NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- Over 85% of the population in the ROCKET-AF trial had a $CHAD_2$ score of 3 or more. The ERG and its clinical advisers consider the population in the trial to be at higher risk of stroke than the population defined in the scope issued by NICE. What is the Committee's view on the generalisability of the ROCKET-AF trial to a UK setting?
- In the warfarin group of the safety-on-treatment population, the mean time in therapeutic range (TTR) for the international normalised ratio (INR) range of 2.0–3.0 was 55%, and the median TTR was 58%. How applicable does the Committee consider this is to UK practice?
- There were three populations used in the analyses in the manufacturer's submission (intention to treat [ITT], per protocol and safety-on-treatment) The ERG noted that the manufacturer preferred to report analyses based on the per protocol and safety-on-treatment population data and perform sensitivity analyses using the ITT population data. The ERG considers that the ITT population would better reflect the treatment effectiveness results that would be seen in clinical practice. It acknowledges, however, that the

trial population of RE-LY, which provides the main data for the indirect analysis of rivaroxaban with dabigatran, appears to be the most similar to the ROCKET-AF safety-on-treatment population. What is the Committee's view on the most appropriate population to be used in the analyses?

- The ERG noted that subgroup results from ROCKET-AF [redacted] Are there any important subgroups for whom rivaroxaban is more clinically effective?
- The manufacturer conducted a network meta-analysis to provide an estimate of the treatment effect of rivaroxaban compared with dabigatran (110 mg or 150 mg twice daily). The ERG had concerns about the validity of the results from the network meta-analysis conducted by the manufacturer, because of the high levels of statistical heterogeneity; this heterogeneity was not present in the ERG's exploratory network meta-analysis in which the comparators were restricted to those listed in the final scope issued by NICE. What weight does the Committee give to the network meta-analysis undertaken? The trials of rivaroxaban and dabigatran had different levels of warfarin control (TTR) in the warfarin arms. Does the Committee consider this relevant to the interpretation of the network meta-analyses?
- The clinical effectiveness data for rivaroxaban compared with aspirin were obtained from the network meta-analysis based largely on randomised controlled trials of warfarin versus aspirin, suggesting that the patient populations of these trials are likely to be suitable for therapy with warfarin. The ERG therefore considers that the question of the clinical effectiveness of rivaroxaban compared with aspirin in a population for whom warfarin is

considered unsuitable has not been addressed in the manufacturer's submission. Does the Committee agree with the ERG's concern?

- The estimate of cost effectiveness was most sensitive to the cost of anticoagulation monitoring. In addition to the adjustments to the model's structural assumptions and parameters, the ERG conducted a scenario analysis that used lower monitoring costs for warfarin that increased the ICER from £33,758 to £62,568 per QALY gained. What are the most appropriate anticoagulation monitoring costs to include?
- The ERG presented an alternative base-case analysis, which increased the ICER for rivaroxaban compared with warfarin from £18,883 to £33,758 per QALY gained. Does the Committee find the ERG's or the manufacturer's assumptions underpinning this analysis more plausible?
- The manufacturer's economic evaluation assumed that aspirin is the only second-line treatment. However the ERG considers warfarin to be the likely second-line treatment strategy after rivaroxaban and dabigatran. Which second-line treatment does the Committee consider the most appropriate?
- The economic evaluation does not account for sequential treatment with rivaroxaban and warfarin or dabigatran and warfarin. The ERG believes that people who stop therapy with rivaroxaban or dabigatran may be treated with warfarin. What is the Committee's view on the fact that treatment sequencing with rivaroxaban was not included in the manufacturer's economic model or the ERG's exploratory analyses of the model?
- Are there any subgroups for which rivaroxaban is more cost effective (for example, people whose INR is poorly controlled on warfarin)?

1 Background: clinical need and practice

1.1 Atrial fibrillation is the most common heart rhythm disturbance and its main characteristic is an erratic and rapid heartbeat. It leads to deterioration in the mechanical function of the atria and prevents complete expulsion of blood. The blood in the atria becomes

stagnant, which can lead to blood clot formation. These clots can travel throughout the body and, if they travel to the brain, they can cause a stroke.

1.2 Annually in England and Wales 130,000 people experience a stroke episode and there are 60,000 deaths from stroke. More than 20% of these strokes are attributed to atrial fibrillation. The annual risk of stroke is five to six times greater in people with atrial fibrillation than in people with a normal heart rhythm. There is a 30–43% risk of a recurrent stroke within 5 years after the first stroke.

1.3 In people with atrial fibrillation, a stroke is associated with greater mortality, morbidity and longer hospital stays than in those without atrial fibrillation. Approximately a third of people who have a stroke are likely to die within the first 10 days, about a third are likely to make a recovery within 1 month, and the remaining third are likely to be left with disabilities needing rehabilitation. Stroke is the leading cause of disability in adults. Depending on the area of the brain that has been damaged, a patient can experience speech and language problems and/or orientation, movement and memory problems.

1.4 The risk of stroke in people with atrial fibrillation can be reduced with antithrombotic treatment. The choice of antithrombotic treatment should be based on a balance of the benefits of treatment in terms of a reduction in the risk of stroke and other thromboembolic events, versus the increased risk of bleeding associated with anticoagulation or antiplatelet therapy. 'Atrial fibrillation: the management of atrial fibrillation' (NICE clinical guideline 36) recommends that people with atrial fibrillation who are at high risk of stroke should receive anticoagulation with warfarin. People with atrial fibrillation who are at moderate risk of stroke can

be considered for anticoagulation with warfarin or offered aspirin, with the decision made on an individual basis. In people with atrial fibrillation who are at low risk of stroke, such as those under 65 years with no other risk factors, treatment with aspirin is recommended. Anticoagulation may be inadvisable in people with atrial fibrillation who are at high risk of bleeding.

