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

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 10/75

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
11	Section 1.2: text and numbers relating to adverse events amended, and text in last sentence on page deleted.
12	Section 1.2: text in first sentence on the page deleted. Section 1.3: [redacted]
15	Section 1.5.1: ICER using lower warfarin monitoring costs amended.
25	Section 3.2: highlighting of confidential information amended in the last paragraph.
28	Section 3.5: text relating to 30 day follow-up period amended and text in last paragraph relating to follow-up deleted.
34	Section 4.2.1 text and number relating to trial site excluded from analyses amended.
42	Section 4.2.6: text relating to 30 day observation period amended.
43	Section 4.2.7: in table 8 footnote relating to ITT population amended and text and numbers relating to the trial site excluded from analyses amended.
44	Section 4.2.7: text relating to populations used in the analyses amended.
46	Section 4.3.1: [redacted]
55	Section 4.3.3: [redacted].
56	Section 4.3.3: title of table 16 amended.
58	Section 4.3.4: highlighting of confidential information amended in the last paragraph.
61	Section 4.3.5: [redacted].
70	Section 4.5: highlighting of confidential information amended in the text.
76	Section 4.6.1: [redacted].
87	Section 5.3.6: in Table 30 numbers relating to RR and 95% CI for MI amended.
110	Section 5.4.4: text relating to gastrointestinal bleeding amended.
132	Section 7: text and numbers relating to adverse events amended.

[redacted]

The overall safety profile of rivaroxaban and warfarin, from ROCKET AF, were similar (treatment-emergent adverse events: 81.44% vs 81.54%). However, compared with warfarin, rivaroxaban was associated with significantly fewer intracranial bleeding events (0.77% vs 1.18%; $p < 0.05$) but significantly more gastrointestinal bleeding events (3.15% vs 2.16%; $p < 0.001$) and bleeding events requiring transfusion (1.6% vs 1.3%; $p = 0.04$).

Subgroup results from ROCKET AF suggest that people with no prior use of vitamin K antagonists (VKAs) have fewer primary endpoint events (stroke and non-CNS systemic embolism) [redacted] with rivaroxaban compared with those who have previously been treated with a VKA. These data could be interpreted as indicating that VKA-naïve patients potentially achieve a greater benefit from rivaroxaban than those who have previously taken a VKA, such as warfarin.

Data for the subgroup of [redacted]

The manufacturer also compares rivaroxaban with aspirin and dabigatran etexilate (110 mg or 150 mg twice daily) using an NMA in patients suitable for anticoagulation. Results from [redacted]

1.3 [redacted]

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

The ERG considers the ROCKET AF trial to be of generally good quality. However, the ERG considers it important to note that the trial population of ROCKET AF predominantly consists of high risk patients (defined as $CHADS_2$ score ≥3) as 87% of the trial population had a $CHADS_2$ score of 3 or more. The ERG notes that there is limited clinical evidence regarding the efficacy of rivaroxaban in the moderate risk AF population (defined as $CHADS_2$ score 1–2), although the ERG agrees with the manufacturer's suggestion that relative treatment effect is likely be consistent across patient populations at different risk.

The ERG also notes that there is a large variability between the time in therapeutic range (TTR) values for the different trial regions in ROCKET AF and the ERG considers that the overall trial TTR is lower than that generally reported in the United Kingdom (UK) and in other clinical trials. [redacted]

Baseline population characteristics of ROCKET AF indicate that there was a statistically significant difference between the rivaroxaban and warfarin groups in proportion of people who had experienced an MI prior to enrolment in the trial ($p < 0.05$), with more people in the warfarin group having had an MI. History of MI is associated with an increased risk of future MI, thus the warfarin group in ROCKET AF could be at a higher risk of MI compared with the rivaroxaban group. The ERG is of the opinion that this difference in baseline history of MI should be considered when interpreting data on MI from ROCKET AF and the manufacturer's and ERG's NMA.

Dabigatran was listed as a comparator in the final scope issued by NICE and is currently undergoing a NICE technology appraisal, with a decision expected in December 2011. As no direct head-to-head comparative data for rivaroxaban and dabigatran is available, the manufacturer conducted an NMA to provide an estimate of the treatment effect of rivaroxaban compared with dabigatran etexilate (110 mg or 150 mg twice daily). However, the ERG has concerns about the validity of the results from the NMA conducted by the manufacturer due to [redacted]

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

The ERG considers warfarin to be a likely second-line treatment strategy for rivaroxaban and dabigatran. However, the manufacturer's economic evaluation assumes aspirin is the only second-line treatment. Clinical data from the ITT population of ROCKET AF could have been used to inform an evaluation of a change in treatments following discontinuation from rivaroxaban likely to be seen in clinical practice.

