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

STA REPORT

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

BMJ Technology Assessment Group

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

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Date completed: 20/10/2011

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 10/75

Declared competing interests of the authors:
None

Acknowledgements:
The ERG would like to thank Dr Derick Todd and Dr Helen Yarranton for providing clinical advice throughout the project. We would also like to acknowledge Professor Adrian Bagust for offering advice on the health economic evaluation.

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

This report should be referenced as follows:
Edwards SJ, Hamilton V, Nherera L, Trevor N, Barton S. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation: A Single Technology Appraisal. BMJ-TAG, London, 2011

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Samantha Barton	Critical appraisal of the manufacturer's submission; cross checking of manufacturer's search strategies; and critical appraisal of the clinical evidence

All authors read and commented on draft versions of the ERG report

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Abbreviations

AF	Atrial fibrillation
ALT	Alanine transaminase
ASA	Acetylsalicylic acid (aspirin)
BNF	British National Formulary
BMI	Body mass index
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEC	Clinical Events Committee
$CHADS_2$	Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled)
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular Disease, Age 65–74, and Sex category (female)
CI	Confidence Interval
CNS	Central nervous system
CrCl	Creatinine clearance
DIC	Deviance information criterion
ECG	Electrocardiogram
ERG	Evidence Review Group
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GRASP-AF	Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INR	International Normalised Ratio
ITT	Intention-to-treat
IVRS	Interactive voice response system
LYG	Life-years gained
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MI	Myocardial infarction
min	Minute
mL	Millilitre
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence

NMA	Network meta-analysis
OR	Odds ratio
PCT	Primary Care Trust
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PTS	Patient transport service
QALY	Quality adjusted life year
QOF	Quality and Outcomes Framework
RCT	Randomised controlled trial
ROCKET AF	**R**ivaroxaban **O**nce daily oral direct Factor Xa inhibition **C**ompared with vitamin **K** antagonism for prevention of stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation
RR	Relative risk
STA	Single Technology Appraisal
TIA	Transient ischaemic attack
TTR	Time in therapeutic range
UK	United Kingdom
USA	United States of America
VKA	Vitamin K antagonist
vs	versus
VTE	Venous thromboembolism

1 SUMMARY

1.1 Scope of the manufacturer's submission

The manufacturer of rivaroxaban (Xarelto®; Bayer HealthCare) submitted to the National Institute for Health and Clinical Excellence (NICE) clinical and economic evidence in support of the effectiveness of rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (AF).

The manufacturer's submission (MS) diverged from the final scope issued by NICE in the following areas:

- **Population**. The population specified in the scope was adults with non-valvular AF who are at moderate to high risk of stroke and non-central nervous system (CNS) systemic embolism. The manufacturer submitted evidence from a single trial (ROCKET AF), in which the population appears to comprise predominantly patients with a higher risk of stroke based on definitions of moderate and high risk of stroke in clinical guidelines for AF (NICE guideline CG36 and the European Society of Cardiology guidelines). The Evidence Review Group (ERG) considers that the eligibility criteria of ROCKET AF precluded enrolment of patients at low to moderate risk of stroke, that is, those having only one $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA [doubled]) risk factor or those aged ≥65 years old with no high-risk factors.

- **Comparators**. In the MS, the manufacturer does not cover comparisons of rivaroxaban versus dabigatran and rivaroxaban versus antiplatelet agents in the subgroup of people for whom warfarin treatment is unsuitable. However, the manufacturer does cover the comparison of rivaroxaban versus aspirin in people who are suitable for treatment with warfarin using data from a network meta-analysis (NMA). This comparison was not requested in the final scope issued by NICE.

- **Outcomes**. Health-related quality of life (HRQoL) was an outcome listed in the final scope issued by NICE. It is unclear whether the manufacturer collected HRQoL data in the ROCKET AF trial. However, the manufacturer did not present any ROCKET AF-based event- or treatment-related HRQoL data within the clinical evidence submitted. Data on transient ischaemic attack (TIA) were provided as part of the clarification process, but were not included in the manufacturer's economic evaluation.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness evidence for the MS is based on a single clinical trial, ROCKET AF, a Phase III non-inferiority study comparing the clinical efficacy and safety of rivaroxaban with warfarin for the prevention of stroke and non-CNS systemic embolism in at risk patients with non-valvular AF.

The trial data presented within the MS uses three population data sets for the analyses:

1) Per protocol: everyone who was randomised and who did not have a major pre-specified protocol deviation;
2) Safety-on-treatment: everyone who was randomised and who received at least one dose of study medication;
3) Intention-to-treat (ITT): everyone who was randomised regardless of treatment received.

The ERG notes that the length of recorded follow-up varied among the populations. The per protocol and safety-on-treatment population data included endpoints occurring while subjects were taking their study drug and for 2 days after permanent discontinuation of randomised study drug. The ITT population data set included all events, whether the event occurred while the patient was on or off their randomised study drug and was recorded until the end of study date.

The manufacturer uses data from the safety-on-treatment population of ROCKET AF as the main source of clinical effectiveness data within the MS, including within the primary NMA. All safety data provided by the manufacturer was limited to the safety-on-treatment population.

ROCKET AF showed rivaroxaban to be non-inferior to warfarin in preventing stroke and non-CNS systemic embolism in the per protocol, safety-on-treatment and ITT populations ($p < 0.001$ for all populations) at the pre-specified non-inferiority margin of 1.46. In the safety-on-treatment population, ROCKET AF also showed that rivaroxaban is superior to warfarin in preventing stroke and non-CNS systemic embolism ($p = 0.02$). However, superiority was not demonstrated when the ITT population was analysed ($p = 0.12$). Considering the individual components of the composite outcome, rivaroxaban was associated with [redacted], and a statistically significant reduction in non-CNS systemic embolism in the safety-on-treatment population ($p = 0.003$).

[redacted]

[redacted]

The overall safety profile of rivaroxaban and warfarin, from ROCKET AF, were similar (overall adverse event rate: 20.7% vs 20.3%). 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]

[redacted]

1.3 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]

The ERG also carried out an indirect comparison of rivaroxaban versus dabigatran 300 mg/day to assess treatment discontinuation rates. Results from the ERG's analysis suggest that dabigatran 300 mg/day is associated with significantly more treatment discontinuations compared with rivaroxaban or warfarin ($p < 0.05$). The ERG notes that, in the economic model, the manufacturer has assumed equivalent discontinuation rates between rivaroxaban and dabigatran when this may not be correct.

The ERG notes that the comparison of rivaroxaban versus antiplatelet agents in a warfarin unsuitable population was not covered in the MS. The ERG also notes that aspirin is included as a comparator in the manufacturer's NMA and that the data presented in the manufacturer's NMA include randomised controlled trials of warfarin versus aspirin. These data would suggest that the patient populations of these trials are likely to be suitable for therapy with warfarin. Consequently, the ERG does not consider that these data address the decision problem of rivaroxaban versus aspirin in a patient population unsuitable for warfarin.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer conducted a number of different analyses, based on data from the ROCKET AF clinical trial and the manufacturer's NMA.

1.4.1 ROCKET AF-based analysis

Clinical effectiveness data from the safety-on-treatment population of ROCKET AF was used to inform comparisons of rivaroxaban and warfarin in:

- A ROCKET AF-based population;
- A poorly controlled warfarin population;
- A warfarin-naïve population.

The efficacy and safety data observed in ROCKET AF were assumed to be applicable across all the above patient populations. The manufacturer argued that evidence from subgroup analysis of ROCKET AF supported the assumption of equivalent efficacy and safety. Therefore, only the costs associated with warfarin monitoring are varied in the ROCKET AF-based analyses.

The manufacturer conducted each ROCKET AF-based analysis using:

- Only statistically significant point estimates from ROCKET AF (non-significant relative risks [RRs] were assumed to be 1);
- All point estimates, from ROCKET AF, regardless of significance.

The manufacturer's base case analysis used statistically significant point estimates from the safety-on-treatment population of ROCKET AF and estimated an incremental cost-effectiveness ratio (ICER) of £18,833 per quality adjusted life year (QALY) gained. When all point estimates from ROCKET AF were used, the ICER fell to £8,732. In patients who were poorly controlled on warfarin, rivaroxaban dominated, regardless of whether or not significant only data were used to inform the analysis. The ICER obtained for patients who were naïve to warfarin therapy was £15,494 when using only significant data and £6,900 when all data were used.

1.4.2 NMA-based analysis

The manufacturer carried out an NMA that incorporated rivaroxaban, warfarin, dabigatran 150 mg (twice daily), dabigatran 110 mg (twice daily), aspirin and no treatment (placebo), as well as other comparators not specified in the NICE final scope. The manufacturer used the treatment effects estimated by the manufacturer's NMA to inform a fully incremental analysis of rivaroxaban, aspirin and no treatment (placebo) in a patient population with baseline characteristics from a UK observational survey. The incremental analysis revealed that no treatment (placebo) is dominated by aspirin and that rivaroxaban versus aspirin results in an ICER of £2,083. The manufacturer claimed that this analysis was conducted in the warfarin unsuitable population. However, the ERG notes that the trials used to inform this analysis included warfarin as a comparator, indicating that these patients were suitable for therapy with warfarin.

The comparisons between rivaroxaban and dabigatran 150 mg (twice daily) and dabigatran 110 mg (twice daily) were conducted using a cost minimisation approach. No differentiation was made between dabigatran 150 mg (twice daily) and dabigatran 110 mg (twice daily) as the unit cost of both treatments is the same; the manufacturer did not incorporate a sequence regimen in the original model (i.e., patients receive dabigatran 150 mg [twice daily] until they reach 80-years-old and then step down to 110 mg [twice daily]). The manufacturer argued that a cost minimisation approach was reasonable because of the absence of a significant difference in any outcome, estimated by the

manufacturer's NMA. The cost minimisation analysis resulted in an estimated additional cost of £913 with dabigatran. The manufacturer did not employ the treatment effects estimated by the manufacturer's NMA to inform a comparison between rivaroxaban and warfarin.

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 £55,106 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 the cost of anticoagulation monitoring was disaggregated by INR range, the ICERs substantially increased from £18,883 per QALY gained to £27,281 per QALY gained.

1.5.2 NMA-based analysis

The ERG conducted a fully incremental analysis of aspirin, no treatment (placebo), warfarin, rivaroxaban and dabigatran based on both the manufacturer's NMA and the ERG's NMA. The incremental analyses revealed that the relevant comparison was between dabigatran and rivaroxaban. The ERG used the point estimates obtained from the manufacturer's NMA and the ERG's NMA to obtain ICERs of £131,000 and £34,680, respectively. The ERG identified the following limitations present in the manufacturer's model:

- 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;
- The assumption of equivalent discontinuation rates;
- 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 exclusion of dyspepsia as an adverse event.

With the exception of the removal of risk suspension and the inclusion of TIA and dyspepsia in the model, the ERG was able to account for all the limitations listed above; adjustments resulted in the dominance of rivaroxaban for analysis based on the manufacturer's NMA and an ICER of £12,701 for the analysis based on the ERG's NMA, respectively. The ERG notes that the model is highly sensitive to the discontinuation rates used and a small change has the power to reverse the direction of benefit. Probabilistic sensitivity analysis conducted on the manufacturer's model following the incorporation of the treatment effects of the ERG's NMA and the adjustments recommended by the ERG revealed that dabigatran was dominant 45% of the time and dominated 35% of the time.

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

1.6.1 Strengths

The ROCKET AF trial is a large, well conducted trial. The manufacturer conducted an NMA to provide indirect estimates of the effectiveness of rivaroxaban in comparison with dabigatran, thus providing data for this key comparator listed in the final scope issued by NICE.

1.6.2 Weaknesses

The NMA conducted by the manufacturer to provide data for the clinical effectiveness and safety of dabigatran, aspirin and placebo for use in the economic model had high levels of heterogeneity, as well as considerable uncertainty around the point estimates. The manufacturer did not discuss these issues in the MS. The ERG conducted an exploratory NMA using a more restricted network of treatments. The ERG's NMA had much lower levels of heterogeneity and was associated with less uncertainty around the point estimates.

The manufacturer did not present any ROCKET AF-based event- or treatment-related HRQoL data within the clinical evidence submitted, although the ERG acknowledges that this may not have been collected. The manufacturer thus does not present any HRQoL data for rivaroxaban in the clinical effectiveness section of the MS. The HRQoL data utilised in the manufacturer's economic model is derived from published sources assessing the QoL of the different health states rather than treatment-dependent utilities.

The manufacturer has no direct head-to-head data for rivaroxaban versus dabigatran and so the ability to draw conclusions for this comparison is limited by the uncertainty around the indirect effect estimates generated from the NMA.

The economic model presented by the manufacturer has a number of potential flaws, including a lack of adjustment of bleeding risk or utility by age and an assumption of equivalent discontinuation rates for treatments for which there is an absence of any direct head-to-head data. Implementing treatment discontinuation rates from the ERG's NMA in the economic model has a profound impact on the overall ICERs generated.

1.6.3 Areas of uncertainty

The ROCKET AF population used in the analyses presented in the MS and the economic model are the safety-on-treatment population, although the ERG believes that the ITT population would better reflect the treatment effectiveness results that would be seen in clinical practice. However, the ERG acknowledges 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. The ERG is unsure of what impact using the ROCKET AF ITT population would have on the ICERs.

The manufacturer's base case model is driven by the cost of anticoagulation monitoring rather than the differential effectiveness of the comparators and thus any change in monitoring costs has substantial impact on the base case ICER. In addition, any change in monitoring cost directly affects

the ICERs for well controlled and poorly controlled patients on warfarin. Patients poorly controlled require more monitoring visits and those patients whom are well controlled require fewer visits.

1.7 Key issues

In summary, the ERG believes the key issues to be as follow:

- The reliability of the results of the cost effectiveness of warfarin in comparison with rivaroxaban is limited by the uncertainty around the frequency of INR monitoring in warfarin-treated patients in the economic model, which is driven by cost of anticoagulation monitoring rather than clinical effectiveness;

- The absence of direct comparative data from a randomised controlled trial comparing rivaroxaban with dabigatran etexilate in patients suitable for anticoagulation;

- The safety and clinical benefit of rivaroxaban compared with dabigatran etexilate and aspirin in patients who are not suitable for warfarin has not been addressed in the MS;

- Lack of QoL data for people taking rivaroxaban;

- The manufacturer's assumption that treatment discontinuation rates are the same between treatments in the absence of any direct evidence to suggest otherwise has a substantial impact on the ICERs;

- The data for rivaroxaban efficacy in people at moderate risk of stroke is limited.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

In the Context section of the manufacturer's submission (MS; Section 2),[1] the manufacturer provides details on atrial fibrillation (AF) and the associated risk factors for stroke, along with an overview of the key issues related to these health conditions.

Summaries of the epidemiology of AF and stroke in patients with AF data presented in the MS are provided in Box 1 and Box 2, respectively. All information is taken directly from the MS.

Box 1. Epidemiology of atrial fibrillation

AF is the most common sustained cardiac arrhythmia (1), estimated to affect 1–2% of the population (2).

The prevalence of AF increases rapidly with age, and men are more often affected than women (3). Epidemiological studies conducted in the UK have shown AF to be fairly uncommon in people aged under 50 years, but to be found in ~1% of people aged 55-64 years, increasing to 7-13% at 85+ years(3–7).

Data collected as part of the Quality and Outcomes Framework (QOF) for 2009/2010, indicate a prevalence of atrial fibrillation of 1.4% in England (8) and 1.69% in Wales (9).

Box 2. Epidemiology of stroke in patients with atrial fibrillation

AF confers a 5-fold increase in the risk of stroke, and one in five of all strokes is attributed to this arrhythmia (2). Not only is AF a major risk factor for stroke, but when strokes occur in association with AF, the patients suffer increased levels of mortality, morbidity, disability and longer hospital stays compared with stroke patients without AF(1;2).

The risk of death from AF-related stroke is doubled and the cost of care is increased 1.5-fold (2).

The underlying risk of stroke is dependent on the presence or absence of a number of different risk factors.

The risk of stroke in patients with AF varies ranging from an annual risk of 1% in patients aged over 65 years old with no risk factors, to over 12% per year in patients who have a history of prior stroke, transient ischaemic attack or thromboembolism(1).