2 The technology

2.1 Rivaroxaban (Xarelto, Bayer HealthCare) is an anticoagulant that acts by direct inhibition of activated factor X (factor Xa). Factor Xa is a key component in the formation of blood clots. In September 2011 it 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 non-valvular atrial fibrillation with one or more risk factors:

- congestive heart failure
- hypertension
- age 75 years or older
- diabetes mellitus
  prior stroke or transient ischaemic attack (TIA)'.

Rivaroxaban is administered orally. Rivaroxaban will be available as 20 mg film coated tablets. For people with moderate or severe renal impairment, 15 mg tablets will be available.

2.2 According to the summary of product characteristics (SPC) provided by the manufacturer, approximately 14% of the treated patients across the phase III studies experienced adverse reactions. Bleeding and anaemia occurred in approximately 3.3% and 1% of patients, respectively. Other common adverse reactions were nausea and an increase in transaminases.

[redacted]. For full details of side effects and contraindications, see the SPC.

2.3 The provisional cost of rivaroxaban is £[redacted] per day and [redacted] annually. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: 'To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the prevention of stroke and non-central nervous system (CNS) systemic embolism in people with non-valvular atrial fibrillation'.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with non-valvular atrial fibrillation who are at moderate to high risk of stroke and non-CNS systemic embolism	Adults with non-valvular atrial fibrillation with one or more risk factors for stroke and systemic embolism, such as congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischaemic attack

The manufacturer stated that the difference in the populations in the decision problem and in the final scope issued by NICE was because it considered stroke risk to be a continuum. The European Society of Cardiology (ESC) guidelines recommend a risk-factor-based approach for stroke risk assessment, rather than using the 'low', 'moderate' and 'high' risk classification as recommended in 'Atrial fibrillation: the management of atrial fibrillation' (NICE clinical guideline 36).

NICE clinical guideline 36 defines people at moderate risk of stroke as:

- those aged 65 years or older with no high risk factors
- those younger than 75 years with hypertension, diabetes, peripheral artery disease or coronary artery disease.

It defines people at high risk of stroke as:

- those with previous ischaemic stroke, transient ischaemic attack or thromboembolic event
- those aged 75 years or older with hypertension, diabetes, peripheral artery disease or coronary artery disease
- those with clinical evidence of valve disease, heart failure or left ventricular dysfunction on echocardiography.

The ESC guidelines define stroke risk using the $CHADS_2$ score as:

- low risk: $CHADS_2$ score of 0
- moderate risk: $CHADS_2$ score of 1–2
- high risk: $CHADS_2$ score of 2 or more.

The ERG commented that the ROCKET-AF trial did not actively enrol people with only one $CHADS_2$ risk factor, or those 65 years or older with no high-risk factors. Over 85% of the ROCKET-AF population had a $CHADS_2$ score of 3 or above. Based on these details, and considering the definitions of moderate and high risk of stroke in NICE clinical guideline 36 and the ESC guidelines, the ERG considered that, in general, the population in the ROCKET-AF trial was at higher risk of stroke than the population defined in the final scope issued by NICE.

The ERG also noted that the manufacturer's submission did not address the population of people for whom warfarin is unsuitable,

and that the ROCKET-AF trial did not include this population. The ERG therefore considered that there are currently no suitable data on rivaroxaban to assess the safety or efficacy in people for whom warfarin is unsuitable.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	Rivaroxaban	Rivaroxaban
	Final scope issued by NICE	**Decision problem addressed in the submission**
Comparators	• Warfarin • Dabigatran In people for whom warfarin is unsuitable: • Antiplatelet agents • Dabigatran	• Warfarin • Dabigatran • Aspirin • No treatment

The manufacturer stated that in clinical practice, some people who are eligible for warfarin therapy but not prescribed it are prescribed aspirin or have no treatment. The manufacturer stated that it had included aspirin as a comparator as it considered aspirin to be the most commonly prescribed antiplatelet for this indication.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	• Stroke • Non-CNS systemic embolism • Myocardial infarction • Mortality • Transient ischaemic attacks • Adverse effects of treatment including haemorrhage • Health-related quality of life	• Stroke • Non-CNS systemic embolism • Myocardial infarction • Mortality • Transient ischaemic attacks • Adverse effects of treatment including haemorrhage • Health-related quality of life

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	• The cost effectiveness of rivaroxaban will be expressed as incremental cost per quality-adjusted life year. • In the base-case analysis a lifetime horizon (30 years) is used for estimating clinical and cost effectiveness. • Costs are considered from the perspective of the NHS and a personal social services perspective.

4 Clinical-effectiveness evidence

4.1 The manufacturer carried out a search of the literature to identify placebo- or active-controlled comparative studies investigating the efficacy and safety of rivaroxaban for stroke prevention in non-valvular atrial fibrillation (AF). The manufacturer identified one randomised controlled trial (ROCKET-AF) that directly compared rivaroxaban with dose-adjusted warfarin. The manufacturer also compared rivaroxaban with aspirin and dabigatran etexilate (110 mg or 150 mg twice daily) using a network meta-analysis in people for whom anticoagulation therapy is considered suitable.