1.5.1 ROCKET AF-based analysis

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

- The lack of disaggregation of the number of visits required by patients within and outside recommended INR control;
- The lack of adjustment of bleeding risk by age;
- The lack of adjustment of utility by age;
- The source of MI risk for patients treated with aspirin;
- The source of post-MI 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 TIA as a potential event.

The structure of the manufacturer's model prohibited the removal of the suspension of further events and the inclusion of TIA as a potential outcome. However, the ERG was able to adjust the manufacturer's model to account for the impact of the other limitations identified, producing an ICER of £33,758 per QALY gained. However, the ERG notes that the removal of the suspension of risk and the inclusion of TIA as an outcome are likely to decrease the ICER. 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, which increased the ICER to £62,568 per QALY gained.

In the subgroup of warfarin-naïve patients, the ERG adjustments increased the ICER for rivaroxaban compared with warfarin from £15,494 to £29,894 per QALY gained. However, when using the ERG's model adjustments, rivaroxaban remained dominant in those patients poorly controlled on warfarin (i.e., those with TTR <60% [target INR of 2–3]).

The ERG considers that the manufacturer's base case model (rivaroxaban vs warfarin) is driven by the cost of anticoagulation monitoring rather than the differential effectiveness of the comparators. When

- people ≥75 years old with hypertension, diabetes, peripheral artery disease or coronary artery disease;
- clinical evidence of valve disease, heart failure or left ventricular dysfunction on echocardiography.

The European Society of Cardiology (ESC) guidelines define stroke risk using the $CHADS_2$ score as:

- $CHADS_2$ score of 0 = low risk;
- $CHADS_2$ score of 1–2 = moderate risk;
- $CHADS_2$ score of >2 = high risk.

ROCKET AF did not actively enrol people with only one $CHADS_2$ risk factor or those ≥65 years old with no high-risk factors, and over 85% of the ROCKET AF population had a $CHADS_2$ score ≥3. Based on these details, and considering the definitions of moderate and high risk of stroke in CG36 and the ESC guidelines, the Evidence Review Group (ERG) and our clinical advisors judge that, in general, the ROCKET AF population is at higher risk of stroke than the population defined in the NICE final scope.

The ERG also notes that, in the MS, the manufacturer does not address the population of patients for whom warfarin is unsuitable, and that the ROCKET AF trial does not include this population. The ERG thus considers that there is currently no suitable data on rivaroxaban to assess the safety or efficacy in patients for whom warfarin is unsuitable.

3.2 Intervention

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Its mode of action involves the inhibition of Factor Xa, which leads to interruption of the intrinsic and extrinsic pathway of the blood coagulation cascade and results in the inhibition of both thrombin formation and the development of thrombi.

The manufacturer reports that rivaroxaban was submitted for regulatory approval for the prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA in December 2010 via the European Union centralised process. [redacted] In addition, rivaroxaban has yet to gain regulatory approval for use in this indication in countries outside of the United Kingdom (UK).

The anticipated licensed dose of rivaroxaban for this indication is 20 mg once daily with a dose reduction to 15 mg once daily in people with moderate or severe renal impairment (defined as creatinine clearance of 30–49 mL/min and 15–29mL/min, respectively).

[redacted]

Site notification date (the date sites were notified by the Executive Committee that the required number of primary endpoint events, as deemed by the Clinical Events Committee, had occurred) was stated in the MS as 28th May 2010, and the median duration of randomised treatment exposure was 590 days (safety-on-treatment population). Additional follow-up data, including the range of treatment duration, was provided by the manufacturer at the clarification stage for this STA. The information provided is discussed further in Section 4.2.5 of this report.

Patients who discontinued blinded, randomised study drug treatment during the study were transitioned to an open-label VKA or other appropriate therapy (e.g., aspirin or no therapy), as determined by the investigator, and then continued in study follow up in the intention-to-treat (ITT) population.