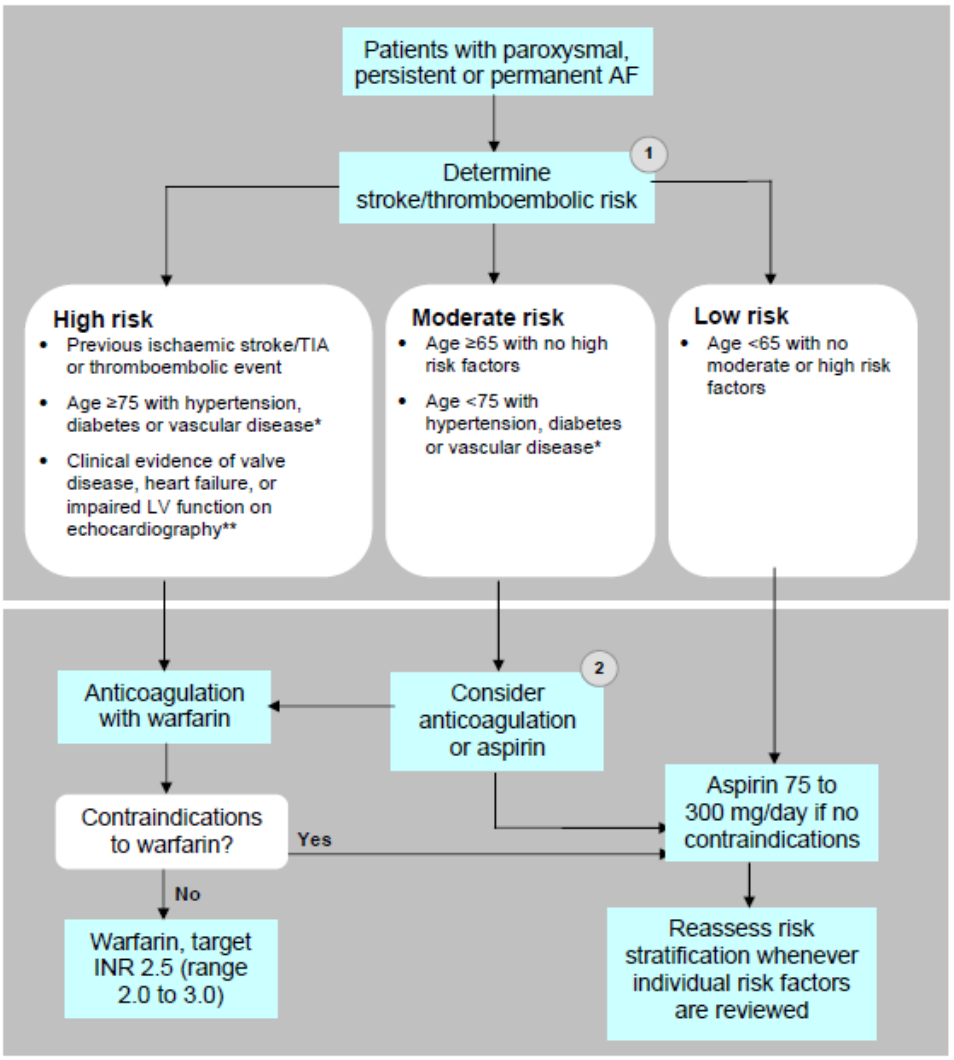
The Evidence Review Group (ERG) and the ERG's clinical expert advisors believe that the manufacturer's description of the underlying health problem is accurate.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer provides an overview of the current National Institute for Health and Clinical Excellence (NICE) guideline (CG36),[2] National Health Service (NHS) Improvement programme

Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation (GRASP-AF)[3] and European stroke risk assessment guidelines[4] (Figure 1 and Box 3), along with a summary of the relevant NICE technology appraisals[5,6] (Table 1).

Figure 1. NICE CG36[2] stroke risk stratification algorithm



1. Note that risk factors are not mutually exclusive, and are additive to each other in producing a composite risk. Since the incidence of stroke and thromboembolic events in patients with thyrotoxicosis appears similar to that in patients with other aetiologies of AF, antithrombotic treatments should be chosen based on the presence of validated stroke risk factors.
2. Owing to lack of sufficient clear-cut evidence, treatment may be decided on an individual basis, and the physician must balance the risk and benefits of warfarin versus aspirin. As stroke risk factors are cumulative, warfarin may, for example, be used in the presence of two or more moderate stroke risk factors. Referral and echocardiography may help in cases of uncertainty.

*Coronary artery disease or peripheral artery disease.

** An echocardiogram is not needed for routine assessment, but refines clinical risk stratification in the case of moderate or severe LV dysfunction and valve disease.

Box 3. Manufacturer's overview of stroke risk assessment

Guidelines recommend that patients with AF should have their underlying level of stroke risk assessed to determine the choice of thromboprophylaxis.

There are a number of different tools for assessing stroke risk. NICE CG36 (1) from 2006 uses the algorithm in Figure 1 (above), although it should be noted that this guideline may be updated, with the

review decision due in August 2011.

$CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] risk index (15) classification system is used as part of the NHS Improvement Programme "GRASP-AF" tool (16). The $CHADS_2$ risk index is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age >75 years, a history of hypertension, diabetes, or recent cardiac failure.

More recently, European guidelines(2) were issued which advocate a different method of assessing stroke risk, CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]. Thus, this acronym extends the $CHADS_2$ scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate.

The European guidelines recommend use of an anticoagulant with one or more of these risk factors.

The European guidelines advocate a risk factor-based approach for stroke risk assessment rather than grouping patients into "low, moderate and high" risk cohorts, given the poor predictive value of such categorisation and the recognition that risk is a continuum(2).

The manufacturer highlights the new CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled], Vascular Disease, Age 65–74, and Sex category [female]) score recommended in the European guidelines for assessment of stroke risk.[4] The manufacturer also highlights that the NICE guideline CG36,[2] at the time of writing of the MS, was under review for potential update, and the ERG notes that NICE has now taken the decision to update CG36. The ERG thinks it important to highlight that in the revised CG36[2] the CHA_2DS_2-VASc may supersede $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA [doubled]) score as the recommended stroke risk algorithm. However, the ERG acknowledges that at the time of enrolment for the key trial cited in support of the MS, (ROCKET AF)[7] the $CHADS_2$ score was one of the most widely used stroke risk algorithms in the United Kingdom (UK).

Table 1. Relevant NICE guidance and technology appraisals

NICE guideline/guidance number	Title	Date of publication
CG36[2]	The management of atrial fibrillation	June 2006, an update of this guideline was agreed in August 2011 and it is currently in the process of being scheduled into the NICE work programme
TA197[5]	Dronedarone for the treatment of non-permanent atrial fibrillation	August 2010
Dabigatran etexilate:[6] appraisal in development	Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation	Appraisal in progress; expected date of publication December 2011

The manufacturer lists all the relevant NICE clinical guidelines and technology appraisals, and the ERG notes that the Single Technology Appraisal (STA) for dabigatran etexilate, which is one of the comparators for rivaroxaban in this STA, is expected to be published in December 2011.[6]

The ERG agrees with the manufacturer's description of warfarin as the current most frequently used oral anticoagulant in the UK, and that it is managed in a variety of primary and secondary care settings, with the exact setting in each area being dependent on local commissioning arrangements.

The manufacturer does not explicitly describe the proposed place of rivaroxaban in the treatment pathway of AF. However, the manufacturer states that the anticipated European licence will be for "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack" and that this equates to a $CHADS_2$ score of ≥1."

The manufacturer presents an estimate of the number of patients who could be eligible for treatment with rivaroxaban in England and Wales, based on the anticipated licence for adults with non-valvular AF and a $CHADS_2$ score ≥1. However, the ERG was unable to access all of the sources cited by the manufacturer and thus the ERG was unable to verify the manufacturer's estimate. The ERG also notes that the manufacturer quotes a different number in the text (662,747) compared with that provided in the MS (669,003 [Table 8; MS; pg 20]). The ERG requested clarification on this and the manufacturer confirmed that the correct estimate of people eligible for treatment with rivaroxaban is 669,003.

The ERG considers it important to note that the manufacturer's estimate of the eligible population may be slightly higher than the true number of eligible patients as the estimate does not account for people in whom the manufacturer states rivaroxaban would be contraindicated, such as those with certain types of hepatic disease.

The ERG is also concerned that the manufacturer is recommending rivaroxaban for people with a $CHADS_2$ score of ≥1 when only one person with a $CHADS_2$ score of 1 was treated with rivaroxaban in the manufacturer's key trial (ROCKET AF).[7] ROCKET AF mainly comprised people with a $CHADS_2$ score ≥3 (87% of the total intention-to-treat [ITT] population), and thus represents a generally high-risk population. The ERG considers that the manufacturer presents limited evidence of the efficacy of rivaroxaban in people at only moderate risk of stroke, that is, those with a $CHADS_2$ score of 1 or 2.

In summary, the ERG considers that the manufacturer's descriptions of the underlying health problem and current service provision are generally accurate, although the ERG has concerns regarding the manufacturer's definition and estimate of the eligible population.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

In the manufacturer's submission (MS), the manufacturer presents the decision problem issued by the National Institute for Health and Clinical Excellence (NICE)[8] and outlines how they have addressed this, along with their rationale for any deviations from the final scope issued by NICE (summarised in Table 2).

Table 2. Summary of the decision problem addressed in the manufacturer's submission

	Final scope issued by NICE	Decision problem addressed in the MS	Manufacturers rationale if different from the scope
Population	Adults with non-valvular AF at moderate to high risk of stroke and non-CNS systemic embolism	Adults with non-valvular AF with one or more risk factors for stroke and systemic embolism, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack	In line with European guidelines(2), stroke risk is a continuum and a risk factor based approach is advocated for stroke risk assessment rather than using "low", "moderate" and "high" risk classifications
Intervention	Rivaroxaban	Rivaroxaban	–
Comparator(s)	Warfarin Dabigatran (subject to ongoing NICE technology appraisal) In people for whom warfarin is unsuitable: Antiplatelet agents; Dabigatran.	Warfarin Dabigatran Aspirin No treatment	In clinical practice, some patients eligible for warfarin but not prescribed it are prescribed aspirin or no treatment. We have specified aspirin as this is the most commonly prescribed antiplatelet in this indication
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	
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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 PSS 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 PSS	

Subgroups to be considered	If evidence allows, consider: people who have not been previously treated with warfarin	If evidence allows, consider: people who have not been previously treated with warfarin	
Special considerations, including issues related to equity or equality	Consideration should be given to the potential advantage of rivaroxaban in terms for its lower requirement for therapeutic monitoring and its fewer drugs interactions compared with warfarin.	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.	
Abbreviations used in table: AF, atrial fibrillation; CNS, central nervous system; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PSS, Personal Social Services.			

3.1 Population

The key trial presented in the MS is the ROCKET AF trial,[7] which included adults with non-valvular persistent or paroxysmal atrial fibrillation (AF) at risk for future stroke.

The ROCKET AF trial definition for 'at risk for future stroke' was people with:

- a history of stroke or transient ischaemic attack (TIA) or systemic embolism; or
- ≥2 of the following risk factors (i.e., $CHADS_2$ [Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA {doubled}] ≥2):
    - congestive heart failure;
    - hypertension;
    - age ≥75 years;
    - diabetes mellitus.

The number of patients included in ROCKET AF without a prior stroke, TIA or non-central nervous system (CNS) systemic embolism and only two risk factors was limited to approximately 10% of the total number of people enrolled in each region. The remaining 90% of the study population was required to have a minimum of three risk factors, if they had not had a previous stroke, TIA or non-CNS systemic embolism. The reason for this requirement is not clear in the MS. The limitation on the recruitment of people having only two risk factors for stroke resulted in the total ROCKET AF population comprising less than 14% of people with a $CHADS_2$ score of 2. The majority of the ROCKET AF population had a $CHADS_2$ score of 3 (44% of total trial population) or 4 (29% of trial population).

The final scope issued by NICE[8] for this single technology appraisal (STA) requested a population at moderate to high risk of stroke. The NICE clinical guideline for AF (CG36[2]) defines moderate risk of stroke as:

- people ≥65 years old with no high risk factors;
- people ≤75 years old with hypertension, diabetes, peripheral artery disease or coronary artery disease.

And high risk of stroke as:

- previous ischaemic stroke, TIA or thromboembolic event;
- 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[4] 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[2] and the ESC guidelines,[4] 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.[8]

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). The anticipated licence also states that rivaroxaban should be used with caution in people with severe renal impairment.

3.3 Comparators

The manufacturer's key trial ROCKET AF is a double-blind RCT designed to demonstrate non-inferiority between rivaroxaban and warfarin for prevention of stroke and systemic embolism, and thus warfarin is the main comparator in the MS. This decision is justified by unreferenced statements that warfarin is the oral anticoagulant most commonly used in UK clinical practice. Clinical advisors to the ERG agree with this statement.

The ERG notes that the manufacturer has combined data on warfarin and other vitamin K antagonists (VKAs) under the label of warfarin in the network meta-analysis (NMA) presented in the MS. Clinical advisors to the ERG suggest that it is acceptable to assume a class effect (i.e. similar safety and efficacy profiles) for VKAs.

Dabigatran etexilate, another new oral anticoagulant, is currently undergoing appraisal in the NICE STA programme[6] for the prevention of stroke and systemic embolism in people with AF, and thus is an important comparator for rivaroxaban in this STA. Dabigatran etexilate was listed in the decision problem issued by NICE[8] as a comparator, and has been included by the manufacturer within a NMA in the MS. The ERG believes this to be the most suitable method for comparison due to the lack of direct head-to-head trial data comparing rivaroxaban versus dabigatran.

The ERG also notes that the manufacturer has used an NMA to provide data from indirect analyses to enable comparisons between rivaroxaban and aspirin, and rivaroxaban and placebo within the submission, although this was not a requirement of the final scope issued by NICE.[8] The final scope issued by NICE[8] did however request the comparisons of rivaroxaban versus dabigatran and rivaroxaban versus antiplatelet agents in people unsuitable for treatment with warfarin although these comparisons were not addressed in the MS. The ERG also notes that this population of people unsuitable for treatment with warfarin was not covered by the key trial in the MS (ROCKET AF).[7]

The manufacturer states that there is significant under-treatment in warfarin-eligible patients and that patients not treated with warfarin may be on aspirin or left untreated. This argument is used to justify their inclusion of aspirin and "no treatment" in the NMA and economic model. The ERG considers it important to highlight that these patients were not necessarily unsuitable for treatment with warfarin.

The NMA presented within the MS also includes additional comparators that were not listed in the NICE final scope,[8] but the manufacturer does not discuss these comparators in the MS. The ERG believes that the omission of these additional comparators from the submission is appropriate (further detail given in Section 4.4.1).

3.4 Outcomes

The ERG notes that the manufacturer does not present data in the MS for the outcomes of TIA and health-related quality of life (HRQoL) from the ROCKET AF trial, both of which were listed as outcomes of interest in the final scope issued by NICE.[8] However, the ERG notes that the manufacturer has included data on TIAs from ROCKET AF in the NMA, and in response to the ERGs clarification questions.

The ERGs clinical expert advisors suggest that HRQoL is an important outcome that should ideally have been measured and presented within the MS. However, the ERG recognises the potential difficulty in interpreting HRQoL data from a double-blind RCT with sham International Normalised Ratio (INR) monitoring, such as ROCKET AF, if the principal factor affecting HRQoL is the impact of INR monitoring. The ERG is aware that HRQoL was assessed in a clinical trial of dabigatran etexilate (RE-LY[9]), although the ERG also acknowledges that RE-LY was an open label trial with no sham INR testing in the dabigatran etexilate group. The ERG does not have access to data on HRQoL from RE-LY and so is unable to comment further on the issue.

The manufacturer presents data for the other outcomes listed in the NICE final scope,[8] along with some additional outcome data, including several composite outcomes, which will be discussed in further detail in the clinical effectiveness section of this report (Section 4).

The ERG notes that the primary outcome of ROCKET AF was to prove non-inferiority between rivaroxaban and warfarin. Following the demonstration of non-inferiority, ROCKET AF was pre-specified to assess for superiority in a series of outcomes [redacted].

The primary efficacy outcome of the ROCKET AF trial was the composite of stroke and non-CNS systemic embolism, and the primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding. The manufacturer also provides data for the individual outcomes from ROCKET AF, although within the NMA they limit adverse effects to bleeding outcomes and do not present results for rivaroxaban compared with any other treatments for the outcome of all adverse effects.

3.5 Time frame

According to the MS, ROCKET AF study enrolment took place between December 2006 and June 2009, and the end of the treatment period (site notification) was determined by the time required to accrue approximately 405 adjudicated primary efficacy endpoint events in the per protocol population (on-treatment). This resulted in differences in the time on study drug between patients based on their date of enrolment.

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 an open-label extension study 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 extension study 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. However, the ERG has concerns regarding the power of the study to demonstrate superiority using the safety-on-treatment and ITT populations. The ERG is thus unable to comment on the suitability of the follow-up period in the ROCKET AF study. This issue is discussed further in Section 4.

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 comment further on this potential benefit given the time constraint in the production of the ERG

report.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

The Evidence Review Group (ERG) considers it important to mention that the manufacturer's submission (MS) consisted of the main submission document[1] (331 pages), which was based on the template issued by the National Institute for Health and Clinical Excellence (NICE),[10] and three additional documents comprising a systematic review protocol[11] (20 pages), systematic review report[12] (201 pages) and a network meta-analysis (NMA) report[12] (114 pages). The three additional documents each contribute to the MS, and within the MS the reader is referenced directly to each for the information required in some sections of the MS.

In the MS, the manufacturer presents a systematic review of studies directly involving rivaroxaban, and a separate NMA including a broader selection of studies. These reviews are discussed separately in the appropriate sections of the ERG report.

4.1.1 Description and critique of manufacturer's search strategy

The manufacturer describes the literature search carried out up to 2nd February 2011. The search involved electronic database searching of Medline, Medline In-Process, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL) and the manufacturer's (Bayer) in-house database, as well as reviewing the reference lists of relevant Cochrane reviews. The search used terms for atrial fibrillation (AF) and the drug names of interest. There were no language restrictions in the manufacturer's search strategy. However, the ERG notes that the EMBASE search was limited to 1988 to date of search rather than the database date of inception (1980) to date of search. The Medline and CENTRAL searches appear to have no date restrictions.

The ERG notes that the manufacturer's searching of reference lists was limited to searching those of relevant Cochrane reviews and one additional relevant review (Hart *et al.*[12]). The additional searches for unpublished literature were limited to the manufacturer's in-house database.

The ERG validated the manufacturer's search in EMBASE, Medline and Medline In-Process, and the Cochrane library (23/09/2011), and generated a comparable number of studies to that generated by the manufacturer's search.

In general, the ERG considers that the manufacturer's search strategies (i.e. Medline, EMBASE and CENTRAL) and search terms were appropriate, and the ERG is not aware of any relevant studies that have been missed by the manufacturer's search.

4.1.2 Description and critique of inclusion/exclusion criteria used in the manufacturer's study selection

The manufacturer provides a table (Table 3) listing the inclusion/exclusion criteria applied in their search for studies that include rivaroxaban as comparator.