4.2 The ROCKET-AF trial was designed as a non-inferiority trial in which a blinded dose of rivaroxaban (20 mg or 15 mg once daily) was compared to open-label warfarin (target INR of 2.0 to 3.0) for the prevention of stroke and thromboembolic events in people with non-valvular atrial fibrillation at risk of future thromboembolic events. People were randomly allocated to one of the two treatment groups with equal probability (1:1 allocation ratio). The study took place in 45 countries including the UK and a total of 14,264 people were enrolled across the two treatment arms (rivaroxaban n = 7131 and warfarin n = 7133). The duration of the treatment period

depended on the time required to obtain approximately 405 adjudicated primary efficacy endpoint events in the per protocol population on treatment. As a result, the time on study treatment varied from patient to patient depending on the time of the patients' enrolment. The expected study duration was approximately 40 months from first patient enrolled to the occurrence of the last event. The median duration of treatment exposure was 590 days.

4.3 The primary efficacy endpoint in ROCKET-AF was the composite of stroke (ischaemic and haemorrhagic bleeding) and non-central nervous system (non-CNS) systemic embolism. The primary safety endpoint was defined as the composite of major bleeding and clinically relevant non-major bleeding.

4.4 A margin of 1.46 for the risk ratio (rivaroxaban/warfarin) was used to assess non-inferiority in preventing stroke and non-CNS embolism in the ROCKET-AF trial. To show non-inferiority, the upper bound of the confidence interval of the hazard ratio for rivaroxaban compared with warfarin had to be less than the margin specified. Once non-inferiority was established for the primary outcome, further analyses investigated superiority of rivaroxaban over warfarin.

4.5 [redacted]. Risk factors for prior stroke, transient ischaemic attack, or non-CNS systemic embolism were well balanced between the two treatment groups. More than 50% of people in the trial received treatment for at least 18 months. The median age (interquartile range) of study patients was 73 (65, 78) years and 60.3% were male. The majority of the trial population had received prior warfarin therapy (62.4%) and 36.5% had received prior acetylsalicylic acid therapy.

4.6 Risk of stroke at baseline was classified according to $CHADS_2$ score (a clinical prediction rule for the risk of stroke in people with atrial fibrillation whereby each risk [congestive heart failure, hypertension, age, diabetes mellitus and prior stroke or transient ischaemic attack] is given a score and the total is then transferred into a percentage risk of stroke). The mean $CHADS_2$ score was 3.4 for the rivaroxaban group and 3.46 for the warfarin group, and 99.8% of the trial population had a baseline $CHADS_2$ of 2 or more.

4.7 Three analyses were defined in the manufacturer's submission for the efficacy analysis: the randomised/ITT set, the safety-on-treatment set (all ITT patients who had taken at least one dose of study drug and were followed for events) and the per-protocol set (all ITT patients excluding those who have major pre-defined protocol deviations). The primary non-inferiority analysis of the ROCKET-AF trial was conducted on the per protocol and the safety-on-treatment population data sets. The superiority analyses were conducted on the safety population data sets. In addition to the analyses in the per protocol and safety populations, sensitivity analyses were also performed to assess non-inferiority and superiority in the ROCKET-AF ITT population. The primary safety analysis was conducted on safety population data.

4.8 A number of pre-planned subgroup analyses were conducted, although only three of the subgroups were stratified at randomisation. These were by region, prior use of vitamin K antagonists, history of prior stroke, transient ischaemic attack and non-CNS systemic embolism. Other subgroups included prior chronic acetylsalicylic acid use, gender, age, race, renal function, body mass index, weight, congestive heart failure, hypertension, diabetes, type of atrial fibrillation, proton pump inhibitor use at baseline, and prior myocardial infarction. Results were summarised

by subgroup based on data from the safety-on-treatment and ITT populations.

4.9 The non-inferiority of rivaroxaban compared with warfarin was established for the primary outcome (composite of stroke and non-CNS systemic embolism) in both the per protocol and safety populations at the risk ratio margin of 1.46. Superiority of rivaroxaban over warfarin was also demonstrated in the safety population. However superiority of rivaroxaban was not demonstrated for this outcome in the sensitivity analysis using the ITT population data set. Further details of these results are shown in table 1.

Table 1 ROCKET-AF primary efficacy endpoint (stroke and non-CNS embolism results)

Population	Rivaroxaban			Warfarin			Rivaroxaban versus warfarin		
	N	Total	Event rate (100 pt-yr)	N	Total	Event rate (100 pt-yr)	HR (95% CI)	Non-inferiority p value	Superiority p value
Per protocol, as treated[a, b¶]	6,958	188	1.7	7,004	241	2.2	0.79 (0.66 to 0.96)	< 0.001*	[redacted]
Safety-on-treatment[a¶]	7,061	189	1.7	7,082	243	2.2	0.79 (0.65 to 0.95)	[redacted]	0.02*
ITT[a, c]	7,081	269	2.1	7,090	306	2.4	0.88 (0.75 to 1.03)	< 0.001*	0.12
• Events on-treatment		188	1.7		240	2.2	0.79 (0.66 to 0.96)		0.02*
• Events off-treatment		81	4.7		66	4.3	1.10 (0.79 to 1.52)		0.58

[a] Median follow-up was: 590 days for per protocol, as treated; 590 days for safety-on-treatment; and 707 days for ITT.

[b] Per protocol, as treated is the primary analysis.

[c] All follow-up in ITT population is to site notification.

* Statistically significant.