At the end of study visit, patients were transitioned from study drug to an open-label VKA or other appropriate therapy (e.g., aspirin or no therapy) as determined by the investigator and followed up in a post-treatment observation period for approximately 30 days. These follow-up data are not presented within the MS. The ERG agrees with the manufacturer's decision not to include these data as they are not randomised and do not include patients taking rivaroxaban, and so the post-treatment observation period does not directly inform the NICE decision problem for this appraisal.

The ERG notes that ROCKET AF achieved sufficient follow-up to reach its primary efficacy end point for assessment of non-inferiority.

3.6 Other relevant factors

Neither the manufacturer nor the ERG is aware of any specific equity or equality issues relevant to this technology appraisal.

The ERG notes that in the final scope issued by NICE it is stated that consideration should be given to the potential advantage of rivaroxaban in terms of its lower requirement for therapeutic monitoring and its fewer drug interactions compared with warfarin. The manufacturer highlights in the MS that rivaroxaban is administered at a fixed dose once daily and does not require routine monitoring of coagulation parameters during treatment. This is in contrast to warfarin where there is a requirement for regular monitoring of INR and adjustment of warfarin dose to ensure anticoagulation is maintained within the desired therapeutic INR range. The association of rivaroxaban with fewer drug interactions than warfarin was not explicitly described within the MS and thus the ERG is unable to

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, although please refer to section 5.3.6 for further discussion on appropriate analysis of this trial

In general, the ERG agrees with the manufacturer's validity and quality assessment for ROCKET AF.

The ERG notes that there was one trial site (93 people) that was excluded from all the efficacy data analysis sets due to violations in Good Clinical Practice guidelines. From the information provided by the manufacturer, the ERG considers that the manufacturer's decision to exclude these data from analyses is appropriate, and that the events at this site were unlikely to be related to the quality of the trial methods.

4.2.2 ROCKET AF population

The ROCKET AF study randomised 14,264 people from 1,178 sites across 45 countries between December 2006 and June 2009. This total included 206 patients from 23 sites in the UK. People were randomised in a 1:1 ratio to either active rivaroxaban or active warfarin. The randomisation was stratified by country, prior use of VKAs, and a history of stroke, transient ischaemic attack (TIA) or non-CNS systemic embolism.

The number of patients without a prior stroke, TIA or non-CNS systemic embolism and who had no more than 2 risk factors was limited to approximately 10% by region of the total number of patients enrolled. The remaining 90% of the study population was required to have a minimum of 3 risk factors if they had not had a previous stroke, TIA or non-CNS systemic embolism.

The ROCKET AF recruitment inclusion/exclusion criteria are listed in Table 6 and baseline characteristics for the intention-to-treat (ITT) population are presented in Table 7. In the MS, the manufacturer reported that [redacted].

Table 6. ROCKET AF inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥18 years; • Persistent or paroxysmal AF documented on ≥2 episodes (one of which is electrocardiographically documented within 30 days of enrolment);	• Prosthetic heart valve; • Planned cardioversion; • AF secondary to reversible disorders (i.e., thyrotoxicosis); • Known presence of atrial myxoma or left ventricular thrombus; • Active endocarditis;

[redacted]

At each follow-up visit a standardised questionnaire was administered and patients were examined to screen for stroke symptoms and clinical events requiring further evaluation. Occurrence and signs of TIA, MI, bleeding complications and procedures were evaluated, along with vital status and any adverse events. Compliance with treatment was checked at each visit and any concomitant medication recorded. Liver function tests were performed at screening and during regularly scheduled routine follow up.

INR monitoring using the point-of-care device provided in the study occurred as clinically indicated, but at least every 4 weeks. The ERG is of the opinion that this testing may be more frequent than the average time between INR monitoring appointments in the UK population, which is around 4 weeks, with a maximum frequency of 12 weeks. The ERG considers that the potentially more frequent INR monitoring in ROCKET AF would potentially introduce bias in favour of warfarin rather than rivaroxaban, assuming more frequent INR monitoring resulted in improved INR control (i.e., improved time in therapeutic range [TTR]). However, the ERG also notes that the TTR in ROCKET AF (mean TTR in safety-on-treatment population was 55%) is not as high as that observed in other similar clinical trials (e.g., TTR in RE-LY was 64%). These data suggest that the INR control in ROCKET AF was not substantially improved by the potentially more frequent INR monitoring.