Table 3. Eligibility criteria used in the search strategies in the manufacturer's submission

Inclusion/exclusion criteria	Clinical effectiveness
Inclusion criteria	**Population:** Chronic non-valvular atrial fibrillation documented by ECG. **Interventions:** Rivaroxaban compared with antithrombotic therapies (for ≥12 weeks) including VKAs, antiplatelet agents, idraparinux, ximelagatran, dabigatran or apixaban; Comparisons of different dosages and intensities of the same drug allowed, as were placebo- or active-controlled studies. **Outcomes:** All strokes (ischaemic or haemorrhagic); intracranial haemorrhage; major extracranial haemorrhage (i.e. all those that were life threatening or led to hospitalisation, blood transfusion or surgery); all-cause mortality; transient ischaemic attack; systemic embolism including details of severity and location; myocardial infarction; composite endpoint (all cause of stroke and non-CNS systemic embolism); minor bleed; cardiovascular mortality as defined by authors; all causes of hospitalisation; cardiovascular related hospitalisations; gastrointestinal bleed; gastrointestinal symptoms/discomfort (e.g. dyspepsia). **Study design:** Randomised controlled trials. **Language restrictions:** none.
Exclusion criteria	**Population:** patients with prosthetic cardiac valves. **Interventions:** cardioversion for recent onset AF.
Abbreviations used in table: AF, atrial fibrillation; CNS, central nervous system; ECG, electrocardiogram; VKA, vitamin K antagonist.	

Studies included were also limited to those published in full, and so any studies available in only abstract format were excluded from the review. The ERG is unable to comment on the impact of this limitation on the overall results as the number of studies reported in abstract format and subsequently excluded due to the absence of a full text publication is not indicated in the PRISMA diagram presented in the MS. However, it is a potential concern that the manufacturer has limited their search to published data and thus excluded an unknown quantity of 'grey' literature.

The ERG agrees with the manufacturer's decision not to include studies conducted in patients with prosthetic heart valves as these patients usually require anticoagulation with warfarin at a different therapeutic International Normalised Ratio (INR) level to people with non-valvular AF.

The ERG also acknowledges that two reviewers independently screened the studies identified from the search for inclusion in the review, thus reducing the risk of potentially relevant studies being missed or for selection bias to occur.

The ERG also considers that the manufacturer's decision to limit the study inclusion criteria to RCTs is appropriate for an evaluation of clinical efficacy. The ERG is not aware of any non-randomised

studies in people taking rivaroxaban that could have had an impact on the overall results of the clinical effectiveness and safety analyses within the MS.

In general, the ERG considers that the inclusion/exclusion criteria were appropriate for the review.

4.1.3 Details of studies identified by the manufacturer

The manufacturer presents an appropriate PRISMA diagram in the MS to depict the inclusion/exclusion of studies throughout the review process.

In total, the manufacturer identified two RCTs in five publications,[14–18] which were relevant to the review (details given in Table 4).

Table 4. Included/excluded studies

Trial number (acronym)	Intervention	Comparator	Population	Primary study reference used in the MS	Included/ Excluded
ROCKET AF	**Rivaroxaban** 20 mg once daily (subjects with moderate renal impairment[†] 15 mg once daily)	Dose-adjusted **warfarin** based on target INR values target INR of 2.5 (range 2.0 to 3.0, inclusive)	Non-valvular atrial fibrillation with a history of stroke/TIA or systemic embolism or ≥2 additional independent risk factors for stroke	Patel *et al*.[7,13]	Included
NCT00494871 J ROCKET-AF18	**Rivaroxaban** 15 mg once daily	Dose-adjusted **warfarin** based on target INR values	Japanese patients with chronic non-valvular atrial fibrillation at risk of stroke and non-CNS systemic embolism	Hori *et al*.[18]	Excluded due to dose of rivaroxaban, clinical practice and population used not considered generalisable to the UK

[†] Defined as calculated CrCl between 30 and 49mL/min, inclusive.

Abbreviations used in the table: CNS, central nervous system; CrCl, creatinine clearance; INR, International Normalised Ratio; mL/min, millilitre per minute; MS, manufacturer's submission; TIA, transient ischaemic attack; UK, United Kingdom.

The key trial in the MS is ROCKET AF. Four publications relating to ROCKET AF were identified by the manufacturer's search: a study design report[14]; ROCKET AF protocol[15]; clinical study report[16]; and an abstract presented at American Heart Association meeting[17]. In addition to the four publications relating to ROCKET AF identified during the literature search, the manufacturer also appropriately includes data from an additional report[7] and its supplementary appendix,[13] which were published after the literature search date for the systematic review.

The second RCT identified by the manufacturer, J ROCKET-AF,[18] is a phase III supportive safety study in a Japanese population. The J ROCKET-AF study used a lower dose of rivaroxaban than ROCKET AF, and the manufacturer states that clinical practice in Japan is different to that in the United Kingdom (UK). In particular, the manufacturer highlights that a lower target INR threshold is typically used in Japan for people aged ≥70 years (INR 1.6–2.6) compared with the target INR typically used in the rest of the world (INR 2.0–3.0). Due to differences between ROCKET AF and J ROCKET-AF in terms of included population and study design, the manufacturer decided not to include data from J ROCKET-AF in the MS. The ERG requested further clarification on the differences between the J ROCKET-AF and ROCKET AF studies at the clarification stage and, after assessment of the manufacturer's response, the ERG agrees with the manufacturer's decision to exclude J ROCKET-AF from the MS. The ERG also notes that the results of the primary safety and primary efficacy endpoint of J ROCKET-AF are broadly similar to those of ROCKET AF.

4.1.4 Details of relevant studies that were not included in the submission

The ERG is not aware of any relevant studies that have been omitted from the MS.

4.2 Summary and critique of submitted clinical effectiveness evidence

ROCKET AF[7] is the only trial used by the manufacturer to provide direct clinical effectiveness evidence on rivaroxaban within the MS. It was an international, multicentre, randomised, double-blind phase III non-inferiority study comparing the clinical efficacy and safety of rivaroxaban with warfarin (vitamin K antagonist; VKA) for the prevention of stroke and non-central nervous system (CNS) systemic embolism in at risk patients with non-valvular AF.

4.2.1 Description and critique of manufacturer's approach to validity assessment

The manufacturer provides a table detailing their critique of the ROCKET AF trial (Table 5).

Table 5. Manufacturer's validity assessment of ROCKET AF

	ROCKET AF
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No

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 (96 people) that was excluded from all the 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;

• Risk for future stroke, including the history of stroke/TIA or systemic embolism **OR** ≥2 of the following ($CHADS_2$ ≥2): ▪ Congestive heart failure or left ventricular ejection fraction ≤35%; ▪ Hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg); ▪ Age ≥75 years; ▪ Diabetes mellitus. *The number of subjects without a prior stroke, TIA or non-CNS systemic embolism and only 2 risk factors was limited by the IVRS to approximately 10% by region of the total number of subjects enrolled, after which subjects were required to have a minimum of 3 risk factors if without a prior stroke, TIA, or non-CNS systemic embolism.*	• Haemodynamically significant mitral stenosis; • Active internal bleeding; • History of, or condition associated with, increased bleeding risk, including: ▪ Major surgical procedure or trauma within 30 days before randomisation; ▪ Clinically significant gastrointestinal bleeding within 6 months before randomisation; ▪ History of intracranial, intraocular, spinal, or atraumatic intraarticular bleeding; ▪ Chronic haemorrhagic disorder; ▪ Known intracranial neoplasm, arteriovenous malformation, or aneurysm; ▪ Planned invasive procedure with potential for uncontrolled bleeding, including major surgery. • Any stroke within 14 days before randomisation; • TIA within 3 days before randomisation; • Indication for anticoagulant therapy for a condition other than AF (eg, VTE) Treatment with: ▪ ASA >100mg daily; ▪ ASA in combination with thienopyridines within 5 days before randomisation; ▪ Intravenous antiplatelets within 5 days before randomisation; ▪ Fibrinolytics within 10 days before randomisation; ▪ Anticipated need for long-term treatment with a nonsteroidal antiinflammatory drug; ▪ Systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 days before randomisation, or planned treatment during the period of the study; ▪ Treatment with a strong inducer of cytochrome P450 3A4, such as rifampicin, phenytoin, phenobarbital, or carbamazepine, within 4 days before randomisation, or planned treatment during the period of the study; ▪ Anaemia (haemoglobin level <10 g/dL) at the screening visit; ▪ Pregnancy or breastfeeding; ▪ Known HIV infection at time of screening; ▪ Calculated creatinine clearance <30 mL/min at the screening visit; • Known significant liver disease (eg, acute clinical hepatitis, chronic active hepatitis, cirrhosis) or alanine aminotransferase >3× the upper limit of normal.
Abbreviations used in table: AF, atrial fibrillation; ASA, acetylsalicylic acid (aspirin); $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); CNS, central nervous system; HIV, Human Immunodeficiency Virus; IVRS, interactive voice response system; TIA, transient ischaemic attack; VTE, venous thromboembolism.	

Table 7. Baseline characteristics of ROCKET AF ITT population

Characteristic		Rivaroxaban (n = 7,131)	Warfarin (n = 7,133)	Total (n = 14,264)
Sex, n (%)	Female	2,830 (39.69)	2,830 (39.67)	5,660 (39.68)
	Male	4,301 (60.31)	4,303 (60.33)	8,604 (60.32)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Age in years	Median (interquartile range)	73 (65 to 78)	73 (65 to 78)	73 (65 to 78)
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline BMI (kg/m²)	Median (interquartile range)	28.3 (25.2 to 32.1)	28.1 (25.1 to 31.8)	28.2 (25.1 to 32.0)
Clinical presentation, type of AF, n (%)	Persistent	5,786 (81.14)	5,762 (80.78)	11,548 (80.96)
	Paroxysmal	1,245 (17.46)	1,269 (17.79)	2,514 (17.62)
	Newly diagnosed/new onset	100 (1.40)	102 (1.43)	202 (1.42)
Prior VKA use, overall, n (%)		4,443 (62.31)	4,461 (62.54)	8,904 (62.42)
Prior chronic aspirin use, n (%)		2,586 (36.26)	2,619 (36.72)	5,205 (36.49)
Clinical risk factors				
$CHADS_2$, mean (SD)		3.48 (±0.94)	3.46 (±0.95)	3.47 (±0.94)
	1, n (%)	1 (0.01)	2 (0.03)	3 (0.02)
	2, n (%)	925 (12.97)	934 (13.09)	1,859 (13.03)
	3, n (%)	3,058 (42.88)	3,158 (44.27)	6,216 (43.58)
	4, n (%)	2,092 (29.34)	1,999 (28.02)	4,091 (28.68)
	5, n (%)	932 (13.07)	881 (12.35)	1,813 (12.71)
	6, n (%)‡	123 (1.72)	159 (2.23)	282 (1.98)
Congestive heart failure, n (%)		4,467 (62.65)	4,441 (62.27)	8,908 (62.46)
Diabetes mellitus, n (%)		2,878 (40.36)	2,817 (39.49)	5,695 (39.93)
Hypertension, n (%)		6,436 (90.25)	6,474 (90.76)	12,910 (90.51)
Prior stroke/TIA/non-CNS systemic embolism, n (%)		3,916 (54.92)	3,895 (54.61)	7,811 (54.76)
Prior myocardial infarction, n (%)‡		1,182 (16.58)	1,286 (18.03)	2,468 (17.30)
Creatinine clearance (mL/min)	Median (interquartile range)	67 (52 to 88)	67 (52 to 86)	67 (52 to 87)
Peripheral vascular		401 (5.62)	438 (6.14)	839 (5.88)

disease, n (%)				
Chronic obstructive pulmonary disease, n (%)		754 (10.57)	743 (10.42)	1,497 (10.49)
Medications prior to start of study treatment, n (%)*	Beta-blockers	4,631 (65.12)	4,686 (65.77)	9,317 (65.45)
	Diuretics	4,289 (60.32)	4,248 (59.62)	8,537 (59.97)
	Angiotensin-converting enzyme inhibitors	3,915 (55.06)	3,845 (53.96)	7,760 (54.51)
	Statins	3,055 (42.96)	3,077 (43.19)	6,132 (43.07)
	Digitalis glycosides	2,758 (38.78)	2,768 (38.85)	5,526 (38.82)
	Aspirin	2,726 (38.33)	2,759 (38.72)	5,485 (38.53)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

*Table based on ITT population, except for medication section where rates are based on the safety-on-treatment population with n = 7,111 in the rivaroxaban group and n = 7,125 in the warfarin group.

‡ $p < 0.05$ for the between-group comparison.

Abbreviations used in table: BMI, body mass index; $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); CNS, central nervous system; ITT, intention-to-treat; mL/min, millilitre per minute; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Overall, 54.8% of patients had a history of stroke, TIA, or non-CNS systemic embolism, with prior strokes occurring in [redacted] of the study population. In addition, 62.4% of patients had received prior therapy with VKA.

The mean $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA [doubled]) score was 3.48 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.

[redacted] had moderate renal impairment, which was defined as a baseline creatinine clearance (CrCl) of 30 to 49 mL/min (millilitre per minute), and thus were eligible to receive the lower dose of rivaroxaban (15 mg) or the lower rivaroxaban placebo dose. In the ITT population for the rivaroxaban group, [redacted]

The ERG notes that the baseline characteristics for the ITT population in ROCKET AF generally appear well balanced between the two trial groups, although the ERG note that significantly fewer

people in the rivaroxaban group have had a previous myocardial infarction (MI) compared with the warfarin group (1,182 people in rivaroxaban group versus 1,286 people in warfarin group; $p < 0.05$).

The ERG considers it important to note that the population in ROCKET AF is at higher risk of stroke than the population defined in the final scope issued by NICE.[8] The final scope issued by NICE includes patients with a $CHADS_2$ score of 1 or more whereas the ROCKET AF baseline population (ITT) included only 3 patients (0.02% of total population) with a $CHADS_2$ of 1 (1 person in rivaroxaban group, 2 in warfarin group). The majority of patients in ROCKET AF had a baseline $CHADS_2$ score of 3 (44% of ROCKET AF baseline ITT population) or 4 (29% of ROCKET AF baseline ITT population).

[redacted] A clinical advisor to the ERG has suggested that the $CHADS_2$ scores of the population in ROCKET AF may reflect the UK population that would currently be most likely to be treated with warfarin and thus would also represent the population who would potentially be treated with rivaroxaban.

4.2.3 ROCKET AF intervention and comparator(s)

The rivaroxaban group received 20 mg rivaroxaban once daily plus matching oral warfarin placebo titrated to a sham INR of 2.5. Patients with moderate renal impairment (defined as CrCl 30–49 mL/min) at time of randomisation received 15 mg rivaroxaban once daily plus the standard matching oral warfarin placebo.

The warfarin group received oral warfarin once daily (tablet strengths used in the study were 1 mg, 2.5 mg and 5 mg), titrated to a target INR of 2.5 (range 2.0–3.0, inclusive) plus matching oral rivaroxaban placebo once daily. Patients with moderate renal impairment did not require any specific change to warfarin dose, although they received the matching placebo for the 15 mg rivaroxaban tablets.

4.2.4 ROCKET AF outcomes

The primary efficacy endpoint in ROCKET AF was a composite of:

1. Stroke (ischaemic and haemorrhagic [including all intracerebral or intraparenchymal bleeding]);
2. Non-CNS systemic embolism.

Stroke was defined as a sudden, focal neurologic deficit resulting from a presumed cerebrovascular cause that was not reversible within 24 hours and not due to a readily identifiable cause, such as tumour or seizure. An event matching this definition and lasting less than 24 hours was considered a TIA. Any death within 30 days of the onset of stroke was regarded as 'fatal stroke'.

Non-CNS systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely causes (e.g., trauma, atherosclerosis or instrumentation). Where atherosclerotic peripheral arterial disease pre-existed, diagnosis of lower extremity emboli required angiographic demonstration of abrupt arterial occlusion.

The ERG notes that the manufacturer's definition of Non-CNS systemic embolism includes those diagnosed by radiological examination.

[redacted] Systemic embolism may have otherwise remained clinically silent and not been identified in routine clinical practice. The ERG thus believes that using this criterion for the diagnosis of systemic embolism in ROCKET AF may result in overestimation of the rates of systemic embolism in comparison with those rates expected to be seen in normal clinical practice.

The ERG also notes that haemorrhagic stroke events are an adverse effect of anticoagulation treatment, although they have been captured within the stroke clinical efficacy outcome in ROCKET AF. However, the ERG acknowledges that the endpoint of all stroke is used as an outcome in some clinical trials in this disease area, and that this includes both ischaemic and haemorrhagic strokes (e.g., RE-LY[9]). However, the ERG is unsure whether haemorrhagic strokes were also counted in the safety bleeding outcomes of ROCKET AF.

The primary safety endpoint in ROCKET AF was defined as a composite of:

1. Major bleeding;
2. Clinically relevant non-major bleeding.

Bleeding was defined as major if it was clinically overt and associated with a fall in haemoglobin concentration of >2 g/dL, or if it led to transfusion of two or more units of packed red blood cells or

whole blood, occurred in a critical site (i.e., intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal), or was attributable to a fatal outcome.

Clinically relevant non-major bleeding was defined as overt bleeding not meeting the 'major bleeding' criteria but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study treatment, or associated with any other discomfort, such as pain or impairment of activities of daily life.

All other overt bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding were classified as minor bleeding.

The secondary endpoints in ROCKET AF were:

1. Composite of stroke, non-CNS systemic embolism, and vascular death;
2. Composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death;
3. All-cause mortality;
4. Individual components of the composite primary and major secondary endpoints;
5. Stroke outcome;
6. Individual bleeding event categories;
7. Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0.

Treatment compliance was also recorded during ROCKET AF and was measured by rivaroxaban/rivaroxaban placebo pill counts.

The ERG also notes that assessment of treatment satisfaction using questionnaires in a subset of the total trial population was listed as an exploratory outcome in the protocol for ROCKET AF, although the results from these assessments are not presented in the MS.