The analyses highlighted in teal are part of the pre-specified closed hierarchical testing procedure.

Abbreviations used in table: 95% CI, 95% confidence Interval; CNS, central nervous system; HR, hazard ratio; ITT, intention-to-treat.

4.10 For the primary safety endpoint of major or non-major clinically relevant bleeding, the results from the safety population data for ROCKET-AF suggest a comparable safety profile for rivaroxaban compared with warfarin, with no statistically significant difference between the two treatments.

4.11 The manufacturer stated that the results of the subgroup analyses were consistent across all pre-specified subgroups for the primary efficacy outcome, as well as for the people receiving a reduced dose of rivaroxaban (15 mg once daily). Following a request from the ERG the manufacturer provided subgroup analyses for the safety-on-treatment and ITT populations in people with prior vitamin K antagonist use and those with no prior vitamin K antagonist use (for the summary of results, see table 2), and for people with a TTR below 60% and for those with a TTR above 60% (for summary of results, see table 3).

Table 2 Subgroup analysis results for prior vitamin K antagonist use versus no prior vitamin K antagonist use from the ROCKET-AF trial.

Outcomes	Safety-on-treatment		Intention-to-treat	
	Prior VKA HR* (95% CI)	No prior VKA HR* (95% CI)	Prior VKA HR* (95% CI)	No prior VKA HR* (95% CI)
Efficacy				
Primary efficacy endpoint	0.84 (0.66 to 1.08)	0.72 (0.53 to 0.97)	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Primary ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Primary haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Non-CNS systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Vascular death	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]
				Safety
Principal safety endpoint (a)	[redacted]	[redacted]	[redacted]	[redacted]
Major	[redacted]	[redacted]	[redacted]	[redacted]
Non-major clinically relevant	[redacted]	[redacted]	[redacted]	[redacted]
Gastro-intestinal major bleed	[redacted]	[redacted]	[redacted]	[redacted]

* HRs (hazard ratios) are for rivaroxaban versus warfarin.

[redacted]

Table 3 Subgroup data for centre time in therapeutic range (TTR below 60% versus TTR 60% or above) from the ROCKET-AF trial

	[redacted]	
Outcomes	[redacted]	[redacted]
Efficacy		
Primary efficacy endpoint	[redacted]	[redacted]
Stroke	[redacted]	[redacted]

Primary ischaemic stroke	[redacted]	[redacted]
Primary haemorrhagic stroke	[redacted]	[redacted]
Non-CNS systemic embolism	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Vascular death	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]
Safety		
Principal safety endpoint (a)	[redacted]	[redacted]
Major	[redacted]	[redacted]
Non-major clinically relevant	[redacted]	[redacted]
Gastro-intestinal major bleed	[redacted]	[redacted]
[redacted]		

4.12 The manufacturer undertook a Bayesian network meta-analysis comparison analysis that compared rivaroxaban with warfarin, aspirin, no treatment and dabigatran. The clinical evidence comparing rivaroxaban with warfarin was obtained from the ROCKET-AF trial. Studies used for the other comparators were obtained from a systematic literature search. The manufacturer identified 18 studies in total for inclusion in the network meta-analysis, which included one study comparing rivaroxaban with warfarin, seven comparing aspirin with placebo or control, eight comparing warfarin with aspirin, one comparing vitamin K antagonist with clopidogrel plus aspirin and one comparing dabigatran with aspirin. The manufacturer reported network meta-analysis results for the outcomes using the ROCKET-AF safety-on-treatment population data set. Table 4 summarises the results from the manufacturer's network meta-analysis. At the request of the

ERG, the manufacturer also provided the results for the outcomes using the ROCKET-AF ITT population dataset.

Table 4 Summary of odd ratios for rivaroxaban compared with selected comparators using ROCKET-AF safety-on-treatment population (OR below 1 favours rivaroxaban, OR above 1 favours comparator)

Outcome	Adjusted-dose warfarin	ASA (aspirin)	Dabigatran 110 mg (twice daily)	Dabigatran 150 mg (twice daily)	Placebo
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Composite (ischaemic stroke and systemic embolism)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke/intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minor bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Statistically significant at the 5% level.

Abbreviations used in table: 95% CI, 95% Confidence Interval; ASA, acetylsalicylic acid; MS, manufacturer's submission; OR, odds ratio.

4.13 Health-related quality of life data were not submitted by the manufacturer.

ERG comments

4.14 The ERG judged that the ROCKET-AF trial was of good quality and the [redacted]. However the ERG noted that there was a statistically significantly greater number of people who had a prior history of myocardial infarction at baseline in the warfarin group in the trial compared with the rivaroxaban group. The ERG also noted that patients recruited to the ROCKET-AF trial experienced significant comorbidity. The ERG therefore considered the population not representative of the whole patient population in the UK with atrial fibrillation, but instead that it represented a group at a higher risk of stroke and thromboembolic events.

4.15 The ERG highlighted that the ROCKET-AF population used in the analyses presented in the manufacturer's submission was the safety-on-treatment population. The ERG considered that the ITT population would better reflect the treatment effectiveness results that would be seen in clinical practice. However, the ERG acknowledged that the trial population of RE-LY, which provides the main data for the indirect analysis of rivaroxaban with dabigatran, appears to be most similar to the ROCKET-AF safety-on-treatment population.