A 12-lead electrocardiogram (ECG) and clinical laboratory tests were performed annually.

At the end of study visit (or earlier if patients discontinued study drug treatment early), patients were transitioned to open-label warfarin or other appropriate regimen (alternative VKA, aspirin or no therapy) as determined by the investigator and were then followed up for an additional 30 days in a post-treatment observation period. [redacted]

4.2.7 Details and critique of the statistical approach used

Table 8 provides an overview of each of the different populations used in the analyses in the MS.

Table 8. Definitions of the populations used in the analyses in the manufacturer's submission

Population	Definition	Follow-up period	Number of people included in analyses	Number of patients excluded from analyses
Intention-to-treat (ITT)	All patients uniquely randomised	Until date of site notification (i.e. double blind trial end point), regardless of treatment received	14,171	93 people from protocol violating site*
Per protocol	All ITT patients, excluding those with major pre-defined protocol deviations	Until 2 days after permanent discontinuation of randomised study medication	13,962	93 people from protocol violating site* 209 people with major protocol deviations
Safety-on-treatment	All ITT patients who had taken at least one dose of study medication	Until 2 days after permanent discontinuation of randomised study medication	14,143	93 people from protocol violating site* 28 people who did not take any of their randomised study medication
Note: In the ITT population there was a median of 117 days of follow-up assigned medication (i.e., patients were off randomised treatment and taking open-label vitamin K antagonist or other appropriate regimen as determined by the investigator). * Excluded only from efficacy analyses.				

The primary objective of the ROCKET AF trial was to test the hypothesis that rivaroxaban is non-inferior to warfarin for the prevention of stroke or systemic embolism in the per protocol population. The per protocol population was pre-specified as all patients who received at least one dose of study medication and did not have a major pre-defined protocol violation. Patients were followed for events whilst receiving the study drug and for two days after study drug discontinuation.

The non-inferiority margin was defined as 1.46 with a one sided alpha level of 0.025, and the manufacturer stated that, to provide a power of 95%, a minimum of 363 events would be required. However, assuming a 14% dropout rate, a minimum of 14,000 patients to observe 405 events was selected. This minimum number of events was achieved for the primary outcome in the pre-specified population. The MS and a published paper on the design of ROCKET AF**Error! Reference source not found.** explain the rationale behind selecting a 1.46 non-inferiority margin however the ERG was unable to verify this using the published sources cited in the MS.' The ERG does however note that the non-inferiority margin of 1.46 was also used in the RE-LY trial for assessing dabigatran etexilate versus warfarin in a similar indication. The ERG also notes that in the manufacturer's submission for the dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation STA a second non-inferiority margin of 1.38 was reported and cited as being the preferred margin of non-inferiority of the US Food and Drug Administration (FDA).

The ERG notes that it has been reported that the choice of non-inferiority margin and population used in the statistical analysis of non-inferiority trials can result in the introduction of bias in the results. However, the ERG also notes that the manufacturer presents the non-inferiority analysis for both the per protocol and ITT ROCKET AF populations. This is a commonly used approach in non-inferiority trials, with the trial often only being considered positive if non-inferiority is demonstrated in both the ITT and per protocol populations.

In ROCKET AF, the ERG notes that the manufacturer [redacted] assess for superiority in a list of primary and secondary outcomes should rivaroxaban be found to be non-inferior to warfarin in preventing stroke and systemic embolism (primary efficacy outcome) in the per protocol population. To meet the criterion of superiority in ROCKET AF, the upper limit of the 2-sided confidence interval for the respective analysis had to be less than 1.

In addition to the analyses in the per protocol and safety-on-treatment populations, [redacted] were also performed to assess non-inferiority and superiority in the ROCKET AF ITT population.

The ERG considers that the ROCKET AF ITT population reflects what would be expected in routine clinical practice in terms of treatment sequencing and outcome effects. However, the ERG notes that the manufacturer prefers to report analyses based on the safety-on-treatment population data, stating that the protocol for ROCKET AF specifies that the safety-on-treatment population will be used in efficacy and safety analyses. The ERG also acknowledges that the manufacturer provides efficacy analyses for both the ITT and safety-on-treatment populations. The results from the two population data sets are compared and discussed further in Section 4.3.2.