All suspected outcome events were independently assessed by a Clinical Events Committee (CEC), whose members were blinded to the treatment assignments.

The ERG considers that, in general, the manufacturer's choice of outcomes presented within the MS is appropriate, although the ERG acknowledges that the TIA rates for ROCKET AF were not explicitly stated in the MS. In response to a request for clarification, the manufacturer highlighted that TIA was captured within their adverse event reporting and was not listed as a main individual outcome category. For this reason, the results were not reported separately within the MS, although they were included within the NMA and also supplied to the ERG in response to our request for clarification.

The other outcome requested within the final scope issued by NICE but not reported within the MS is health-related quality of life (HRQoL). The ERG considers that if these data had been captured from a trial, such as ROCKET AF, they would have been useful as they would have identified any impact that the benefits or harms of rivaroxaban have on HRQoL compared with warfarin. However, the ERG also acknowledges the limitations in interpreting such data in view of the double-blind nature of ROCKET AF with some form of INR monitoring (INR or sham INR) occurring in both treatment groups, which precludes identification of any difference in HRQoL related to INR monitoring as patients on rivaroxaban would not normally require INR monitoring.

4.2.5 ROCKET AF subgroup analyses

Subgroup analyses specified *a priori* were:

- Region;
- Prior VKA use;
- History of a prior stroke (ischaemic or unknown type), TIA or non-CNS systemic embolism;
- $CHADS_2$ score;
- Prior chronic acetylsalicylic acid (ASA) use;
- Sex;
- Age;
- Race;
- Renal function;
- Body mass index;
- Weight;
- Congestive heart failure;
- Hypertension;
- Diabetes;
- AF type;
- Proton pump inhibitor use at baseline;
- Prior myocardial infarction (MI).

Analyses of treatment efficacy were also performed according to the percentage time each clinical site spent within INR range.

The ERG notes that a large number of subgroup analyses were conducted in ROCKET AF, although only three of the subgroups were stratified at randomisation (region, prior VKA use, and history of a prior stroke, TIA or non-CNS systemic embolism).

4.2.6 ROCKET AF follow-up

Patients in both the rivaroxaban and warfarin groups were followed up at week 1, week 2, week 4 and then monthly up until the 'End of Study visit' (within 30 days of the date of site notification [28th May 2010]; site notification took place once the pre-specified number of on-treatment primary clinical efficacy endpoint 'events' had occurred).

[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%).[9,19] 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 an open-label extension observation period.

[redacted]

[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
ITT	All patients uniquely randomised	Until date of site notification (i.e. double blind trial end point), regardless of treatment received	14,171	96 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	96 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	96 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 an alternative anticoagulant). Abbreviations used in table: ITT, intention-to-treat.				

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.[7] 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[14] 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.[20,21] 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.[22] 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[19] 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.[23] 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.[19]

In ROCKET AF, the ERG notes that the manufacturer [redacted] to 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 safety-on-treatment 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, sensitivity analyses 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%.[9] Also of note is that 62% of the RE-LY trial population were Western European or North American,[24] whereas only 34% of the ROCKET AF population were based in North America or Western Europe. The TTRs from ROCKET AF and RE-LY are higher in Western Europe and North America subgroups compared with other regions, which suggests that warfarin monitoring and control are more rigorous in North America and Western Europe. Thus, the considerable variation in locality of patients noted between RE-LY and ROCKET AF may at least partly account for the lower mean TTR seen in ROCKET AF. However, the manufacturer suggests that the low TTR observed in ROCKET AF may be due to the large proportion of people in the trial with high $CHADS_2$ scores. The manufacturer cites previous research[25] which suggests some of the underlying conditions that contribute to a patient's $CHADS_2$ score are associated with poorer INR control. The ERG considers that the low TTR reported in ROCKET AF could bias the results of the study against warfarin and thus overinflate the relative efficacy of rivaroxaban.

[redacted]

[redacted] The ERG notes that a similar result was reported in RE-LY, with warfarin-experienced patients having a 67.2% TTR compared with 61.8% for naïve patients.[24]

In the MS, considerable variation in TTRs across study centre regions was reported, with North America having the highest overall INR control followed by, in order, Western Europe, Latin America, Asia Pacific and, finally, Eastern Europe (data reported in Table 9).

[redacted]

Abbreviations used in table: INR, International Normalised Ratio.					

(Table 10). This trend in INR control has also been noted in another study.[25]

Table 10.

		Mean (%)	Median (%)

The discontinuation of study medication data reported in the MS consisted of much lower numbers compared with that reported in the FDA briefing document.[26] 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.

The discontinuation of study medication rates reported in the FDA briefing report indicate that 2,520 rivaroxaban patients (35.44%) and 2,468 warfarin patients (34.64%) permanently discontinued their study medication early.

In response to clarification questions, the manufacturer provided details of the antithrombotic drugs that patients in the ITT population received after discontinuation of their double-blind study medication.

It is reported in the MS that the ITT population were followed-up for a median of 117 days post discontinuation of their randomised study drug; that is, patients were off randomised treatment but still included in the analyses according to the treatment they were initially randomised to. The median duration of treatment with randomised study drug (safety population) was 590 days.

[redacted].

4.3.2 ROCKET AF treatment effectiveness results

The primary efficacy endpoint of ROCKET AF was the composite of stroke and non-CNS systemic embolism. The objective of demonstrating rivaroxaban to be non-inferior to warfarin in preventing stroke and non-CNS embolism was met using the non-inferiority margin of 1.46 in both the per protocol and safety-on-treatment trial populations.

Superiority of rivaroxaban over warfarin was also demonstrated in the prevention of stroke and systemic embolism in the safety-on-treatment population (Hazard Ratio [HR] 0.79; 95% CI: 0.65 to 0.95). However, superiority of rivaroxaban was not demonstrated for this outcome in the sensitivity analysis using the ITT population data set (HR 0.88; 95% CI: 0.75 to 1.03) despite the trend towards favouring treatment with rivaroxaban. Table 11 presents data on the primary end point of ROCKET AF for all populations analysed.

Table 11. 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[#†¶]	6,958	188	1.7	7,004	241	2.2	0.79 (0.66 to 0.96)	<0.001*	[redacted]
Safety-on-treatment[#¶]	7,061	189	1.7	7,082	243	2.2	0.79 (0.65 to 0.95)	[redacted]	0.02*
ITT[#‡]	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

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

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

[‡] 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.

The ERG notes that, although discontinuation rates in the rivaroxaban and warfarin groups are similar, there is a substantially larger number of events in the rivaroxaban group compared with the warfarin group during the 'off-treatment' period (i.e., when patients had stopped study drug early and transitioned to open-label VKA or other treatment). The manufacturer highlights that

[redacted]

[redacted] People transitioning from rivaroxaban to warfarin in ROCKET AF took an average of 13 days to reach a therapeutic INR, whereas patients in the warfarin group took an average of only 3 days to reach a therapeutic INR when transitioning to open-label warfarin. The manufacturer also points out that the timing and type of event in the rivaroxaban arm suggest that the events were associated with suboptimal anticoagulation over the transition period from rivaroxaban to a VKA, and that this transition may be addressed more swiftly in true clinical practice. However, the ERG is unsure of the validity of this proposal and considers that, in clinical practice, it would be necessary for people discontinuing rivaroxaban and starting warfarin to go through a period of warfarin dose finding to reach a therapeutic INR. However, the ERG is unable to identify a reason for this observed difference.

Statistical significance was achieved for superiority in the primary efficacy end point in the safety-on-treatment" population, and so the analyses of the secondary efficacy endpoints were carried out according to the manufacturer's pre-specified hierarchical testing procedure. Tables 12 and 13 present results of these additional analyses in the safety-on-treatment and ITT populations, respectively.

Table 12. Incidence and event rates of secondary efficacy endpoints in the ROCKET AF safety-on-treatment population, as adjudicated by the CEC

Endpoint	**Rivaroxaban (n = 7061)**		**Warfarin (n = 7082)**		**Rivaroxaban versus warfarin**	
	n (%)	**Event rate (100 pt-yr)**	**n (%)**	**Event rate (100 pt-yr)**	**HR (95% CI)**	**p-value**
Major Secondary Endpoint 1 Composite of stroke, non-CNS embolism and vascular death	346 (4.90)	3.11	410 (5.79)	3.63	0.86 (0.74 to 0.99)	0.034*
Major Secondary Endpoint 2 Composite of stroke, non-CNS embolism, vascular death and myocardial infarction	433 (6.13)	3.91	519 (7.33)	4.62	0.85 (0.74 to 0.96)	0.010*
Other efficacy endpoints						
All stroke	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.7 to 1.03)	0.092
• Primary haemorrhagic stroke	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37 to 0.93)	0.024*
• Primary ischaemic stroke	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75 to 1.17)	0.581
• Unknown stroke type	7 (0.10)	0.06	11 (0.16)	0.10	0.65 (0.25 to 1.67)	0.366
Stroke outcome						
• Death	47 (0.67)	0.42	67 (0.95)	0.59	0.71 (0.49 to 1.03)	0.075
• Disabling stroke	43 (0.61)	0.39	57 (0.80)	0.50	0.77	0.188

					(0.52 to 1.14)	
• Non-disabling stroke	88 (1.25)	0.79	87 (1.23)	0.77	1.03 (0.76 to 1.38)	0.863
• Unknown	7 (0.10)	0.06	12 (0.17)	0.11	0.59 (0.23 to 1.50)	0.271
Non-CNS systemic embolism	5 (0.07)	0.04	22 (0.31)	0.19	0.23 (0.09 to 0.61)	0.003*
Myocardial infarction	101 (1.43)	0.91	126 (1.78)	1.12	0.81 (0.63 to 1.06)	0.121
All-cause mortality	208 (2.95)	1.87	250 (3.53)	2.21	0.85 (0.70 to 1.02)	0.073
• Vascular death	170 (2.41)	1.53	193 (2.73)	1.71	0.89 (0.73, 1.10)	0.289
• Non-vascular death	21 (0.30)	0.19	34 (0.48)	0.30	0.63 (0.36 to 1.08)	0.094
• Unknown death	17 (0.24)	0.15	23 (0.32)	0.20	0.75 (0.40 to 1.41)	0.370

Notes to accompany table:

1) Stroke outcome is based on investigator's assessment of modified Rankin scale score: 0–2 = non-disabling; 3–5 = disabling; and 6 = death;

2) Event rate 100 pt-yr: number of events per 100 patient years of follow up;

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

4) 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; CEC, Clinical Events Committee; CNS, central nervous system; HR, hazard ratio.

Table 13. [redacted]

Endpoint	**Rivaroxaban (n = 7,081)**		**Warfarin (n = 7,090)**		**Rivaroxaban versus warfarin**	
	n (%)	**Event rate (100 pt-yr)**	**n (%)**	**Event rate (100 pt-yr)**	**HR (95% CI)**	**p-value**
Major Secondary Endpoint 1 Composite of stroke, non-CNS embolism and vascular death	[redacted]					
Major Secondary Endpoint 2 Composite of stroke, non-CNS embolism, vascular death and myocardial infarction	[redacted]					
Other efficacy endpoints						
All stroke	[redacted]					
• Primary haemorrhagic stroke	[redacted]					

• Primary ischaemic stroke	[redacted]					
• Unknown stroke type	[redacted]					
Stroke outcome						
• Death	[redacted]					
• Disabling stroke	[redacted]					
• Non-disabling stroke	[redacted]					
• Unknown	[redacted]					
Non-CNS systemic embolism	[redacted]					
Myocardial infarction	[redacted]					
All-cause mortality	582 (8.22)	4.5	632 (8.91)	4.9	0.92 (0.82 to 1.03)	0.15
• Vascular death	[redacted]					
• Non-vascular death	[redacted]					
• Unknown death	[redacted]					

Notes to accompany table:

1) Stroke outcome is based on investigator's assessment of modified Rankin scale score: 0–2 = non-disabling; 3–5 = disabling; and 6 = death;

2) Event rate 100 pt-yr: number of events per 100 patient years of follow up;

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

4) 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; CEC, Clinical Events Committee; CNS, central nervous system; HR, hazard ratio; ITT, intention-to-treat.

In concordance with the primary efficacy endpoint, it can be seen that for major secondary endpoint 1 and major secondary endpoint 2, rivaroxaban in the safety-on-treatment population achieved superiority over warfarin (major secondary endpoint 1, p = 0.034; major secondary endpoint 2, p = 0.010). However, [redacted]

When compared with warfarin, rivaroxaban was associated with a statistically significant reduction of non-CNS systemic embolisms in the safety-on-treatment population (p = 0.003), and, [redacted]

Although 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, [redacted] Rivaroxaban was also associated with a statistically non-significant higher rate of non-disabling strokes in the safety-on-treatment (p = 0.863) and [redacted] population. The ERG also considers it important to note that significantly more people had a history of prior MI at baseline in the warfarin group compared with the rivaroxaban group. The ERG thus considers that as previous MI is one of the risk factors for future MI, it is possible that the significantly lower number of people with previous MI in the rivaroxaban group (compared with the warfarin group, p < 0.05) has resulted in fewer MIs in this treatment group during the study. The ERG thus considers it important to highlight that the MI results from ROCKET AF should be interpreted with caution.Haemorrhagic stroke is a potential adverse event of treatment with anticoagulants. Primary haemorrhagic stroke was statistically significantly lower in the rivaroxaban group compared with the warfarin group in the safety-on-treatment (p = 0.024) [redacted] population suggesting treatment with warfarin is more likely to lead to haemorrhagic stroke. This finding is in keeping with the other safety findings from ROCKET-AF discussed in section 4.3.5.

4.3.3 ROCKET AF subgroup analyses

The manufacturer conducted numerous subgroup analyses, as discussed in section 4.2.4; however, the presentation of the results of these analyses is limited in the MS to the primary efficacy outcome (composite of stroke and non-CNS systemic embolism) in the safety-on-treatment and ITT populations. The manufacturer also reports in the MS that the results of the subgroup analyses were consistent across all pre-specified subgroups for the primary efficacy outcome, as well as for the patients receiving a reduced dose of rivaroxaban (15 mg once daily). The ERG considers it important to highlight a selection of the subgroup analysis results.

The ERG notes that, of the assessments for an interaction across a subgroup for a patient characteristic, the only analysis for which the interaction reached statistical significance was prior stroke/TIA/systemic embolism in the safety-on-treatment population (p = 0.039 for primary efficacy outcome). The ERG also notes that for both the ITT and safety-on-treatment analyses there were

significantly fewer primary efficacy end point events in the rivaroxaban group than in the warfarin group in people with no prior stroke/TIA/systemic embolism (safety-on-treatment analysis: HR 0.59; 95% CI: 0.42 to 0.83, ITT analysis: HR 0.71; 95% CI: 0.54 to 0.94).

In the MS, there are statistically significant differences between rivaroxaban and warfarin in some of the other subgroups assessed (e.g., safety-on-treatment population: age ≥75 years subgroup, rivaroxaban vs warfarin, HR 0.67; 95% CI: 0.51 to 0.88) for the primary efficacy outcome.

The ERG acknowledges that randomisation was stratified by region of enrollment, prior use of VKAs and prior stroke, TIA or non-CNS systemic embolism, and thus these parameters are the subgroups in which analyses of rivaroxaban versus warfarin should ideally be performed. However, the ERG notes that ROCKET AF was not powered to detect statistically significant differences for interactions across a subgroup or differences between treatments within subgroups and so any findings should be interpreted with caution.

The subgroup of people who had not previously been treated with warfarin was listed in the NICE final scope[8] and so the ERG requested additional information from the manufacturer as this subgroup was not specifically addressed within the MS (i.e., only data for the primary efficacy analysis was provided in the MS). The results supplied by the manufacturer for the safety-on-treatment and ITT populations in people with prior VKA use versus no prior VKA use are presented in Table 14. According to the manufacturer, prior VKA use was defined in ROCKET AF as VKA use for 6 weeks or longer at the time of screening, and VKA naïve was defined as no use of VKA within 6 weeks prior to randomisation. The manufacturer highlights that the VKA naïve subgroup was therefore made up of patients with no prior VKA use and also patients who may have used VKAs previously but not used them within the 6 weeks prior to randomisation.

[redacted]

Table 14. Subgroup analysis results for prior VKA use versus no prior VKA use from ROCKET AF

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	0.84	0.72	[redacted]	[redacted]

endpoint	(0.66 to 1.08)	(0.53 to 0.97)		
Stroke	[redacted]	[redacted]	[redacted]	[redacted]
• Primary ischemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
• Primary hemorrhagic 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 are for rivaroxaban versus warfarin.				
[redacted]				

The ERG notes that, in the North America subgroup, there is a notable difference between the HRs for the primary efficacy endpoint in the ITT population (rivaroxaban vs warfarin: HR 0.95; 95% CI: 0.64 to 1.42) and the safety-on-treatment population (HR 0.58; 95% CI: 0.34 to 1.01). These data highlight that there is a difference in some cases between the results using the ROCKET AF safety-on-treatment population as opposed to the ITT population. The ERG also notes that for the primary efficacy endpoint there is a greater number of statistically significant results in subgroup analyses based on data from the safety-on-treatment population compared with subgroup analyses in the ITT population (12 vs 2).

Given the large variability in warfarin INR TTR across the different regions (Table 9), the ERG requested results for all outcomes reported in ROCKET AF for the Western Europe subgroup as this group includes UK patients and also has an INR TTR that is comparable to that more frequently reported in the UK. The manufacturer provided results for the safety-on-treatment, ITT and per protocol populations for efficacy outcomes and the safety-on-treatment population for safety outcomes. The ERG includes the safety-on-treatment and ITT data as the ERG considers that these populations are the most appropriate for assessing clinical effectiveness (data presented in Table 15).