4.16 The ERG also noted that there was a large variability between the TTR values for the different trial regions in ROCKET-AF and the ERG considered that the overall trial TTR was lower than that generally reported in the UK and in other clinical trials. [redacted]

[redacted]The ERG commented that the network meta-analysis conducted by the manufacturer had high levels of heterogeneity, as well as considerable uncertainty around the point estimates. The ERG noted that the manufacturer did not discuss these issues in its submission. The ERG therefore conducted an exploratory network meta-analysis using a more restricted network of treatments (for further details see section 4.19).

4.17 The ERG stated that the manufacturer did not present any ROCKET-AF-based event- or treatment-related health-related quality of life data within the clinical evidence submitted, although the ERG acknowledged that this may not have been collected.

4.18 The ERG undertook an exploratory network meta-analysis comparing rivaroxaban with dabigatran etexilate, aspirin, placebo, and adjusted standard dose warfarin. The ERG included data from 8 of the 18 studies used by the manufacturer in its network meta-analysis. The eight studies included: one study comparing dabigatran with warfarin, one study comparing rivaroxaban with warfarin, three studies comparing aspirin with warfarin and three studies comparing warfarin with placebo. The ERG judged that only including these eight trials would reduce the amount of heterogeneity in the network. Only comparable dosing strategies were included (that is, rivaroxaban 20 mg per day, dabigatran etexilate 300 mg per day, aspirin 300 mg per day, and dose-adjusted warfarin aiming at a target INR range between 2 and 3). A fixed-effect model was used because of the high degree of

homogeneity between the included trials. The results of the ERG's exploratory meta-analysis are shown in table 5.

Table 5 Results from the network meta-analysis and pair-wise meta-analysis conducted by the ERG using warfarin as a baseline (OR below 1 favours comparator; OR above 1 favours warfarin)

Outcome	NMA	Meta-analysis
	Mean OR 95% CI	**Mean OR 95% CI**
Ischaemic stroke		
Placebo vs warfarin	3.51* (1.81 to 6.40)	3.22* (1.75 to 5.92)
Aspirin vs warfarin	1.56 (0.93 to 2.50)	1.49 (0.92 to 2.42)
Dabigatran vs warfarin	0.78* (0.60 to 1.00)	0.77* (0.60 to 0.99)
Rivaroxaban vs warfarin	0.91 (0.73 to 1.13)	0.91 (0.73 to 1.13)
Systemic embolism		
Placebo vs warfarin	2.50 (0.40 to 8.97)	1.55 (0.41 to 5.94)
Aspirin vs warfarin	0.99 (0.13 to 3.46)	0.78 (0.19 to 3.16)
Dabigatran vs warfarin	0.64 (0.29 to 1.23)	0.61 (0.31 to 1.22)
Rivaroxaban vs warfarin	0.24* (0.07 to 0.54)	0.23* (0.09 to 0.60)
Major extracranial bleed[a]		
Placebo vs warfarin	0.58 (0.17 to 1.41)	0.55 (0.21 to 1.45)
Aspirin vs warfarin	0.68 (0.32 to 1.24)	0.66 (0.34 to 1.27)
Dabigatran vs warfarin	1.08 (0.92 to 1.26)	1.08 (0.92 to 1.26)
Rivaroxaban vs warfarin	1.14 (0.96 to 1.33)	1.13 (0.97 to 1.33)
Minor extracranial bleed		
Placebo vs warfarin	0.62* (0.43 to 0.87)	0.61* (0.43 to 0.87)
Aspirin vs warfarin	0.57* (0.33 to 0.91)	0.56* (0.36 to 0.92)
Dabigatran vs warfarin	0.88* (0.82 to 0.96)	0.88* (0.82 to 0.95)
Rivaroxaban vs warfarin	1.04 (0.95 to 1.13)	1.04 (0.95 to 1.13)

Intracranial bleed		
Placebo vs warfarin	0.50 (0.01 to 2.43)	0.49 (0.09 to 2.69)
Aspirin vs warfarin	0.47 (0.15 to 1.08)	0.45 (0.18 to 1.14)
Dabigatran vs warfarin	0.41* (0.27 to 0.60)	0.41* (0.28 to 0.60)
Rivaroxaban vs warfarin	0.66* (0.46 to 0.92)	0.65* (0.46 to 0.92)
Myocardial infarction		
Placebo vs warfarin	20.14 (0.64 to 142.70)	3.97 (0.44 to 35.75)
Aspirin vs warfarin	1.32 (0.67 to 2.36)	1.24 (0.67 to 2.29)
Dabigatran vs warfarin	1.43 (1.02 to 1.97)	1.41 (1.02 to 1.95)
Rivaroxaban vs warfarin	0.81 (0.61 to 1.05)	0.80 (0.62 to 1.04)
Discontinuation		
Placebo vs warfarin[b]	0.68* (0.50 to 0.91)	0.68* (0.50 to 0.91)
Aspirin vs warfarin	0.57 (0.11 to 1.70)	0.47 (0.13 to 1.78)
Dabigatran vs warfarin	1.36* (1.24 to 1.48)	1.36* (1.24 to 1.48)
Rivaroxaban vs warfarin	1.04 (0.97 to 1.11)	1.04 (0.97 to 1.11)

*Statistically significant at the 5% level.

[a]Excluding WASPO as this outcome was identified by the investigators as likely to be specific to the population studied and is therefore not generalisable to a wider population.

[b]Excluding AFASAK as this outcome was identified by the investigators as likely to be skewed by patients not being adequately informed of the frequency of blood tests in the warfarin group.