4.3 Summary and critique of clinical effectiveness results from ROCKET AF

4.3.1 ROCKET AF treatment compliance and discontinuations

Mean treatment compliance was based on the proportion of days for which the study drug was taken, and was reported to be [redacted]% for both rivaroxaban and rivaroxaban placebo.

The compliance of warfarin could not be measured directly due to the individual patient variation in dosing; thus, the manufacturer used the intake of rivaroxaban placebo and blood INR levels as surrogate measures of treatment compliance.

In the warfarin group of the safety-on-treatment population, the mean time in therapeutic range (TTR) for the INR range of 2.0 to 3.0 was 55%, and the median TTR was 58%. The ERG notes that these TTR values are somewhat lower than the TTR reported in other trials which include a UK population, such as RE-LY (warfarin vs dabigatran) which reported an overall trial TTR of 64.4%.**Error! Reference source not found.** Also of note [redacted].

Table 10. [redacted]

[redacted]	[redacted]	[redacted]	
		Mean (%)	Median (%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

[redacted]

[redacted]

The discontinuation of study medication data reported in the MS consisted of much lower numbers compared with that reported in the FDA briefing document.**Error! Reference source not found.** The numbers presented in the flow diagram in the MS state that 1,691 patients in the rivaroxaban group and 1,584 patients in the warfarin group discontinued their study drug early. The MS states that these numbers do not include patients who were lost to follow up, experienced a primary endpoint event or death, did not receive any study drug or from GCP/closed site. Of these discontinuations, 594 in the rivaroxaban group and 496 in the warfarin group were due to adverse events. The remaining discontinuations were reported to be for withdrawal of consent from study drug and follow up, patient decision to stop study drug but continue follow up and "other reasons", which were not discussed further in the MS.

Table 15. Results for [redacted] subgroup versus whole trial data for ROCKET AF

Outcomes	Safety-on-treatment		Intention-to-treat	
	[redacted] HR* (95% CI)	Full trial data HR* (95% CI)	[redacted] HR* (95% CI)	Full trial data HR* (95% CI)
Efficacy				
Primary efficacy endpoint	[redacted]	0.79 (0.65 to 0.95)	[redacted]	0.88 (0.75 to 1.03)
Stroke	[redacted]	0.85 (0.7 to 1.03)	[redacted]	[redacted]
• Primary ischemic stroke	[redacted]	0.94 (0.75 to 1.17)	[redacted]	[redacted]
• Primary hemorrhagic stroke	[redacted]	0.59 (0.37 to 0.93)	[redacted]	[redacted]
Non-CNS systemic embolism	[redacted]	0.23 (0.09 to 0.61)	[redacted]	[redacted]
Myocardial infarction	[redacted]	0.81 (0.63 to 1.06)	[redacted]	[redacted]
Vascular death	[redacted]	0.89 (0.73 to 1.10)	[redacted]	[redacted]
All-cause mortality	[redacted]	0.85 (0.7 to 1.02)	[redacted]	0.92 (0.82 to 1.03)
Safety				
Principal safety endpoint (a)	[redacted]	1.03 (0.96 to 1.11)	[redacted]	[redacted]
Major	[redacted]	1.04 (0.9 to 1.2)	[redacted]	[redacted]
Non-major clinically relevant	[redacted]	1.04 (0.96 to 1.13)	[redacted]	[redacted]
Gastro-intestinal major bleed	[redacted]	[redacted]	[redacted]	[redacted]

* HRs are for rivaroxaban versus warfarin.

[redacted]

The overall low warfarin INR TTR (for all regions) observed in ROCKET AF, compared with other trials carried out in Western Europe populations and RE-LY, could influence the generalisability of the results to the UK population. The ERG thus requested some additional data from the manufacturer for the subgroups of patients with a TTR <60% and those with a TTR ≥60%. [redacted]

[redacted]

However, the ERG would like to highlight that randomisation in ROCKET AF was not stratified by TTR and so these data should be interpreted with caution.

Table 16. [redacted]

	[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		
Non-major clinically relevant		
Gastro-intestinal major bleed		
[redacted]		

Major	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90 to 1.20)	0.58
• Haemoglobin • Haematocrit drop	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03 to 1.44)	0.02*
• Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01 to 1.55)	0.04*
• Critical organ bleeding(s)	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53 to 0.91)	0.007*
• Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31 to 0.79)	0.003*
• Intracranial haemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47 to 0.93)	0.02*
Non-major clinically relevant bleeding	1,185 (16.7)	11.8	1,151 (16.2)	11.4	1.04 (0.96 to 1.13)	0.35
Minimal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes to accompany table:

1) Minimal events are not included in the principal safety endpoint;

2) Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate;

3) p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.