[redacted]

[redacted]

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] 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. Subgroup data for centre time in therapeutic range (TTR <60% versus TTR ≥60%) from ROCKET AF

	[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]		

[redacted]

The ERG acknowledges that the manufacturer does not draw any conclusions based on any of the subgroup results, and that the subgroups were not powered at the start of the trial to detect statistically significant differences in treatment effect. The ERG considers that the manufacturer's approach to interpreting the subgroup analyses results is appropriate, given that there are many subgroup analyses and thus a high likelihood that significant results could be occurring by chance alone.

4.3.4 ROCKET AF safety results and adverse events

The ERG notes that the safety results for ROCKET AF presented by the manufacturer are limited to the safety-on-treatment population.

For the primary safety endpoint of major or non-major clinically relevant bleeding, the results from ROCKET AF suggest a comparable safety profile for rivaroxaban compared with warfarin, with no statistically significant difference between the two treatments (p = 0.44; full results presented in Table 17).

The rate of the individual outcomes of major bleeding and clinically relevant non-major bleeding were also similar between the rivaroxaban and warfarin groups, with no significant difference between warfarin and rivaroxaban for these outcomes (major bleeding, p = 0.58; clinically relevant non-major bleeding, p = 0.35; Table 17). However, the breakdown of major bleeding indicates that, compared with warfarin, rivaroxaban was associated with significantly lower intracranial haemorrhage (p = 0.02), critical organ bleeding (p = 0.007) and fatal bleeding rates (p = 0.003).

Rivaroxaban was associated with significantly higher rates of bleeding requiring blood transfusion (p = 0.04) and bleeds resulting in significant drops in haemoglobin or haematocrit (p = 0.02).

Within the fatal bleeding category, [redacted]

Table 17. Results of ROCKET AF safety endpoints based on safety-on-treatment population

Safety endpoint	Rivaroxaban (n = 7,111)		Warfarin (n = 7,125)		Rivaroxaban versus warfarin	
	n (%)	Event rate (100 Pt-yr)	n (%)	Event rate (100 Pt-yr)	Hazard ratio (95% CI)	p-value
Principal Safety Endpoint Composite of all major and	1,475 (20.7)	14.9	1,449 (20.3)	14.5	1.03 (0.96 to 1.11)	0.44

non-major clinically relevant bleeding events						
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. However, the ERG considers that the data suggest that with increasing age there is an increase in risk of bleeding adverse events associated with both rivaroxaban and warfarin. In particular, in patients aged <75 years, fewer principal safety outcome events (composite of major and non-major clinically relevant) occurred in the rivaroxaban group compared with the warfarin group in ROCKET AF. However, in people aged ≥75 years more principal safety outcome events occurred in the rivaroxaban group compared with the warfarin group.

All adverse events were coded by MedDRA (Medical Dictionary for Regulatory Activities) version 13.0. Treatment-emergent adverse events were defined as those events starting on or after first dose of study drug up to 2 days after the last dose of study medication.

The overall incidence of treatment-emergent adverse events was similar in the rivaroxaban and warfarin groups (81.44% with rivaroxaban vs 81.54% with warfarin; Table 18).

Table 18. ROCKET AF adverse events

Adverse events	**Rivaroxaban (n = 7,111)**	**Warfarin (n=7,125)**	**Rivaroxaban minus warfarin**
	n (%)	**n (%)**	**Diff. (%), (95% CI [%])[a]**
Post baseline adverse events	[redacted]	[redacted]	[redacted]
Treatment-emergent adverse events	5,791 (81.44)	5,810 (81.54)	[redacted]
Adverse events with onset >2 days from stop of study treatment	[redacted]	[redacted]	[redacted] *
Serious adverse events	[redacted]	[redacted]	[redacted]
Post baseline adverse events	[redacted]	[redacted]	[redacted]
Treatment-emergent serious adverse events	[redacted]	[redacted]	[redacted]
Serious adverse events with onset >2 days from stop of study treatment	[redacted]	[redacted]	[redacted] *
Post baseline adverse events leading to permanent study drug discontinuation	[redacted]	[redacted]	[redacted]

[a] Estimate and 95% CI for the difference in incidence proportion between rivaroxaban and warfarin based on asymptotic methods for a single 2x2 table. The CI is calculated when there are at least 5 events (both treatment groups combined) and at least 1 event in each treatment group.

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

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

[redacted]

In the MS, the manufacturer provides a list of the 15 most frequently occurring investigator-reported treatment-emergent adverse events occurring in the rivaroxaban group. The manufacturer reports that the incidence and types of adverse event were similar between the rivaroxaban and warfarin groups, although significantly more patients in the rivaroxaban group had epistaxis (10.14% vs 8.55%; $p < 0.05$) and haematuria (4.2% vs 3.4%; $p < 0.05$) compared with patients in the warfarin group.

The overall most frequent adverse events associated with rivaroxaban were epistaxis (10%), peripheral oedema (6%) and dizziness (6%), and the most frequent adverse events occurring in the warfarin were epistaxis (9%), nasopharyngitis (6%) and dizziness (6%).

[redacted]The ERG was aware that the incidence of dyspepsia was high in the dabigatran etexilate group of the RE-LY[9] (dabigatran versus warfarin) trial and thus requested data from the manufacturer of rivaroxaban on the dyspepsia rate in ROCKET AF for comparison purposes. [redacted] By contrast, when considering the RE-LY trial,[9] patients in the warfarin arm did not receive a placebo dabigatran etexilate tablet and thus the difference in dyspepsia rates was attributed to the coating of the dabigatran etexilate tablets. The ERG acknowledges that, in RE-LY, dyspepsia occurred in over 5% of people in the warfarin group and in over 11% of people in the dabigatran group, [redacted]

The ERG also note that to enhance absorption of dabigatran, a low pH is required and therefore, dabigatran capsules contain dabigatran-coated pellets with a tartaric acid core.[9] It has been suggested that this resulting acidity may at least partly explain the increased incidence of dyspeptic symptoms with dabigatran.[9] The ERG note however, that tartaric acid is not present in rivaroxaban.

The manufacturer also reported in the MS that, in light of the liver function abnormalities associated with the withdrawn oral thrombin inhibitor ximelagatran,[27] hepatotoxicity risk was also closely monitored in the ROCKET AF study. The overall liver safety profile of rivaroxaban was shown to be comparable with that of warfarin, with no evidence of imbalance in laboratory parameters (such as alanine transaminase levels) [redacted]

4.3.5 [redacted]

4.3.6 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 or ITT analyses 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.

- The sites of bleeding events differ between rivaroxaban and warfarin with significantly more GI bleeds and significantly fewer haemorrhagic strokes and intracranial haemorrhages occurring in the rivaroxaban group of the ROCKET AF safety on treatment population.

4.4 Network meta-analysis

4.4.1 Methods

The lack of direct head-to-head trial data for rivaroxaban compared with the treatments, other than warfarin, listed in the final scope issued by NICE,[8] required the manufacturer to conduct a NMA to enable comparison of rivaroxaban with aspirin and dabigatran (110 mg and 150 mg). The manufacturer also reported outcomes for placebo, although these were not requested in the final scope issued by NICE.[8]

The manufacturer conducted a separate systematic review to identify trials for inclusion in the NMA. In the systematic review, the manufacturer used predominantly the same sources and inclusion/exclusion criteria as used in the search for studies for the systematic review of rivaroxaban versus warfarin discussed in Sections 4.1.1 and 4.1.2. The key difference in the inclusion/exclusion criteria of the systematic review for the NMA was that studies of any combination of the intervention treatments, including placebo/control and different doses of the same drug, were allowed. The treatments covered by the systematic review for the NMA were VKAs, antiplatelet agents, idraparinux, ximelagatran, dabigatran and apixaban.

Inclusion in the NMA was limited to trials reporting data for the following comparators (also known as 'restricted comparators' set): placebo; aspirin; clopidogrel plus aspirin; dabigatran 110 mg or 150 mg; apixaban; rivaroxaban; and adjusted-dose warfarin. A more extensive set of comparators was included in a sensitivity analysis ('full comparator' set). The 'full comparator' set included the treatments listed in the 'restricted comparators' analysis, together with fixed-dose warfarin, fixed-dose warfarin plus aspirin, adjusted-dose warfarin plus aspirin, low-dose warfarin, low-dose warfarin plus aspirin, dabigatran 150 mg plus aspirin, dabigatran 50 mg, dabigatran 50 mg plus aspirin, triflusal plus low-dose warfarin, triflusal, idraparinux, ximelagatran and indobufen. The reasons for the selection of the treatments included in either the 'restricted comparators' set or 'full comparators' set is not further explained in the MS. The ERG notes that several of the treatments included in the NMA are not routinely used in this disease area in UK clinical practice or have been withdrawn by their manufacturer, for example, ximelagatran.

The ERG notes that the manufacturer uses the ROCKET AF safety-on-treatment population data set for the main NMA, although the manufacturer also performs some sensitivity analyses that use the ITT ROCKET AF population data set. The main NMA uses the restricted comparators and ROCKET AF safety-on-treatment population. The sensitivity analyses carried out were:

1. Restricted comparators, ROCKET AF ITT population;
2. Full comparators, ROCKET AF safety-on-treatment population;
3. Restricted comparators, ROCKET AF ITT population, blinded studies only.

The ERG thinks it important to highlight potential issues with combining data from the trials included in the manufacturer's NMA. The ERG acknowledges that the trials included in the NMA vary in date of conduct and that trial procedures and reporting have evolved over time. Bearing these factors in mind, the ERG acknowledges that it is difficult to assess fully the populations in all the trials included in the manufacturer's NMA, and thus difficult to comment on their comparability in terms of the population data set used and trial conduct. The ERG acknowledges the manufacturer's argument that the ROCKET AF safety-on-treatment population may be most similar to the data reported in the other trials included in the NMA. In particular, the ERG notes that the results from RE-LY, the key study in the dabigatran etexilate for atrial fibrillation STA submission,[28] appears to be consistent with the ROCKET-AF safety-on-treatment population. However, it is not clear from the RE-LY publication when people were censored as discontinuing study drug in the ITT population.

Also, as previously discussed, the ERG considers that the ROCKET AF ITT population most accurately represents the likely treatment pathway in clinical practice in the UK; that is, should rivaroxaban be introduced into clinical practice, patients that discontinue treatment are likely to be treated with warfarin. In response to the ERG's clarification questions, the manufacturer provided the results of the NMA using the restricted set of comparators and the ROCKET AF ITT population; these results will be discussed further in section 4.4.5 and compared with the NMA results for the safety-on-treatment population.

Software used

The manufacturer used a Bayesian Markov Chain Monte Carlo (MCMC) simulation approach to the NMA, using WinBUGS software to carry out the NMA. The WinBUGS code used was supplied to the ERG in the manufacturer's response to clarification questions. The ERG validated the results generated by the manufacturer using the WinBUGS code supplied for a sample of outcomes. The ERG also conducted a second validation exercise for a selection of the manufacturer's NMA results using alternative WinBUGS code. In both assessments, the ERG's results were comparable with those generated by the manufacturer.

4.4.2 Outcomes reported in the network meta-analysis

The ERG notes that the primary outcomes in the systematic review used to inform the manufacturer's trial selection for the NMA were slightly different to those reported in the manufacturer's key trial, ROCKET AF. An additional list of secondary outcomes for the systematic review was also compiled by the manufacturer and this included the primary composite outcome from ROCKET AF. A summary of the outcomes selected by the manufacturer for the NMA is presented in Table 19.

Table 19. Outcomes reported in the manufacturer's systematic review and network meta-analysis

Outcomes reported in the systematic review	Outcomes reported in the network meta-analysis
Primary outcomes: • All strokes (ischaemic and haemorrhagic); • Ischaemic stroke; • Intracranial haemorrhage; • Major extracranial haemorrhage; • All-cause mortality. **Secondary outcomes:** • Transient ischaemic attack; • Systemic embolism; • Myocardial infarction; • Composite endpoint: all cause of stroke and non-CNS systemic embolism; • Minor bleed; • Cardiovascular mortality; • All cause of hospitalisation; • Cardiovascular-related hospitalisations; • Gastrointestinal bleed; • Dyspepsia.	• Composite of ischaemic stroke and systemic embolism; • Total stroke; • Ischaemic stroke; • Haemorrhagic stroke/ intracranial haemorrhage; • Systemic embolism; • Myocardial infarction; • Cardiovascular death; • Mortality; • Major haemorrhage (extracranial bleeding); • Minor bleed (clinically relevant non-major bleeding); • Gastrointestinal bleed; • Dyspepsia; • Transient ischaemic attack.

The ERG also notes that some of the outcomes selected by the manufacturer for the NMA were highlighted in the methods of their NMA as not being uniformly reported outcomes for trials in this disease area (e.g., major extracranial haemorrhage). In addition, it was also highlighted that not all the outcomes included in the NMA were reported in the main ROCKET AF results; for example, haemorrhagic stroke and intracranial haemorrhage were not reported in ROCKET AF, and so the respective outcome data were aggregated to create the composite data for input into the NMA. For some trials, it was necessary to calculate absolute data for major extracranial haemorrhage by subtracting intracranial bleeds from total major haemorrhages. The ERG considers it important to note that this approach could affect the validity of the results generated by the NMA as errors could have been inadvertently introduced into the trial level data used and clinical heterogeneity introduced into the network. A more robust approach would have been to contact the individual trial authors to request the necessary data. It is not clear from the MS or accompanying documentation whether data used in the NMA is taken directly from the original publication. In addition, the manufacturer does

provide any sensitivity analysis excluding those trials not reporting the specific outcome of interest and so the ERG is unable to comment further on the likely impact of calculating absolute numbers for individual outcomes on the overall results.

4.4.3 Studies included in the network

In the MS it was unclear how many trials were included in the systematic review and subsequent NMA. The manufacturer presented an updated PRISMA flow diagram in their response to the ERG's clarification questions. Based on their search in February 2011, the manufacturer identified a total of 35 studies in 56 publications for inclusion in the systematic review. Of these 35 studies, only 28 studies (reported in 41 publications) were subsequently included in the NMA. The 7 studies excluded from the NMA were excluded for reasons mostly related to inadequate or unsuitable reporting of results.

An additional 2 studies (2 publications) were identified after the date of the search and included in the NMA, making a total of 30 studies (43 publications) suitable for inclusion in the NMA.

The list of trials included in the manufacturer's systematic review and NMA is given in Appendix 9.1.

The ERG validated the manufacturer's selection of trials for the NMA by comparing them with those used in the MS for dabigatran etexilate[28] and published research in the area.[29] The manufacturer did not provide a network diagram giving an overview of the trials included in the NMA; however, they did provide network diagrams detailing the trials included in the analyses for each of the NMA outcomes. The outcome in the main NMA (restricted comparator, ROCKET AF safety-on-treatment population) that was informed by the largest number of trials in the network was total stroke, which used 19 trials with data from a total of 40 trial groups. By contrast, the outcome of dyspepsia used a network of 3 trials with data from a total of 7 groups. Adjusted-dose warfarin, aspirin and placebo had the most data points to inform the network. Many of the other comparators in the network were limited to data from a single trial.

The ERG also acknowledges that the manufacturer performed quality assessments for each of the trials included in the NMA, which indicate considerable variation in the quality of the trials. The ERG considers that disparity among trials in terms of quality is to be expected given the evolution of trial reporting over the time period during which the studies included in the network were conducted. The ERG acknowledges that the small number of trials informing some of the links within the NMA limits attempts to assess issues surrounding trial quality within sensitivity analyses in the NMA.

4.4.4 Heterogeneity

In the MS, the manufacturer states that the NMA was run using a random effects model to make allowance for heterogeneity among studies. However, the ERG notes that the WinBUGS codes

supplied at the clarification response stage by the manufacturer suggest that for 10 of the outcomes assessed in the NMA the manufacturer has used a random effects model, but for the remaining three outcomes they have used a fixed effects model. No rationale has been provided for this use of the fixed effects model in some outcomes.

The ERG considers that the manufacturer's description and discussion of the methods and findings from their assessment of heterogeneity in the NMA is inadequately reported in the MS. However, the manufacturer provided details of the model fit (residual deviance and numbers of unconstrained data points) and values for tau, the statistical quantification of heterogeneity, in response to the ERG's clarification questions. Although the results show that the models used by the manufacturer were generally good fitting, [redacted] The ERG notes that the 95% Credible Intervals (CrI) presented in the NMA for some of the treatments that are informed by a single study are much wider than those reported in the original studies. The ERG considers that the 95% CrI in the manufacturer's NMA may be due to an incoherent underlying dataset which could be caused by clinical heterogeneity in the wider network of trials informing the NMA.

The ERG considers a potential source of the clinical heterogeneity within the manufacturer's NMA could be a result of the combination of trials with clinical differences, such as different doses of drugs (e.g., aspirin 75 mg and 150 mg). The ERG has thus carried out exploratory analyses to assess the effect of using a more homogeneous set of trials; discussed in Section 4.5.

4.4.5 Results of the network meta-analysis

[redacted] Results from the NMA for the ROCKET AF safety-on-treatment and ITT populations are presented in Tables 20 and 21, respectively.

Table 20. [redacted] (OR <1 favours rivaroxaban, OR >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]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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

[redacted]The ERG also considers it important to note that in the trial informing the rivaroxaban MI data set, (ROCKET AF), significantly more people had a history of prior MI at baseline in the warfarin group compared with

the rivaroxaban group ($p < 0.05$). The ERG thus considers that as previous MI is one of the risk factors for future MI, the benefit observed with rivaroxaban in reducing the risk of MI compared to other comparators in the NMA may be confounded and should be interpreted with caution.

[redacted]

Table 21. [redacted] (OR <1 favours comparator, OR >1 favours rivaroxaban)

Outcome	Adjusted-dose warfarin	ASA (aspirin)	Dabigatran 110mg	Dabigatran 150mg	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]

[redacted]

Abbreviations used in table: 95% CI, 95% Confidence Interval; ASA, acetylsalicylic acid; OR, odds ratio; ITT, intention-to-treat.