Abbreviations used in table: 95% CI, 95% confidence interval; 95% CrI, 95% credible interval; ERG, Evidence Review Group; NMA, network meta-analysis; OR, odds ratio; vs, versus.

5 Comments from other consultees

5.1 The professional groups noted that people with atrial fibrillation are at increasing risk of developing stroke and non-CNS systemic embolism. They explained that the main prophylactic therapy currently available is warfarin, which can be inconvenient for both

clinicians and patients because of the need for frequent monitoring and dose adjustment throughout treatment. Currently if people are not eligible to take warfarin the only therapeutic option is aspirin, which evidence suggests is not as clinically effective in preventing stroke as warfarin. The professional groups considered the ROCKET-AF trial design to be the gold standard and generalisable to a UK setting, and demonstrated comparable efficacy and safety with warfarin.

5.2 The patient groups highlighted that rivaroxaban is perceived by patients to be safer and less volatile than warfarin as people do not need to keep their INR in a therapeutic range to prevent clotting or bleeding episodes. Patients also value the reduced monitoring requirements and hence fewer GP or hospital visits with rivaroxaban compared with warfarin. Professional groups also highlighted the absence of the need for regular blood tests associated with warfarin was of particular value to patients.

6 Cost-effectiveness evidence

6.1 The manufacturer developed a Markov model that compared rivaroxaban (20 mg once daily) with warfarin (adjusted dose warfarin at 4.5 mg once daily, target INR 2.5, range 2.0 to 3.0), aspirin (150 mg once daily) dabigatran (110-150 mg twice daily), and no treatment. The population in the model is the same as the ROCKET-AF safety-on-treatment population. The model has a lifetime time horizon and a UK NHS perspective.

6.2 The model has 22 health states: anticoagulant initiation, stable atrial fibrillation (on or off therapy), minor stroke (on or off therapy), major stroke (on or off therapy), post major stroke (on therapy), minor bleed (on or off therapy), major bleed (on or off therapy), intracranial bleed (on or off therapy), post intracranial bleed (on

therapy), systemic embolism (on or off therapy), post intracranial bleed (off therapy), systemic embolism (off therapy), myocardial infarction (on or off therapy), post myocardial infarction (on or off therapy) and death (on or off therapy).

6.3 The ROCKET-AF trial results for the safety-on-treatment population were used to inform the efficacy estimates for rivaroxaban compared with warfarin, rivaroxaban compared with warfarin in people whose atrial fibrillation is poorly controlled on warfarin, and the vitamin K antagonist naive model populations. The characteristics of the population for the analyses of rivaroxaban compared with aspirin, dabigatran and no treatment were based on the patient characteristics of a UK GP practice based survey (Gallagher et al. 2008) and efficacy estimates were obtained from the network meta-analysis.

6.4 The manufacturer classified all model events as either transient or permanent depending on associated long-term costs and consequences. Systemic embolism, minor extracranial bleeds and major extracranial bleeds were assumed to have no lasting clinical or economic sequelae and as such were considered transient events in the model. Minor stroke, major stroke, intracranial bleeding and myocardial infarction were considered by the manufacturer to be permanent events, in the sense that they have lasting clinical and economic sequelae. Consequently, the manufacturer developed post-event health states to account for the different risks, costs and utilities associated with surviving a permanent event.

6.5 The manufacturer highlighted that increasing age was an important risk factor for ischaemic stroke and systemic embolism, and adjusted the baseline risk of these events to account for increases

in patients' age as they transition through the model. Risks were calculated using the Framingham risk equations. In the model, a weighted average relative risk (weighted by the proportion of patients in each risk group at initiation) is calculated for each age group and applied to the baseline risk as patients enter that age group. The risks of extracranial bleeding, intracranial bleeding and myocardial infarction were assumed to be independent of time and, therefore, were not adjusted for.

6.6 The baseline risk of each event was adjusted according to the treatment regimen the patient was receiving. Patients may stop their primary therapy and switch to a pre-specified secondary therapy at any time (see table 6), although the risk adjustment applied for the remainder of that cycle will be that of the primary therapy. The probabilities of treatment discontinuation for warfarin and rivaroxaban were based on data obtained from the ROCKET-AF trial. The initial and subsequent quarterly probabilities of discontinuation for patients receiving rivaroxaban are [redacted] and [redacted] respectively. Warfarin discontinuation is initially [redacted] per quarter and [redacted] thereafter. The manufacturer assumed that the probability of discontinuation for aspirin, dabigatran and placebo was equivalent to that of rivaroxaban, given the similarity of administration between these interventions.

Table 6 Treatment sequence

Primary therapy	Secondary therapy
Rivaroxaban	Aspirin
Warfarin	Aspirin
Aspirin	No treatment
Dabigatran	Aspirin
No treatment	Aspirin

6.7 As the ROCKET-AF trial did not include a generic measure of health-related quality of life (such as the EQ-5D) that could be used to estimate utilities in the model, health state utility values and treatment-related utility values in atrial fibrillation were obtained from published sources identified via systematic literature searching. See table 7 for the utility values used in the manufacturer's model. The estimates of resources and costs were obtained from NHS reference costs for 2009/10 and systematic literature searching. The information provided by the NHS reference costs and the manufacturer's literature review did not provide sufficient information of the management of anticoagulation in the UK. The manufacturer therefore commissioned a survey to investigate the current anticoagulation management practices of primary care trusts across the UK. On the basis of the results from the survey, the manufacturer assumed that warfarin monitoring took place in both primary and secondary care. The manufacturer's model categorised monitoring costs into the following distinct phases: initiation, maintenance, and re-initiation. The manufacturer's model calculated the quarterly cost of initiation, maintenance and re-initiation by taking a weighted average of each cost; the cost of the individual phases was weighted by the proportion of people treated in primary and secondary care, as indicated by the manufacturer's survey. See table 8 for the costs associated with the different phases of warfarin monitoring used in the manufacturer's base case.