*Statistically significant at nominal 0.05 (two-sided).

Abbreviations used in table: 95% CI, 95% Confidence Interval.

The bleeding events captured in the principal safety endpoint occurred at different sites in each treatment group. In the rivaroxaban group, bleeding occurred more frequently at sites throughout the gastrointestinal tract (224 bleeds with rivaroxaban vs 154 bleeds with warfarin; $p < 0.001$). By contrast, in the warfarin group, critical organ bleeding (e.g. intracranial bleeding: 55 bleeds with rivaroxaban vs 84 bleeds with warfarin; $p < 0.05$ and intraparenchymal bleeding: 37 bleeds with rivaroxaban vs 56 bleeds with warfarin; $p < 0.05$), and non-traumatic bleeding (33 bleeds with rivaroxaban vs 54 bleeds with warfarin; $p < 0.001$) were more common.

The ERG also requested data from the manufacturer on bleeding adverse events broken down by patient age, which the ERG acknowledges is not a randomised comparison and so any conclusions drawn from these data should be interpreted with caution. [redacted]

4.3.5 [redacted] Summary of ROCKET AF results

- Rivaroxaban was demonstrated to be non-inferior to warfarin in the prevention of stroke and non-CNS systemic embolism.

- Superiority of rivaroxaban over warfarin was demonstrated in the primary efficacy endpoint, major secondary endpoint 1 and major secondary endpoint 2 in the safety-on-treatment population although superiority was not demonstrated for these outcomes in the ITT population (sensitivity analysis).

- Rivaroxaban did not reach superiority over warfarin in the safety-on-treatment [redacted] for the outcomes of all-cause mortality, vascular deaths, non-vascular deaths, MI, all strokes and primary ischaemic strokes

- Substantially larger number of events occurred in the rivaroxaban group compared with the warfarin group during the 'off-treatment' period, and the time to reach therapeutic INR dose of open label warfarin was considerably longer in the rivaroxaban group.

- [redacted]

- [redacted]

- [redacted]

- The results from ROCKET AF suggest a generally comparable safety and adverse event profile for rivaroxaban compared with warfarin although rivaroxaban was associated with significantly higher rates of bleeding requiring blood transfusion.

Table 22. Direct versus indirect estimates for rivaroxaban versus adjusted-dose warfarin from ROCKET AF

Outcome	ROCKET AF results as reported in the MS	NMA results
	HR (95% CI)	OR (95% CrI)
Composite	0.79 (0.66 to 0.96)	[redacted]
Total stroke	0.85 (0.7 to 1.03)	[redacted]
Ischaemic stroke	0.94 (0.75 to 1.17)	[redacted]
Haemorrhagic stroke/intracranial haemorrhage	Not reported as a composite in MS	[redacted]
Systemic embolism	0.23 (0.09 to 0.61)	[redacted]
Myocardial infarction	0.81 (0.63 to 1.06)	[redacted]
Cardiovascular death	0.89 (0.73 to 1.10)	[redacted]
Mortality	0.85 (0.70 to 1.02)	[redacted]
Major haemorrhage	1.04 (0.9 to 1.20)	[redacted]
Minor bleed	1.04 (0.96 to 1.13)	[redacted]
Gastrointestinal bleed	Not reported in MS	[redacted]
Transient ischaemic attack	Not reported in MS	[redacted]

4.5 *Additional work carried out by the ERG*

As part of the ERG's evaluation of the network meta-analysis presented in the MS, the ERG requested information on the heterogeneity and inconsistency in the network of randomised controlled trials. The manufacturer provided a table of information listing [redacted]

The ERG performed an exploratory NMA to evaluate whether using a simplified network based exclusively on the treatments of interest listed in the final scope issued by NICE [redacted] The ERG's exploratory work focused on those outcomes that inform the health economic analysis. The comparators included were:

rivaroxaban; dabigatran etexilate; aspirin; placebo; and adjusted standard dose warfarin. The outcomes assessed were:

significant difference between rivaroxaban and dabigatran etexilate for major gastrointestinal bleed (OR 1.01; 95% CI: 0.74 to 1.38).