[redacted]

4.4.6 Rivaroxaban direct pair-wise results compared with the network meta-analysis results

Results from the direct and indirect comparisons of rivaroxaban versus adjusted-dose warfarin are summarised in Table 22: ROCKET AF estimates are reported as HRs and the NMA estimates as ORs (the ERG has assumed that the HRs and ORs in this case are broadly equivalent).

The manufacturer reported that the direct study data from ROCKET AF for the comparison of rivaroxaban versus adjusted-dose warfarin are consistent with the indirect findings from the NMA. The ERG agrees with the manufacturer (based on assumption that HRs from ROCKET AF are comparable with the ORs from the NMA) on this point, but considers it important to highlight that in the case of systemic embolism, although the point estimates from direct trial data and the NMA are similar, the direct data significantly favours rivaroxaban whereas the difference between treatment groups in the indirect estimate is not statistically significant. The ERG also notes that as the only trial informing the comparison of rivaroxaban versus adjusted-dose warfarin in the NMA is ROCKET AF, the NMA results are close to the original trial data results, although the 95% CrI are substantially wider than would be expected in a coherent NMA for all but the primary composite outcome.

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 the residual deviance, number of unconstrained data points, and quantification of heterogeneity (tau). The ERG notes that there was reasonable agreement between the number of unconstrained data points and residual deviance (as would be expected in a good fitting model).[30] However, the value of tau was always >1 for all outcomes assessed, with the exception of gastrointestinal bleeds (tau 0.23), which indicates substantial heterogeneity in the network.[31]

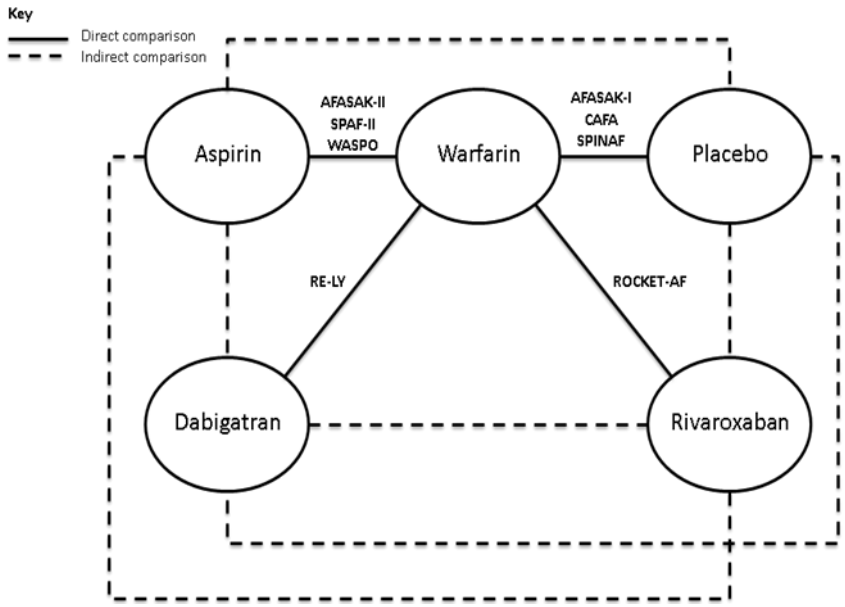
The ERG performed an exploratory NMA to evaluate whether using a simplified network based exclusively on the treatments of interest listed in the final scope issued by NICE[8] would reduce the amount of heterogeneity in the analyses. The ERG's exploratory work focused on those outcomes that inform the health economic analysis. The comparators included were: rivaroxaban; dabigatran etexilate; aspirin; placebo; and adjusted standard dose warfarin. The outcomes assessed were: ischaemic stroke; systemic embolism; major extracranial bleed; minor extracranial bleed; intracranial

bleed; and MI. In addition, the ERG assessed discontinuation as the economic model indicated this to be a key parameter.

Trials for inclusion in the ERG's NMA were selected from published meta-analyses evaluating antithrombotics for stroke prevention in AF.[12],[29] Final trial selection was validated against the trials selected for inclusion in the NMA in the manufacturer's submission for this STA and those selected for inclusion in the ERG report[19] and manufacturer's submission[28] for the dabigatran etexilate in AF STA. In addition, trials selected to inform the ERG's NMA were assessed for comparability based on patient population, severity of disease, and treatments received. In particular, to ensure a homogeneous set of trials for analysis, only comparable dosing strategies were included (i.e., rivaroxaban 20 mg/day, dabigatran etexilate 300 mg/day, aspirin 300 mg/day, and dose-adjusted warfarin aiming at a target INR range between 2 and 3). Incorporating dissimilar trials has been shown to have a profound impact on the results of NMA.[32] Dabigatran etexilate 220 mg/day was excluded from the NMA because the economic model supplied by the manufacturer cannot accommodate a treatment strategy of 300 mg/day stepping down to 220 mg/day once a patient has reached 80-years-old.

The trial network created by the ERG is depicted in Figure 2; this network forms a "radiating star",[33] in which warfarin is the treatment that links the other treatments together.

Figure 2. Network of 8 randomised controlled trials[7,9,37,38,40,42,43,44] informing the network meta-analysis conducted by the Evidence Review Group



Fixed and random effects models were explored and the model that had the lowest Deviance Information Criterion (DIC) was selected when reporting results. DIC measures the fit of the model

while penalising for the number of effective parameters.[34] The OR was used as a summary statistic for all analyses as it has been shown to be associated with less heterogeneity in meta-analysis than risk difference or relative risk.[35] Similar to the manufacturer's approach, all analyses were conducted using WinBUGS and a Bayesian MCMC simulation.[36] As Bayesian statistical inference provides the probability that an estimate will take a particular value, results are presented with a 95% CrI rather than a 95% Confidence Interval (CI).[31] In addition, pair-wise meta-analysis of all individual direct comparisons of treatments with warfarin was conducted.

The results of the additional analyses carried out by the ERG are presented in Table 23. Similar to the NMA presented in the MS, for each outcome there was reasonable agreement between the number of unconstrained data points and residual deviance. In marked contrast to the NMA in the MS, the homogeneity of the trials included in the network resulted in the fixed effects model being preferred for all outcomes assessed.

Table 23. Results from the NMA and pair-wise meta-analysis conducted by the ERG using warfarin as a baseline (OR <1 favours comparator; OR >1 favours warfarin)

Outcome	**NMA**	**Meta-analysis**
	Mean OR 95% CrI	**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[†]		
• 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‡	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.

†Excluding WASPO[37] 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.

‡Excluding AFASAK-I[38] 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.

Generally, the results from the NMA and the pair-wise meta-analysis are in agreement, suggesting a consistent network of trials.[39] The single substantial difference between the two analyses was the

estimated OR for placebo versus warfarin for MI (OR 20.14 vs OR 3.97 for the NMA and the pair-wise meta-analysis, respectively). This disparity between the analyses is likely to be because the analysis is based on a single trial with few events informing the estimate (1/260 warfarin vs 4/265 aspirin).[40]

The outcomes that would be considered statistically significant in the NMA compared with warfarin are (excluding placebo): reduction in ischaemic stroke with dabigatran etexilate; reduction in systemic embolism with rivaroxaban; reduction in minor extracranial bleeds with dabigatran etexilate and aspirin; reduction in intracranial bleeds with dabigatran etexilate and rivaroxaban; increase in MI with dabigatran etexilate; and increase in discontinuation with dabigatran etexilate.

Overall, use of a network of randomised controlled trials restricted to those that directly inform the decision problem that is the focus of this STA results in a more consistent analysis that provides greater precision around the effect estimates than that provided in the MS. The effect of this more coherent analysis is explored in the Economic Evaluation section of this ERG report.

4.5.1 Rivaroxaban versus dabigatran etexilate

Rivaroxaban and dabigatran etexilate are both new oral direct thrombin inhibitors that are currently being evaluated by NICE in the STA programme. The final scope issued by NICE[8] specifically requests a comparison between these treatments. One of the strengths of the NMA approach is that it simultaneously compares all treatments within the network.[36] As such, it is possible to estimate the treatment effects of any treatment within the network relative to any other treatment within the network. Table 24 presents the results for the comparison of rivaroxaban 20 mg/day and dabigatran etexilate 300 mg/day. In addition to the results from the NMA, the results of an adjusted indirect comparison using warfarin as a common comparator are also provided. The method employed for the adjusted indirect comparison was originally described by Bucher and colleagues.[41]

The results of the NMA and the adjusted indirect comparison are consistent with one another. There is a general trend in favour of dabigatran etexilate for ischaemic stroke, major extracranial bleed, and intracranial bleed, and a statistically significant difference (at the 5% level) in favour of dabigatran etexilate for minor extracranial bleed. There is a trend in favour of rivaroxaban for systemic embolism and a significant difference (at the 5% level) favouring rivaroxaban in MI and discontinuation. However, the ERG also considers it important to note that in the trial informing the rivaroxaban MI data set, (ROCKET AF), significantly more people had a history of prior MI at baseline in the warfarin group compared with the rivaroxaban group ($p < 0.05$). The ERG thus considers that as previous MI is one of the risk factors for future MI, the benefit observed with rivaroxaban in reducing the risk of MI compared to dabigatran etexilate may be confounded and should be interpreted with caution.

Table 24. Results from the network meta-analysis and adjusted indirect comparison conducted by the ERG comparing rivaroxaban 20 mg/day and dabigatran etexilate 300 mg/day (OR <1 favours rivaroxaban; OR >1 favours dabigatran etexilate)

Outcome	NMA	Adjusted indirect comparison
	Mean OR (95% CrI)	**Mean OR (95% CI)**
Ischaemic stroke	1.19 (0.84 to 1.65)	1.18 (0.84 to 1.64)
Systemic embolism	0.43 (0.10 to 1.16))	0.37 (0.11 to 1.22)
Major extracranial bleed	1.06 (0.84 to 1.31)	1.05 (0.84 to 1.31)
Minor extracranial bleed	1.18* (1.04 to 1.32)	1.18* (1.05 to 1.32)
Intracranial bleed	1.68 (0.96 to 2.73)	1.61 (0.96 to 2.70)
Myocardial infarction	0.58* (0.37 to 0.87)	0.57* (0.37 to 0.87)
Discontinuation	0.76* (0.68 to 0.86)	0.76* (0.68 to 0.85)
*Statistically significant at the 5% level. Abbreviations used in table: 95% CI, 95% Confidence Interval; 95% CrI, 95% Credible Interval, OR, odds ratio.		

In addition, the ERG carried out an adjusted indirect comparison between rivaroxaban and dabigatran etexilate for dyspepsia and major gastrointestinal bleed. Dyspepsia was identified in the RE-LY trial as the only adverse event occurring significantly more often with dabigatran etexilate than with warfarin (11.3% vs 5.8%, respectively; $p < 0.0001$).[9] While not presented in the MS, in response to the ERG's clarification questions, the manufacturer provided the incidence of dyspepsia from ROCKET AF ([redacted]). An adjusted indirect comparison of these results demonstrates patients are at significantly more risk of dyspepsia with dabigatran etexilate than with rivaroxaban (OR 1.80; 95% CI: 1.32 to 2.46). The dabigatran etexilate coating has been proposed as a possible cause for the observed increase in dyspepsia with dabigatran etexilate compared with warfarin in RE-LY.[9]

Major gastrointestinal bleed was identified in the MS as occurring significantly more often with rivaroxaban than warfarin (3.15% vs 2.16, respectively; $p < 0.001$; MS; pg 97). In the RE-LY trial, dabigatran etexilate was also associated with more major gastrointestinal bleeds than warfarin (1.57% vs 1.07%, respectively, $p < 0.001$).[28] An adjusted indirect comparison of these results demonstrates no 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]

- [redacted]

4.6.2 Clinical issues

- The ERG considers the ROCKET AF population to be at a higher risk of stroke than the population defined in the NICE final scope.

- The conclusions drawn for the efficacy of rivaroxaban in the outcome of MI are potentially confounded as significantly more people had a history of prior MI at baseline in the warfarin group compared with the rivaroxaban group in the key rivaroxaban trial, ROCKET AF.

- The mean time in therapeutic range (TTR) for the INR range of 2.0 to 3.0 in ROCKET AF was lower than that typically seen in Western Europe clinical trial populations.

- No clinical data for the safety and efficacy of rivaroxaban in people unsuitable for warfarin is presented in MS.

- The ERG considers that there is substantial clinical heterogeneity within the manufacturer's NMA as a result of the combination of trials with clinical differences, such as different doses of drugs (e.g., aspirin 75 mg and 150 mg).

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the manufacturer. The manufacturer provided a written submission of the economic evidence along with an electronic version of the Microsoft© EXCEL-based economic model. Table 25 summarises the location of the key economic information within the manufacturer's submission (MS).

Table 25. Summary of key information within the manufacturer's submission

Information	Section (MS)
Details of the systematic review of the economic literature	6.1
Model structure	6.2.2 to 6.2.5
Technology	6.2.7 to 6.2.8
Clinical parameters and variables	6.3
Measurement and valuation of health effects and adverse events	6.4
Resource identification, valuation and measurement	6.5
Sensitivity analysis	6.6
Results	6.7
Validation	6.8.1
Subgroup analysis	6.9
Strengths and weaknesses of economic evaluation	6.10.3 to 6.10.4
Abbreviations used in table: MS, manufacturer's submission.	

5.2 Overview of manufacturer's review of the cost-effectiveness evidence

The manufacturer described in detail the search strategy implemented to identify published cost-effectiveness evidence in evaluating antithrombotics for stroke prevention in atrial fibrillation (AF). The Evidence Review Group (ERG) is satisfied that all appropriate databases were searched and that the search terms and inclusion/exclusion criteria used were reasonable. The ERG notes that conference abstracts were excluded and only English language papers were considered. However, the ERG is confident that no relevant studies have been missed. The search identified five cost-utility studies.[45,46,47,48,49] Data were extracted from these papers and the quality assessment of each paper is presented in the MS (MS; pgs 121–130). None of the studies identified considered rivaroxaban for the prophylactic treatment of stroke and systemic embolism. However, the data extracted from these studies were used to inform the assumptions and inputs of the manufacturer's model. The manufacturer commented that the Markov model was the most common choice of model and that "the

cost effectiveness of different treatments is often influenced by the choice of stratification and other variables".

5.3 Overview of manufacturer's economic evaluation

The manufacturer used a Markov state transition model to evaluate the clinical and economic outcomes associated with prophylactic rivaroxaban treatment in patients with AF.

5.3.1 Intervention and comparators

Adjusted-dose warfarin is the current standard of care for the prevention of stroke and systemic embolism in patients with AF, who are at moderate to high risk of stroke. Warfarin is the main comparator for rivaroxaban in the manufacturer's economic evaluation. As stipulated in the final scope issued by the National Institute for Health and Clinical Excellence (NICE),[8] the manufacturer also compares rivaroxaban with dabigatran (110 mg twice daily or 150 mg twice daily). Dabigatran is currently undergoing NICE technology appraisal.[50] In addition to this, the manufacturer compares rivaroxaban with aspirin and with no treatment (placebo) in patients eligible for anticoagulation (those at moderate to high risk of stroke).

5.3.2 Population

The manufacturer's base case analysis of rivaroxaban versus warfarin uses the patient characteristics and clinical effectiveness data observed in the safety-on-treatment population of the ROCKET AF clinical trial. Economic evaluations were also conducted in patients who were:

- Poorly controlled on warfarin;
- Vitamin K antagonist (VKA) naïve;
- Receiving aspirin or no treatment (placebo);
- Receiving dabigatran (110 mg twice daily or 150 mg twice daily).

Patient characteristics and clinical effectiveness data from the safety-on-treatment population of ROCKET AF were also used to inform the evaluation of rivaroxaban versus warfarin in patients poorly controlled on warfarin and patients naïve to VKA therapy. The analyses of rivaroxaban in patients who were receiving aspirin, no treatment or dabigatran are based on patient characteristics from an observational survey carried out in the United Kingdom (UK)[51] and the clinical effectiveness estimates generated by the manufacturer's network meta-analysis (NMA; see Section 4.4 for more details).