Table 7 Utility values used in the manufacturer's model

Health state	Utility
Stable atrial fibrillation – not on treatment	0.779
Stable atrial fibrillation – maintained on warfarin treatment	0.779
Stable atrial fibrillation – maintained on other therapy	0.779
Stable atrial fibrillation – initiating warfarin treatment	0.779
Minor stroke	0.6410
Major stroke	0.1890
Post minor stroke	0.7189
Post major stroke	0.4819
Systemic embolism	0.6601
Minor bleed	0.7767
Major bleed	0.5990
Intracranial bleed	0.6000
Post intracranial bleed	0.7400
Myocardial infarction	0.683
Post myocardial infarction	0.6848

Table 8 Costs associated with the different phases of warfarin monitoring used in the manufacturer's base case

Monitoring phase	Number of visits	Primary care cost	Secondary care cost[a]	Cost used in the manufacturer's base-case model[b]
Initiation	Warfarin naïve = 9 Warfarin experienced = 5	£175.50[c]	£168.92[c]	£181.29
Maintenance	5	£135.00	£123.45	£135.57
Re-initiation	7	£189.00	£172.83	£189.79

a Includes the cost of patient transport service applied to 8.55% of patients.

b Weighted by the proportion of patients treated in primary and secondary care: assumed to be 66.45% and 33.55%, respectively, in the manufacturer's base-case analysis.

c Weighted by the proportion of patients who were warfarin naïve and experienced, determined to be 37.5% and 62.5%, respectively, in the manufacturer's base case.

6.8 The manufacturer presented the base-case analysis; rivaroxaban versus warfarin using only statistically significant data from the ROCKET-AF safety-on-treatment population. The manufacturer also presented the results of the following four subgroup analyses: rivaroxaban versus warfarin in people whose INR is poorly controlled on warfarin; rivaroxaban versus warfarin in people naive to warfarin; and rivaroxaban versus aspirin and versus no treatment (placebo) – full incremental results and rivaroxaban versus dabigatran. The results of the manufacturer's base-case analysis and subgroup analyses are summarised in table 9.

Table 9 Base case and subgroup cost-effectiveness results

Analysis	Technology	Total		Incremental		ICER (£)
		Costs (£)	QALYs	Costs (£)	QALYs	
ROCKET-AF-based analyses						
Manufacturer's base case	Warfarin	8,200	6.998	–	–	–
	Rivaroxaban	8,941	7.037	740	0.039	18,883
Poorly controlled warfarin patients	Warfarin	8,941	6.998	–	–	–
	Rivaroxaban	10,423	7.037	1,482	0.039	Rivaroxaban dominates
Warfarin-naïve patients	Warfarin	8,333	6.998	–	–	–
	Rivaroxaban	8,941	7.037	607	0.039	15,494
NMA-based analyses						
Aspirin	Aspirin	10,367	6.409	–	–	–
	Rivaroxaban	11,249	6.833	883	0.424	2,083
Dabigatran (either dose)	Dabigatran	13,310	6.712	–	–	–
	Rivaroxaban	12,397	6.712	–913	0	Rivaroxaban dominates

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year.

6.9 The manufacturer also presented the results of a fully incremental analysis between rivaroxaban, aspirin and no treatment (placebo). However, no treatment (placebo) was dominated by aspirin and is therefore not presented in table 10.

Table 10 Rivaroxaban, aspirin and no treatment (placebo) full incremental analysis

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline	ICER incremental
Aspirin	10,367	6.409	–	–	–	–
No therapy (placebo)	10,753	6.285	386	–0.124	Dominated	Dominated
Rivaroxaban	11,249	6.833	883	0.424	2,083	2,083

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

6.10 The manufacturer carried out two scenario analyses to assess the robustness of the ROCKET-AF-based analysis (rivaroxaban versus warfarin). Scenario 1 assessed the effect of using all efficacy point estimates from the safety-on-treatment population analyses of the ROCKET-AF trial. Scenario 2 used only statistically significant efficacy point estimates from the ITT population analysis of the ROCKET-AF trial. Both scenarios resulted in a lower cost-effectiveness estimate, compared with the manufacturer's base-case ICER. The scenario 1 analysis resulted in an ICER of £8732 per QALY gained, and the scenario 2 analysis resulted in an ICER of £17,927 per QALY gained.

6.11 The manufacturer carried out extensive one-way sensitivity analysis on the base case, scenario analyses and all subgroup analyses conducted as part of the submission, with the exception of the subgroup analysis of dabigatran. The main drivers of the model results were consistent across analyses, with the cost of warfarin monitoring in primary care having a major impact on all ROCKET-AF-based analyses.

6.12 The probabilistic sensitivity analyses indicated that rivaroxaban had a 75% probability of being cost effective at a threshold of £20,000 per QALY gained and an 88% probability at £30,000 per QALY gained.