4.6 Summary of clinical effectiveness results and critique

4.6.1 Clinical results

- Rivaroxaban was demonstrated to be non-inferior to warfarin in the prevention of stroke and non-CNS systemic embolism.

- Superiority of rivaroxaban over warfarin was demonstrated in the primary efficacy endpoint, major secondary endpoint 1 and major secondary endpoint 2 in the safety-on-treatment population of ROCKET AF although superiority was not demonstrated for these outcomes in the ITT population (sensitivity analysis).

- Rivaroxaban does not reach superiority over warfarin for the outcomes of all-cause mortality, vascular deaths, non-vascular deaths, MI, all strokes and primary ischaemic strokes in ROCKET AF.

- Rivaroxaban is associated with significantly higher rates of bleeding requiring blood transfusion when compared to warfarin.

- Significantly more GI bleeds occur with rivaroxaban compared with warfarin, and significantly more haemorrhagic strokes and intracranial haemorrhages occur with warfarin.

- [redacted].

- [redacted]

- [redacted]

5.3.6 [redacted] Treatment effectiveness

The manufacturer conducted several different analyses using clinical effectiveness data from the ROCKET AF trial and the manufacturer's NMA (discussed in Section 4.4).

ROCKET AF-based analyses

The base case analysis used the safety-on-treatment population of ROCKET AF to inform a comparison between rivaroxaban and warfarin. The baseline event risk was obtained from the warfarin arm of ROCKET AF and converted into a quarterly risk using standard formulae.**Error! Reference source not found.** RRs for rivaroxaban (compared with warfarin) were calculated from the ROCKET AF efficacy data and applied to the baseline risk. Where non-significant differences were observed, the RR was assumed to be 1. The manufacturer conducted scenario analysis using: all point estimates obtained from the safety-on-treatment population analysis (hereafter referred to as the safety-on-treatment point estimate analysis) and significant only data from the intention-to-treat (ITT) population (hereafter referred to as the ITT significant only analysis). Table 30 summarises the baseline and RRs obtained from the safety-on-treatment and ITT analyses of ROCKET AF.

Table 30. Treatment effectiveness parameters used in analyses based on data from ROCKET AF

Event	**Baseline quarterly risk**		**RR (relative to warfarin)**		
	Event probability (95% CI)	**Source**	**RR (95% CI)**	**RR used in significant only analysis**	**Source**
Base case analysis: rivaroxaban versus warfarin					
Ischaemic stroke	0.36% (0.31% to 0.41%)	Warfarin arm of ROCKET AF (safety-on-treatment population)	0.94 (0.75 to 1.17)	1.00	ROCKET AF (safety-on-treatment population)
Systemic embolism	0.05% (0.03% to 0.07%)		0.23 (0.09 to 0.61)	0.23	
Minor extracranial bleed	[redacted]		1.04 (0.96 to 1.13)	1.00	
Major extracranial bleed	[redacted]		1.14 (0.98 to 1.33)	1.00	
Intracranial bleed	[redacted]		0.67 (0.47 to 0.93)	0.67	
MI	0.28% (0.24% to 0.33%)		[redacted]	1.00	
ITT analysis: rivaroxaban versus warfarin					
Ischaemic stroke	0.41% (0.36% to 0.46%)	Warfarin arm of ROCKET AF (ITT	[redacted]	1.00	ROCKET AF (ITT population)
Systemic	0.05%		[redacted]	[redacted]	

embolism	(0.04% to 0.07%)	population)			
Minor extracranial	2.54%	Warfarin arm of	1.04	1.00	ROCKET AF (safety-on-

Table 47. [redacted] (OR <1 favours rivaroxaban; OR>1 favours comparator; adapted from MS; Table 25; pg 88)

Comparator	OR (95% CI)
Warfarin	[redacted]
ASA (aspirin)	[redacted]
Dabigatran 110 mg (twice daily)	–
Dabigatran 150 mg (twice daily)	–
Placebo	[redacted]
Abbreviations used in table: ASA, acetylsalicylic acid; [redacted] OR, odds ratio; [redacted]	

