of the time that the INR in people already taking warfarin would need to be in the target range for the ICERs for dabigatran compared with warfarin to be above £30,000 per QALY gained. Assuming an INR monitoring cost of £241.54 per annum, the manufacturer and ERG estimated an average of 83% to 85% and 75% to 76% of the time respectively. The Committee noted that this would apply to only a proportion of the whole population. The Committee was aware that the average time spent in therapeutic range for the UK centres in the RE-LY trial was 72%, and in the UK-based study by Jones et al. (2005) there was an average time in therapeutic range of 67.9%. It noted the ERG's analysis that explored the effects of time in therapeutic range on the cost effectiveness of dabigatran compared with

warfarin. This calculated the ICER for the people with the best-controlled INR (that is, within range 83.7% of the time) at £47,000 per QALY gained. However, this figure incorporated INR monitoring costs of £241.54 (per annum) and the ICER reduced considerably if higher INR monitoring costs of £414.90 per annum were used. The Committee concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option, and that the ICER for the whole population should be the basis of the recommendation.

4.21 The Committee was mindful of the higher gastrointestinal bleeding rates associated with dabigatran and of the relatively short-term safety data compared with the established standard of care, warfarin. It was also mindful that for those with very well-controlled INR on warfarin, the clinical benefits are likely to be less than for those with poorly controlled INR. The Committee therefore concluded that the decision about whether to start treatment with dabigatran in people with atrial fibrillation should be made after an informed discussion between the responsible clinician and the person about the safety risks and benefits of dabigatran compared with warfarin. It also concluded that, for people currently receiving warfarin, the potential risks and benefits of switching to dabigatran should be considered in light of their level of INR control.

4.22 The Committee considered whether there were any equalities considerations affecting population groups protected by equality legislation and concluded that there were no equality issues relating to this appraisal that needed addressing in the guidance.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has atrial fibrillation and the healthcare professional responsible for their care thinks that dabigatran etexilate is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Professor A E Ades
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Christopher Earl
Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Mrs Eleanor Grey
Lay member

Professor Jonathan Grigg
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont
Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin
Consultant Endocrinologist, North Devon District Hospital

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Dr Alec Miners
Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr David Newsham
Lecturer (Orthoptics), University of Liverpool

Ms Pamela Rees
Lay member

Dr Ann Richardson
Lay member

Dr Paul Robinson
Medical Director, Merck Sharp & Dohme

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

Mr Mike Spencer
Assistant Director Patient Experience, Cardiff and Vale University Health Board

Mr David Thomson
Lay member

Mr William Turner
Consultant Urologist, Addenbrooke's Hospital

Dr John Watkins
Clinical Senior Lecturer and Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Anthony S Wierzbicki
Consultant in Metabolic Medicine and Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Dr Olivia Wu
Reader in Health Economics, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Christian Griffiths
Technical Lead

Zoe Charles
Technical Adviser

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

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

- Spackman E, Burch J, Faria R, et al. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: Evidence Review Group Report (February 2011)

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Boehringer Ingelheim

Professional or specialist, and patient or carer groups:

- AntiCoagulation Europe (ACE)
- Anticoagulation Specialist Association (ASA)
- Arrhythmia Alliance (Atrial Fibrillation Association affiliated)
- British Association of Stroke Physicians
- British Cardiovascular Intervention Society (BCIS)
- British Heart Foundation
- British Society for Haematology
- Clinical Leaders of Thrombosis (CLOT)

- Heart Rhythm UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- South Asian Health Foundation
- Stroke Association

Other consultees:

- Department of Health
- NHS Salford
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Bayer
- Bristol–Myers Squibb
- Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE), University of York
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Care Improvement Scotland
- National Institute for Health Research Health Technology Assessment Programme
- Sanofi Aventis

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on dabigatran by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to

comment on the ACD.

- Professor Michael Laffan, Professor of Haemostasis and Thrombosis, nominated by the Royal College of Pathologists and British Society for Haematology – clinical specialist
- Professor Gregory Lip, Clinical Cardiologist, nominated by the British Cardiovascular Society – clinical specialist
- Dr Caroline Lovelock, Senior Clinical Lecturer, nominated by the Royal College of Physicians – clinical specialist
- Diane Eaton, nominated by AntiCoagulation Europe (ACE) – patient expert
- Joanne Jerrome, Assistant Director nominated by the Atrial Fibrillation Association – patient expert

The following individuals were nominated as NHS Commissioning experts by the selected PCT allocated to this appraisal. They gave their NHS commissioning personal view on dabigatran by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Andy Sutton, selected by NHS Salford – NHS commissioning expert

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Boehringer Ingelheim

Update information

July 2021: Recommendation 1.2 was updated to include the other anticoagulants approved by NICE.

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