6.13 The ERG considered a Markov model to be an appropriate choice for modelling the chronic condition of atrial fibrillation. The ERG noted that the manufacturer chose a cycle length of 3 months and that only one event per 3-month cycle would be permitted because of the nature of the model. The manufacturer acknowledged that, in reality, people may experience more than one event in 3 months, but clinical opinion considered that the probability of experiencing

more than one event in 3 months would be low. The ERG agreed that the assumption of one event per model cycle is a necessary and reasonable assumption. However, the ERG noted that the manufacturer's model also suspends the risk of further events in the subsequent model cycle. The ERG considers that this additional suspension of risk is likely to bias the analysis against the more effective treatment as the overall event rate will be lower, and as such the potential to demonstrate clinical and economic benefits will also be lower.

6.14 The ERG identified the following limitations to the manufacturer's model's structural assumptions and parameter sources:

- the lack of disaggregation of the number of visits needed by people who were within and outside recommended INR control
- the lack of adjustment of risk of bleeding by age
- the lack of adjustment of utility by age
- the source of myocardial infarction risk for people treated with aspirin
- the source of post-myocardial infarction mortality risk
- the double counting of re-initiation costs of warfarin monitoring
- the suspension of the risk of further events for the subsequent model cycle following an event
- the exclusion of transient ischaemic attack as a potential event.

6.15 The ERG presented an alternative base case in which, where possible, adjustments were made to account for the limitations identified (see section 6.14). The alternative base-case ICER was £33,758 per QALY gained. Similarly, for warfarin-naive people, after incorporation of the ERG's model adjustments the ICER for rivaroxaban compared with warfarin increased from £15,494 to £29,894 per QALY gained. However, rivaroxaban remained

dominant in those people whose INR was poorly controlled on warfarin, following the incorporation of the ERG's model adjustments. The structure of the manufacturer's model precluded the removal of risk suspension and the addition of transient ischaemic attack as a potential event. Consequently, the ERG was unable to fully quantify the impact of these limitations on the ICERs. However, the ERG considered that the suspension of risk and exclusion of transient ischaemic attack as an event would favour warfarin (that is, the removal of these limitations would decrease the ICER), because warfarin is generally less effective than rivaroxaban (based on safety-on-treatment population of ROCKET-AF).

6.16 The ERG considered that the manufacturer's base-case model is driven by the cost of anticoagulation monitoring rather than the differential effectiveness of the comparators. The ROCKET-AF trial showed that, for most outcomes, there was no statistically significant difference between rivaroxaban and warfarin. The ERG highlighted that when the cost of anticoagulation monitoring was disaggregated by INR range the ICERs significantly increased from £18,883 per QALY gained to £27,281 per QALY gained. In addition to this, the ERG's scenario analysis using alternative anticoagulation monitoring costs (discussed by the Appraisal Committee in the ongoing appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation) increased the ICER to £62,568 per QALY gained.

6.17 The ERG was concerned that the network meta-analysis presented by the manufacturer had high levels of heterogeneity, which were not shown when the ERG conducted its own network meta-analysis restricting the network to the comparators specified in the final scope issued by NICE. When the ERG applied the treatment

effects estimated by the ERG's network meta-analysis to the manufacturer's model, an ICER of £34,680 per QALY gained was obtained for dabigatran versus rivaroxaban. The ERG applied further adjustments to account for the following limitations: the absence of a post-systemic embolism health state, the lack of adjustment of bleeding risk by age, the lack of adjustment of utility by age, the archaic source of post-MI mortality risk, and the assumption of equivalent discontinuation rates. This reduced the ICER to £12,701. Exploratory analysis, assuming an equivalent ability of rivaroxaban and dabigatran to prevent myocardial infarction, further decreased the ICER to £3578.

6.18 The ERG noted the presence of conflicting bias in the model, with limitations of risk suspension and the absence of transient ischaemic attack and dyspepsia as adverse events. Removing risk suspension is likely to favour dabigatran (that is, reduce the ICER), whereas the inclusion of transient ischaemic attack and dyspepsia is likely to increase the ICER. Furthermore, the ERG noted that there is a large amount of uncertainty in the model and that the model is highly sensitive to even small changes to the discontinuation rates. Therefore, the ERG considered that the results of the probabilistic sensitivity analysis should be taken into account when considering the ERG's alternative ICER for dabigatran versus rivaroxaban. The probabilistic sensitivity analysis indicated that dabigatran was dominant in 45% of the 1000 runs and dominated in 35% of runs.

7 Equalities issues

7.1 No equality issues were raised in the submission or during consultation on the draft scope.

8 Innovation

8.1 During consultation on the draft scope, consultees suggested that rivaroxaban should be considered to be innovative given its potential advantage in terms of its lower need for therapeutic monitoring. Some people may not be on treatment because of the difficulties of regular therapeutic monitoring, so more people would be able to be on treatment and have good INR control.

9 Authors

Helen Tucker
Technical Lead

Nicola Hay
Technical Adviser

with input from the Lead Team (Paul Robinson, Alec Miners and Pamela Rees).

Appendix A: Supporting evidence

Related NICE guidance

Published

- The management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/guidance/CG36
- Dronedarone for the treatment of non-permanent atrial fibrillation. NICE technology appraisal guidance 197 (2010). Available from www.nice.org.uk/guidance/TA197
- Thoracoscopic exclusion of the left atrial appendage in atrial fibrillation (with or without other cardiac surgery) for the prevention of thromboembolism. NICE interventional procedure guidance 400 (2011). Available from www.nice.org.uk/guidance/IPG400
- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 349 (2010). Available from www.nice.org.uk/guidance/IPG349

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. Expected date of publication December 2011.