Gastrointestinal bleeding

The ERG observed that the risk of gastrointestinal bleeding is significantly higher with rivaroxaban than with warfarin (3.15% with rivaroxaban versus 2.16% with warfarin; $p < 0.001$), whereas there is no significant difference between treatments in the risk of major extracranial bleeding (5.55% with rivaroxaban versus 5.42% with warfarin). In the clarification response, the manufacturer stated that any rationale for the difference between rivaroxaban and warfarin in gastrointestinal bleeding would be pure speculation. In the model, the manufacturer has included gastrointestinal bleeding as a component of major extracranial bleeding. The ERG notes that the aggregation of gastrointestinal bleeding with all major extracranial bleeding may not accurately capture the differential risks associated with treatment and may bias the analysis towards rivaroxaban. The ERG carried out exploratory analyses to investigate the potential effect on the incremental cost-effectiveness ratio (ICER) of aggregating gastrointestinal bleeding with major extracranial bleeding. The risks of gastrointestinal bleeding reported in the safety-on-treatment population of ROCKET AF (baseline quarterly risk with warfarin = 0.3%, RR with rivaroxaban 1.46; $p < 0.001$) were used in place of the risks of major extracranial bleeding (baseline quarterly risk with warfarin = 0.7%, RR with rivaroxaban 1.14; $p > 0.5$). The influence of these changes on the ICER is displayed in Section 6.

Dyspepsia

The ERG notes that gastrointestinal-related adverse events, such as dyspepsia, have not been included in the economic model. During the clarification process, the ERG requested that the manufacturer provide the rates of dyspepsia in the warfarin and rivaroxaban arms of ROCKET AF, along with a revised model that included dyspepsia as an adverse event. The manufacturer provided the number and percentage of patients experiencing dyspepsia in ROCKET AF ([redacted] rivaroxaban patients and [redacted] warfarin patients). However, the manufacturer declined to revise the economic model

7 DISCUSSION

The manufacturer presents the case for the use of rivaroxaban compared with adjusted-dose warfarin for the prevention of stroke and systemic embolism in patients with AF based on data from the ROCKET AF trial. The Evidence Review Group (ERG) considers the ROCKET AF trial to be of good quality. However, the ERG has concerns about the generisability of the data from ROCKET AF to the UK population with AF. The NICE final scope**Error! Reference source not found.** specifies a moderate to high risk population whereas the ROCKET AF trial represents only high-risk patients, as 87% of the trial population had a $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA [doubled]) score of 3 or more. The ERG notes there is an absence of direct evidence regarding the efficacy of rivaroxaban in the lower risk AF population but accepts the manufacturer's proposition that relative treatment effect is likely be consistent across patient populations at different risk.

The manufacturer also compares rivaroxaban with aspirin and dabigatran etexilate (110 mg or 150 mg twice daily) in the population of patients suitable for anticoagulation, based on data from the manufacturer's network meta-analysis (NMA). Dabigatran etexilate is currently undergoing NICE technology appraisal**Error! Reference source not found.** and is included in the manufacturer's economic evaluation as an alternative comparator for rivaroxaban using a cost minimisation approach. The ERG notes that the manufacturer has not presented a comparison of rivaroxaban with aspirin in the warfarin unsuitable patient population, as specified in the NICE final scope.

The manufacturer used data from the safety-on-treatment population of the ROCKET AF trial in the base case to compare rivaroxaban and warfarin, arguing that the safety-on-treatment population of ROCKET AF provides an unbiased estimate of the relative effect of treatment. The intention-to-treat (ITT) population consisted of patients that moved on to alternate therapy following discontinuation from randomised treatment; approximately [redacted] of patients in each group subsequently received open-label warfarin. The ERG believes that an assessment of the rivaroxaban/warfarin treatment pathway using data from the ITT population is the preferred base case as it reflects the likely clinical effectiveness of the intervention in real-life clinical practice.

Overall, the safety profile of rivaroxaban and warfarin, from ROCKET AF, were similar (treatment-emergent adverse events: 81.44% vs 81.54%). However, compared with warfarin, rivaroxaban was associated with fewer intracranial bleeding events (0.77% vs 1.18%) but more gastrointestinal bleeding events (3.15% vs 2.16%).

The base case economic evaluation was conducted using statistically significant data from the safety-on-treatment population of the ROCKET AF trial. The manufacturer's estimated base case incremental cost-effectiveness ratio (ICER) is £18,883 per quality adjusted life year (QALY) gained.