5.3.3 Model structure

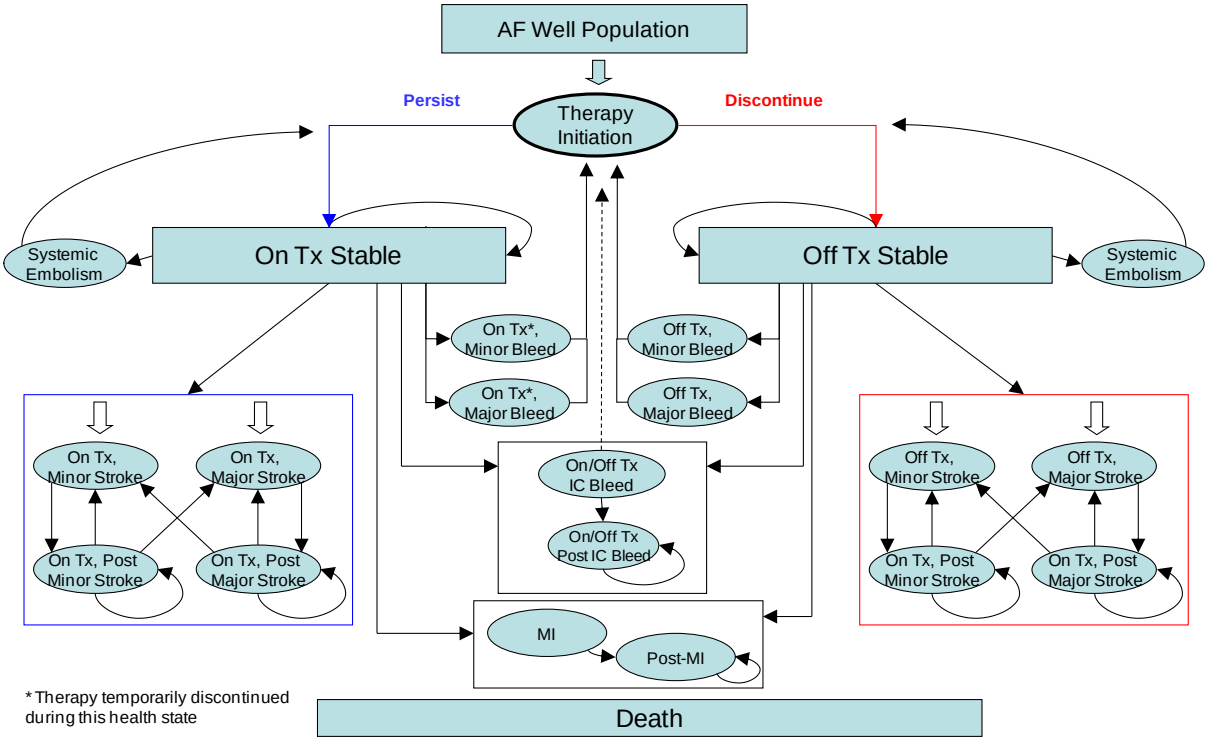
The manufacturer's model has 22 health states (Figure 3), including the absorbing state of death. Patients transition through the model in cycles of three months, accumulating the utility associated with each health state they enter, together with the costs of treatment, events and subsequent

monitoring. Patients enter the model with stable AF and receive prophylactic treatment with either anticoagulation or antiplatelet therapy. All patients are then exposed to the risk of the following events:

- Minor stroke;
- Major stroke;
- Systemic embolism;
- Minor extracranial bleeding;
- Major extracranial bleeding;
- Intracranial bleeding (including haemorrhagic stroke);
- Myocardial infarction (MI);
- Death.

All events, including adverse events, are modelled as explicit health states. Once an event has occurred, the risk of an additional event is suspended for one model cycle (three months).

Figure 3. Model structure (reproduced from MS; Figure 17; pg 134)



Note: The figure is a simplification of the model schematic; patients in the post-minor/major stroke and post-MI health states are still at risk of all transient and permanent model events.

Abbreviations used in figure: IC, intracranial; MI, myocardial infarction; MS, manufacturer's submission; Tx, therapy.

Transient and permanent events

The manufacturer classified all model events as either transient or permanent, depending on the 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. The manufacturer stated that the assumption that extracranial bleeding is not associated with long-term clinical or economic sequelae was based on expert opinion; the clinical experts consulted by the manufacturer reported "that the need for specific follow up care is rare" (MS; pg 136). As part of the clarification process, the ERG asked the manufacturer to expand on the rationale for applying the same assumption to systemic embolism. The manufacturer noted that the long-term consequences of a systemic embolism are highly variable depending on the location of the emboli. In addition, the manufacturer commented that the number of systemic embolic events observed in ROCKET AF is "too low for meaningful estimations to be calculated for the distribution of embolic events by location". The manufacturer also stated that there is a paucity of cost and health-related quality of life (HRQoL) data on the long-term sequelae of systemic embolism. This is discussed in more detail in Section 5.4.4.

Minor stroke, major stroke, intracranial bleeding and MI are considered by the manufacturer to be permanent events, in the sense that they have lasting clinical and economic sequelae. Consequently, the manufacturer has developed post-event health states to account for the different risks, costs and utilities associated with surviving a permanent event.

Age-adjusted baseline risk

The manufacturer highlighted that increasing age is 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. Table 26 lists the relative risk (RR) of stroke or systemic embolism by age and baseline risk group; risks were calculated using the Framingham risk equations.[52]

Table 26. Relative risk of systemic embolism and stroke by age (adapted from MS; Table 37; pg 146)

$CHADS_2$ score	**RR of systemic embolism and stroke by age**							
	55–59	**60–64**	**65–69**	**70–74**	**75–79**	**80–84**	**85–89**	**90+**
1	0.571	0.714	0.857	1.000	1.143	1.286	1.429	1.786
2	0.667	0.750	0.833	1.000	1.167	1.250	1.500	1.750
≥3	0.667	0.762	0.857	1.000	1.143	1.286	1.476	1.714

Abbreviation used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); RR, relative risk.

In the model, a weighted average RR (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 risk of extracranial bleeding, intracranial bleeding and MI are assumed to be independent of time and, therefore, are not adjusted for age. This is discussed further in Section 5.4.4.

Post-event health states

As discussed above, minor stroke, major stroke, intracranial bleeding and MI have post-event health states to capture the long-term costs and consequences associated with each event. Once patients have entered any of the post-event health states, they are still at risk of all temporary and permanent events; however, the occurrence of a temporary event does not result in a change of health state.

Analyses that are based on data from the manufacturer's NMA incorporate an increase in the risk of ischaemic stroke for patients in the post-minor stroke, post-major stroke and post-intracranial bleed health states. The higher risk of ischemic stroke is calculated by applying the RR (1.9, Gage *et al*.[53]) of ischaemic stroke in higher risk patients (compared to moderate patients) to the risk of ischaemic stroke in moderate patients. The majority of patients in ROCKET AF are high risk at baseline; therefore, no increase in the risk of ischaemic stroke was applied to patients in the post-stroke event health states when analysis was based on ROCKET AF. The higher risk of stroke continues to be adjusted for age using the same weighted RRs previously described.

5.3.4 Treatment discontinuation and switching

The baseline risk of each event is adjusted according to the treatment regimen the patient is receiving. Patients may discontinue their primary therapy and switch to a pre-specified secondary therapy at any time (Table 27), although the risk adjustment applied for the remainder of that cycle will be that of the primary therapy. The ERG notes that the option of warfarin as a second-line treatment is not available in the manufacturer's model. Quarterly discontinuation probabilities for rivaroxaban and warfarin were calculated from data 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 is equivalent to that of rivaroxaban, given the similarity of administration between these interventions. This is discussed further in Section 5.4.4.

Table 27. Treatment sequence

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

After initiation of treatment with anticoagulant, patients who do not experience an event transition to the 'on treatment stable' or 'off treatment stable' health state, depending on whether they remain on their primary therapy or switch to secondary therapy. It is important to note that 'off treatment stable' does not mean the patient is receiving 'no treatment', rather they are receiving second-line treatment.

The occurrence of an event may have an impact on the treatment a patient receives; changes in treatment based on model events are summarised in Table 28. In brief, some events incur a temporary discontinuation of therapy, some events result in permanent discontinuation of therapy and many events trigger the re-initiation of primary therapy in those patients who have previously switched to secondary therapy.

Table 28. Event driven treatment discontinuation and switching

Event	Patients receiving first-line treatment at the time of the event		Patients receiving second-line treatment at the time of the event
Temporary events			
Systemic embolism	Temporary discontinuation of primary therapy		No effect
Minor/major extracranial bleed	Temporary discontinuation of primary therapy		Temporary discontinuation of therapy followed by re-initiation of primary therapy
Permanent events			
Minor/major ischaemic stroke	Temporary discontinuation of primary therapy		Temporary discontinuation of therapy followed by re-initiation of primary therapy
Intracranial bleed	Permanent discontinuation for patients with $CHADS_2$ score ≤2	Temporary discontinuation for patients with $CHADS_2$ score ≥3	Temporary discontinuation of therapy
MI	All patients are assumed to continue on primary therapy		
Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); MI, myocardial infarction.			

The MS states that "In most cases of a minor or major bleed, physicians will advise that anti-thrombotic therapy be continued for AF patients. There may be individual exceptions, but as a ground rule, this treatment sequence was considered by clinical experts to be the more acceptable" (MS; pg 161). For this reason, the model allows the temporary discontinuation of prophylactic treatment during an acute bleeding event. However, the manufacturer does not report any rationale for the

temporary discontinuation of therapy during an acute stroke event. However, clinical advice received by the ERG indicates that prophylactic treatment would be suspended following a stroke event, sometimes for up to two weeks. Similarly, the rationale for the re-initiation of primary therapy in second-line patients following a bleeding event is not given. As part of the clarification process, the ERG asked the manufacturer to state the rationale for re-initiation of primary therapy following a minor or major extracranial bleeding event. The manufacturer stated that "Once a patient experiences a bleed event and is untreated, clinical advice indicated that they would be re-initiated on antithrombotic therapy as they would be under the care of a physician for the acute treatment of their bleed event and their history of AF would trigger therapy." This is discussed further in Section 5.4.4.

5.3.5 Parameters and values

Table 29 summarises all safety-on-treatment population parameters and values used in the manufacturer's model; only significant relative treatment effects, calculated from data from ROCKET AF are used in the manufacturer's base case, all non-significant RRs are assumed to be 1. The manufacturer has taken a cost minimisation approach to the comparison of rivaroxaban with dabigatran and as such has assumed that all treatment effects for dabigatran are equivalent to those calculated for rivaroxaban from the manufacturer's NMA.

Table 29. Summary of variables applied in the economic model including treatment effectiveness

Model variables	**Values/sources**			
Drug costs	**Drug acquisition**		**Drug administration**	
	Costs per day	**Costs per cycle**	**Costs per cycle**	
Rivaroxaban	[redacted]	£192.00	Initiation = £36.00	
Warfarin	£0.12	£10.98	Initiation = £181.00 Maintenance = £136.00 Re-initiation = £190.00	
Aspirin	£0.02	£1.49	Initiation = £36.00	
Dabigatran	£2.52	£230.00	Initiation = £36.00	
Baseline risk of events per quarter	**ROCKET AF-based analyses**		**NMA-based analyses**	
	Baseline warfarin risk (95% CI)	**Source**	**Baseline placebo risk (95% CI)**	**Source**
Ischaemic stroke	0.36% (0.31% to 0.41%)	Warfarin arm of ROCKET AF (safety-on-treatment population)	1.14% (0.86% to 1.43%)	AFI[54]
Systemic embolism	0.05% (0.03% to 0.07%)		0.13% (0.094% to 0.157%)	
Minor extracranial bleed	[redacted]		0.61% (0.46% to 0.76%)	EAFT[55]
Major extracranial bleed	[redacted]		0.12% (0.09% to 0.14%)	
Intracranial bleed	[redacted]		0.03% (0.02% to 0.04%)	
MI	0.28% (0.24% to 0.33%)		0.49% (0.37% to 0.62%)	SAFT[56]

RR for rivaroxaban	ROCKET AF-based analyses		NMA-based analyses	
	Relative risk vs warfarin (95% CI)	**Source**	**Risk relative vs placebo (95% CI)**	**Source**
Ischaemic stroke	0.94[¥] (0.75 to1.17)	ROCKET AF (safety-on-treatment population)	N/A	
Systemic embolism	0.23 (0.09 to 0.61)			
Minor extracranial bleed	1.04[¥] (0.96 to 1.13)			
Major extracranial bleed	1.14[¥] (0.98 to 1.33)			
Intracranial bleed	0.67 (0.47 to 0.93)			
MI	0.81[¥] (0.61 to 1.06)			
RR for aspirin	**ROCKET AF-based analyses**		**NMA-based analyses (safety-on-treatment population)**	
	Risk relative vs warfarin (95% CI)	**Source**	**Risk relative vs placebo (95% CI)**	**Source**
Ischaemic stroke	1.61 (1.22 to 2.08)	Hart[57]	[redacted]	Manufacturer's NMA (safety-on-treatment population)[12]
Systemic embolism	1.61 (1.22 to 2.08)		[redacted]	
Minor extracranial bleed	0.59 (0.30 to 1.16)		[redacted]	
Major extracranial bleed	0.59 (0.30 to 1.16)		[redacted]	
Intracranial bleed	0.44 (0.20 to 0.96)		[redacted]	
MI	0.43 (0.11 to 1.50)*	Manufacturer's NMA[12]	[redacted]	
RR for dabigatran	**ROCKET AF-based analyses**		**NMA-based analyses (safety-on-treatment population)**	
	Relative risk vs warfarin (95% CI)	**Source**	**Relative risk vs placebo (95% CI)****	**Source**
Ischaemic stroke	N/A		[redacted]	Manufacturer's NMA (safety-on-treatment population)[12]
Systemic embolism			[redacted]	
Minor extracranial bleed			[redacted]	
Major extracranial bleed			[redacted]	
Intracranial bleed			[redacted]	
MI			[redacted]	
Stroke-related variables	**Value (95% CI)**		**Source**	
Likelihood that stroke is minor	47.55% Linked to likelihood that stroke is major stroke		ROCKET AF safety-on-treatment population	
Likelihood that stroke is major stroke	52.45% (47.60% to 57.27%)			

Mortality related variables	Value (per cycle) (95% CI)	Source
Major stroke case-fatality	12.58% (9.44% to 15.73%)	ROCKET AF safety-on-treatment population
Major stroke long term	2.63% (0.91% to 13.50%)	Marini *et al*.[58]
Major extracranial bleed case fatality	[redacted]	ROCKET AF safety-on-treatment population
Intracranial bleed case-fatality	[redacted]	
Intracranial bleed long-term mortality	2.63% (0.91% to 13.50%)	Marini *et al*.[58]
MI case-fatality	[redacted]	ROCKET AF safety-on-treatment population
MI long-term mortality	2.68% (0.00% to 6.75%)	Hoit *et al*.[59]
Utility	**Value**	**Source**
Stable AF	0.779	Berg *et al*.[60]
Minor stroke	0.641	Robinson *et al*.[61]
Major stroke	0.189	Robinson *et al*.[61]
Post-minor stroke	0.719	Hallan *et al*.[62]
Post-major stroke	0.482	Hallan *et al*.[62]
Systemic embolism	0.660	Sullivan *et al*.[63]
Minor bleed	0.776	Sullivan *et al*.[63]
Major bleed	0.598	Sullivan *et al*.[63]
Intracranial bleed	0.600	Lenert *et al*.[64]
Post-intracranial bleed	0.740	Haacke *et al*.[65]
MI	0.683	Lacey *et al*.[66]
Post-MI	0.685	Sanders *et al*.[67]
Treatment discontinuation	**Initial**	**Subsequent**
	Value (95% CI)	**Value (95% CI)**
Rivaroxaban	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]

¥Assumed to be 1 in the manufacturer's base case analysis.

*Relative risk vs placebo.

** Assumed to be equivalent to RR for rivaroxaban in manufacturer's model.

Abbreviations used in table: 95% CI, 95% Confidence Interval; AF, atrial fibrillation; MI, myocardial infarction; N/A, not applicable; NMA, network meta-analysis; RR, relative risk.

5.3.6 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.[68] 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%)		0.81 (0.61 to 1.06)	1.00	
ITT analysis: rivaroxaban versus warfarin					
Ischaemic stroke	0.41% (0.36% to 0.46%)	Warfarin arm of ROCKET AF (ITT population)	[redacted]	1.00	ROCKET AF (ITT population)
Systemic embolism	0.05% (0.04% to 0.07%)		[redacted]	[redacted]	
Minor extracranial bleed	2.54% (2.10% to 2.33%)	Warfarin arm of ROCKET AF (safety-on-treatment population)	1.04 (0.96 to 1.13)	1.00	ROCKET AF (safety-on-treatment population)
Major extracranial bleed	0.64% (0.56% to 0.68%)		1.14 (0.98 to 1.33)	1.00	
Intracranial bleed	0.20% (0.17% to 0.24%)		0.67 (0.47 to 0.93)	0.67	
MI	0.28% (0.24% to 0.33%)		0.81 (0.61 to 1.06)	1.00	

Abbreviations used in table: 95% CI, 95% Confidence Interval; ITT, intention-to-treat; MI, myocardial infarction; RR, relative risk.

ROCKET AF-based subgroup analyses

In addition to the base case and scenario analyses, the manufacturer performed subgroup analyses of: patients who were poorly controlled on warfarin; and patients who were naïve to VKA therapy. These analyses were based on the same efficacy and safety data as the base case. The application of equivalent treatment effects to patients who are VKA naïve is based on evidence from pre-specified subgroup analysis of ROCKET AF, which revealed "no significant interaction for treatment effect in the warfarin experienced and naïve patients", p = 0.420 in safety-on-treatment population (MS; pgs 69 and 145). The manufacturer provided two arguments for assuming equivalent treatment effects in the subgroup of patients who are poorly controlled on warfarin. Firstly, the manufacturer correctly highlighted that a randomised comparison of poorly controlled warfarin patients with rivaroxaban patients was not available from ROCKET AF, as the trial was not stratified by International Normalised Ratio (INR) control. Secondly, the manufacturer claimed that evidence from a randomised subgroup analysis (that grouped centres by the level of INR control achieved) revealed some consistency in the relative effect of rivaroxaban versus warfarin, across differing levels of INR control. This is discussed further in Section 5.4.5.

Aspirin

The second-line therapy common to both rivaroxaban and warfarin in the ROCKET AF based analysis is aspirin. The manufacturer calculates the RR (aspirin relative to warfarin) of all model events, with the exception of MI, using RR reduction data from a meta-analysis by Hart *et al*.[57] The RR of MI is assumed to be the same as that for aspirin relative to placebo (Table 31). This is discussed further in Section 5.4.5.

Table 31. Relative event risk with aspirin used in the ROCKET AF based analysis (RR<1 favours aspirin)

Event	RR (95% CI)	Source
Relative risk vs warfarin		
Ischaemic stroke	1.61 (1.22 to 2.08)	Hart[57]
Systemic embolism	1.61 (1.22 to 2.08)	

Minor extracranial bleed	0.59 (0.30 to 1.16)	
Major extracranial bleed	0.59 (0.30 to 1.16)	
Intracranial bleed	0.44 (0.20 to 0.96)*	
Relative risk vs placebo		
MI	0.43 (0.11 to 1.50)	Network meta-analysis, Manufacturer's NMA (safety-on-treatment population)[12]
* Statistically significant. Abbreviations used in table: 95% CI, 95% Confidence Interval; MI, myocardial infarction; RR, relative risk.		

Manufacturer's NMA-based analyses

The manufacturer conducted two further subgroup analyses in: patients receiving aspirin or no treatment; and patients receiving dabigatran. All analyses based on the NMA applied a treatment-specific RR to the baseline event risk with placebo. The baseline risk for each event associated with placebo was sourced from the literature (see Table 31) and treatment-specific RRs were calculated from the odds ratio (OR) obtained from the manufacturer's NMA as follows:

$$RR = \frac{OR}{(1 - p_{baseline}) + (p_{baseline} * OR)}$$

Table 32 summarises the baseline and RRs used for all model events in the manufacturer's NMA-based analyses.

Table 32. Treatment effectiveness parameters used in the manufacturer's NMA-based analyses

Comparison	**Event**					
	Ischaemic stroke	**Systemic embolism**	**Minor extracranial bleed**	**Major extracranial bleed**	**Intracranial bleed**	**MI**
Baseline risk (%) (95% CI)	1.14 (0.86 to 1.43)	0.13 (0.09 to 0.16)	0.61 (0.46 to 0.76)	0.12 (0.09 to 0.14)	0.03 (0.02 to 0.04)	0.49 (0.37 to 0.62)
Source	AFI[54]	AFI[54]	EAFT[55]	EAFT[55]	EAFT[55]	SAFT[56]
RRs (95% CI) vs placebo: safety-on-treatment analysis						
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RRs (95% CI) vs placebo: ITT analysis				
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]		[redacted]
Dabigatran*	[redacted]	[redacted]		[redacted]

* Assumed to be equal to rivaroxaban.

Abbreviations used in table: 95% CI, 95% Confidence Interval; ITT, intention-to-treat; MI, myocardial infarction; NMA, network meta-analysis; RR, relative risk; vs, versus.

The manufacturer assumed that the RR of all model events would be equal for dabigatran and rivaroxaban. The manufacturer argued that equivalence of dabigatran and rivaroxaban is a reasonable assumption based on the results of the manufacturer's NMA. The manufacturer's NMA indicated that there was no significant difference between the two interventions in any outcome. Moreover, the manufacturer argued that the "substantial heterogeneity" between the ROCKET AF[7]and RE-LY[9] trials prohibits the use of point estimates available from the NMA. This is discussed further in Section 5.4.5.

5.3.7 Mortality

The manufacturer's model captures both all-cause and event-specific mortality rates. All-cause mortality was taken from the life tables for England and Wales;[69] the male and female rates were averaged and converted into the quarterly risk required for the model using standard formulae.[68] All model events, with the exception of minor bleeding, systemic embolism and minor stroke, were associated with an excess risk of death, which the manufacturer assumed was independent of treatment. Therefore, data from both arms of ROCKET AF were used to calculate the risk of death associated with a life-threatening event. The risks of death in the post-major stroke, post-intracranial bleed and post-MI health states were sourced from the manufacturer's literature review. The long-term mortality risk in patients following an ischaemic stroke event was taken from an Italian study by Marini *et al*.[58] The MS states that the study by Marini *et al*.[58] was chosen as it was the only source identified that reported long-term mortality rates associated with stroke. No studies were identified that reported the long-term mortality risk associated with an intracranial bleed. Therefore, long-term mortality following an intracranial bleed was assumed to be equal to long-term mortality following a major ischaemic stroke. The long-term mortality associated with MI was taken from a study by Hoit *et al*.[59] Table 33 lists the short- (30-day) and long-term mortality risk associated with each model event.

Table 33. Event-related mortality

Event	30-day mortality risk	Source	Long-term mortality	Source
Systemic embolism	0.00%	Assumption	0.00%	Assumption
Minor stroke	0.00%	Assumption	0.00%	Assumption
Major stroke	12.58%	ROCKET AF safety-on-treatment population	2.63%	Marini *et al*.[58] Annual mortality rate from year 4 (10.1%) converted into a quarterly rate
Minor bleed	0.00%	Assumption	0.00%	Assumption
Major bleed	[redacted]	ROCKET AF safety-on-treatment population	0.00%	Assumption
Intracranial bleed	[redacted]	ROCKET AF safety-on-treatment population	2.63%	Marini *et al*.[58] Assumed to be equivalent to long-term mortality associated with ischaemic stroke
MI	[redacted]	ROCKET AF safety-on-treatment population	2.68%	Hoit *et al*.[59] Annual mortality rate of 10.3% converted into a quarterly rate

Abbreviations used in table: MI, myocardial infarction.

5.3.8 Health-related quality of life

The manufacturer identified two potentially relevant aspects to HRQoL applicable to AF patients receiving antithrombotic therapy: the utility associated with treatment; and the utility associated with events. The double-blind double-dummy nature of the ROCKET AF trial meant that it was not possible to capture utility associated with treatment. It is unclear whether the utility associated with events was collected from ROCKET AF. However, in the clarification response, the manufacturer stated that "It was felt that the QoL impact of events could be captured using values for patients who had event, such as stroke from the literature rather than trying to collect this for the patients having an event in the trial".

The manufacturer conducted a systematic review of the literature to identify studies reporting intervention or health-state-related utility values in patients with AF. The bibliographies of relevant studies identified in the review were hand searched and the review was updated in May 2011 "to include any articles published between May 2010 and May 2011" (MS; pg 170). Overall, the search identified 11 papers that underwent full data extraction; seven studies were used to inform event-related utility values in the model (Table 34). The manufacturer's review did not identify any utility values associated with MI in an AF population. Therefore, the manufacturer conducted a complementary review of the Tufts University CEA Registry, which yielded one UK-based primary study. Table 34 summarises the utility values applied to each health state, the source used, method of implementation of source data and the manufacturer's justification for the choice of source.

Table 34. Summary of quality-of-life values for cost-effectiveness analysis (adapted from MS; Table 49; pg 178)

Health state	Utility	Source	Data used	Justification
Stable AF – not on treatment	0.779	Berg *et al*.[60]	The utility reported for stable AF one year after enrolment	Based on a study identified in the systematic literature review derived using EQ-5D as per NICE reference case
Stable AF – maintained on warfarin treatment	0.779	Berg *et al*.[60]		
Stable AF – maintained on other therapy	0.779	Berg *et al*.[60]		
Stable AF – initiating warfarin treatment	0.779	Berg *et al*.[60]		
Minor stroke	0.641	Robinson *et al*.[61]	Utility value reported for mild stroke	Patient reported utility valuations in the UK, using standard gamble; only study from systematic literature review to provide values for model definitions
Major stroke	0.189	Robinson *et al*.[61]	Utility value reported for major stroke	
Post-minor stroke	0.719	Hallan *et al*.[62]	The reported post-minor stroke utility value of 0.91 is adjusted to the baseline stable AF treatment for use in the model (0.910 x 0.779 = 0.719)	Used a patient and general population reported utility valuations study in Norway as proxy
Post-major stroke	0.482	Hallan *et al*.[62]	The reported post major stroke utility value of 0.61 is adjusted to the baseline stable AF treatment for use in the model (0.610 x 0.779 = 0.482)	
Systemic embolism	0.660	Sullivan *et al*.[63]	The disutility reported for systemic embolism of –0.1199 is applied to the stable AF utility for use in the model (0.779 – 0.120 = 0.660)	EQ-5D scores adjusted for age and gender in the USA as part of a national project. Adjusted for AF population for model use
Minor bleed	0.776	Sullivan *et al*.[63]	The utility of 0.81 reported for a minor bleed is adjusted to the stable AF utility to give the utility associated with minor bleeding (0.779 x 0.810 = 0.631) This utility is only applied for 2 days of the 3 month model cycle, resulting in an overall health state utility of 0.776	
Major bleed	0.598	Sullivan *et al*.[63]	The reported utility decrement of 0.181 is applied to the baseline stable AF UTILITY (0.779 – 0.181 = 0.598)	
Intracranial bleed	0.600	Lenert *et al*.[64]	The utility associated with a central nervous system bleed	General population and physician estimates in USA used as proxy

Post-intracranial bleed	0.740	Haacke *et al*.[65]	The reported post-haemorrhagic stroke utility	Patient-reported outcomes in Germany
MI	0.683	Lacey *et al*.[66]	The utility reported for MI	UK-based primary study using EQ-5D in line with NICE reference case
Post-MI	0.685	Sanders *et al*.[67]	The reported utility of 0.880 is adjusted to the baseline utility for use in the model (0.779 x 0.88 0= 0.685)	Primary study focusing on MI survivors allowing for capture of the post-MI health state
Abbreviations used in table: AF, atrial fibrillation; MI, myocardial infarction; NICE, National Institute for Health and Clinical Excellence; USA, United States of America; UK, United Kingdom.				

Utilities were not adjusted for age and no disutility was applied to patients receiving antithrombotic treatment. The manufacturer argues that the application of a disutility associated with warfarin therapy "may not appropriate for the purposes of health technology assessments (HTAs), which are primarily concerned with health-related utility and not with convenience-related utility" (MS; pg 178). Moreover, the MS states that no evidence is available for the disutility associated with new anti-coagulation therapy. Therefore, the manufacturer assumes that the disutility associated with such treatments would be equivalent to that experienced with aspirin, that is, there is no disutility (MS; pg 179). The manufacturer considers the assumption of no disutility associated with antithrombotic therapy to be conservative in the comparisons of rivaroxaban with warfarin and with dabigatran. This is discussed further in Section 5.4.7.

5.3.9 Resources and costs

In the economic evaluation, the manufacturer identifies two key types of cost: intervention/comparator costs; and health state costs. The costs of adverse events were captured within their associated health states. The model adopted a National Health Service (NHS) and Personal Social Services (PSS) perspective and, therefore, wherever possible, unit costs were taken from NHS Reference Costs 2009/10,[70] Personal Social Services Research Unit (PSSRU)[71] and the British National Formulary 61 (BNF 61).[72] The manufacturer also conducted a systematic review of the literature to provide supplementary information on costs and resource use.

Drug acquisition costs

The costs of the interventions are presented as costs per day for the given dose. Table 35 summarises the unit and daily costs used in the manufacturer's model.

Table 35. Drug acquisition costs (adapted from MS; Table 50; pg 188)

Drug	Strength (mg)	Cost (£) (no of tabs)	Cost per tab (£)	Source for cost	Daily dose (mg)	Source for daily dose	Cost per day (£)
Rivaroxaban	20.0		[redacted]	MS	20.0	MS	[redacted]
Warfarin	0.5	1.49 (28)	0.053	BNF 61[72]	4.5	NICE clinical guideline CG362	0.12
	1.0	0.93 (28)	0.033	BNF 61[72]			
	3.0	0.95 (28)	0.034	BNF 61[72]			

	5.0	1.03 (28)	0.037	BNF 61[72]			
Aspirin	75.0	1.03 (56)	0.018	BNF 61[72]	75.0	Assumption	0.02
Dabigatran	110.0	–	–	–	220.0	Personal communication	2.52
	150.0	–	–	–	300.0		
Abbreviations used in table: BNF, British National Formulary; mg, milligram; MS, manufacturer's submission; NICE, National Institute for Health and Clinical Excellence; tab, tablet.							

Monitoring costs

Warfarin is the only treatment associated with ongoing monitoring costs, and monitoring formed the bulk of the cost associated with warfarin. To help to understand different approaches to oral anticoagulation care, data on which were not identified by the literature search, the manufacturer commissioned a survey of anticoagulation strategies in the UK. Information requested in the survey covered: INR monitoring; resource use; and setting of care. The survey found that the proportion of patients receiving care in different settings for anticoagulation services is as follows:

- Primary Care Anticoagulation Service: [redacted];
- Secondary Care Anticoagulation Service: [redacted];
- Hybrid Anticoagulation Service: [redacted].

On the basis of the results from the survey, the manufacturer assumed that warfarin monitoring took place in both primary and secondary care. Moreover, the manufacturer assumed that patients managed in hybrid clinics would receive 50% of their monitoring in primary care and 50% in secondary care, which led to the supposition that 66.45% and 33.55% of warfarin patients are managed in primary care and secondary care, respectively.

To determine the cost of a visit in primary care, the manufacturer assumed that patient consultations were split equally between GPs and nurses and that the duration of a GP consultation was 11.7 minutes, as stated in the PSSRU.[71] The cost of a visit in primary care was calculated as £27 per visit (including the £3 cost of an INR test). Secondary care costs were derived from the NHS reference costs 2009/10[70] (code 324 for anticoagulant service) by taking a weighted average of consultant and non-consultant led visits. The weightings for this calculation were derived from activity data presented in the NHS reference costs 2009/10[70] and generated costs of £47.19 for the first visit and £24.69 for subsequent visits (MS; Tables 51–53 pgs 189 and 190). NHS-sponsored patient transport services (PTS) are available for patients managed in secondary care. The manufacturer's survey revealed that only 8.55% of patients managed in secondary care use PTS. The cost per visit of the PTS used was £30.96, which was taken from the NHS reference costs 2009/10.[70]

The manufacturer's model categorised monitoring costs into the following distinct phases:

- Initiation;

- Maintenance;
- Re-initiation.

The initiation phase is the process of establishing a patient on warfarin. The cost of initiation is determined by a patient's experience of warfarin therapy. Warfarin-naïve patients require more initial visits compared with warfarin-experienced patients to ensure that their INR is under control. Based on the NHS Clinical Knowledge Summary for management of oral anticoagulation, the manufacturer assumed that warfarin-naïve patients require nine visits in the first three months.[73] By contrast, patients who are experienced with warfarin were assumed to require five visits in the first three months, based on the NICE anticoagulation therapy commissioning and benchmarking tool.[74] The manufacturer's model used a weighted average cost of initiation in primary and secondary care; average cost weighted by the number of patients who were warfarin naïve or experienced on entering the model (Table 36).

The cost of maintenance is the cost associated with subsequent monitoring of a patient who has been established on warfarin therapy. Each patient maintained on warfarin therapy is assumed to require five visits every three months, based on the NICE anticoagulation therapy commissioning and benchmarking tool.[74]

The re-initiation phase is the re-establishment of a patient on warfarin therapy after a period of discontinuation of warfarin therapy. The manufacturer has assumed that prior experience of titrating patients having discontinued warfarin therapy would be used to inform re-establishment on warfarin therapy and would therefore reduce the number of visits required. The manufacturer has assumed that seven visits, rather than nine, would be required to re-establish a patient on warfarin therapy.

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 patients treated in primary and secondary care, as indicated by the manufacturer's survey. The cost of PTS was also applied to 8.55% of patients managed in secondary care. Table 36 summarises the costs and visits associated with warfarin monitoring, as used in the manufacturer's base case analysis.

Table 36. Costs associated with the different phases of warfarin monitoring used in the manufacturer's base-case

Monitoring phase	No. of visits	Primary care cost	Secondary care cost*	Cost used in the manufacturer's base case model[¥]
Initiation	Warfarin naïve = 9 Warfarin experienced = 5	£175.50**	£168.92**	£181.29
Maintenance	5	£135.00	£123.45	£135.57
Re-initiation	7	£189.00	£172.83	£189.79

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

In the manufacturer's model, the cost of monitoring patients receiving warfarin therapy varies according to the health state of the patient. Table 37 summarises the cost of warfarin monitoring associated with each health state in the model. This is discussed further in Section 5.4.8.

Table 37. Warfarin-monitoring costs by health state

Health state	Initiation	Maintenance	Re-initiation
Anticoagulant initiation	✓		
Stable atrial fibrillation		✓	
Minor stroke			✓
Major stroke			✓
Post minor stroke		✓	
Post major stroke		✓	
Minor bleed			✓
Major bleed			✓
Intracranial bleed	✓		
Post-intracranial bleed			✓
Systemic embolism		✓	

Event and adverse event treatment costs

As discussed in Section 5.3.3, the manufacturer categorised events in the model as transient or permanent. Permanent events are those with post-event health states to account for the long-term costs and clinical consequences. Whereas transient events are those events considered to have no lasting clinical or economic sequelae and as such accrue costs in only the cycle of the event. Table 38 summarises the costs applied to each event-related health state.

The majority of cost elements were taken from the appropriate HRG codes of the National Schedule of Reference Costs 2009/10[70] for NHS trusts and Primary Care Trusts (PCTs) combined. When more than one code was considered relevant, a weighted average of the cost associated with these codes was calculated, in which the average cost was weighted by the level of activity reported for each code. For example, the unit cost for acute treatment of a systemic embolism is a weighted average of the cost associated with the codes QZ17A, QZ17B, QZ17C, where the cost is weighted by activity levels reported for each code. When costs were not available from NHS reference costs[70] or the PSSRU,[71] they were taken from the manufacturer's literature review. For example, the cost for the acute treatment of an MI was taken from the annual unit cost per patient reported in NICE clinical guideline CG48.[75]

Table 38. Event-related health state costs

Health state	Cost element	Unit cost (£)	Cost source	Reference description	Total cost (£)
Transient events					
Minor bleed	Minor bleeding: acute treatment	126.34	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined[70]	VB07Z: Accident and Emergency services. Category 2 investigation with category 2 treatment (weighted average)	126.34
Major bleed	Major bleeding: acute treatment	866.00		Cost of a gastro-intestinal bleeding treatment episode. Weighted average of codes: FZ16Z, FZ25A, FZ29Z, FZ30Z, FZ38D, FZ38E, FZ38F, FZ43A, FZ43B, FZ43C	866.00
Systemic embolism	Systemic embolism: acute treatment costs	1,658.12		Cost of non-surgical peripheral vascular disease. Weighted average of codes: QZ17A, QZ17B, QZ17C	1,658.12
Permanent events					
Minor stroke	Stroke: acute treatment	2,829.66	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined: non-elective inpatient[70]	AA22Z: Non-transient Stroke OR Cerebrovascular Accident, Nervous system infections or Encephalopathy	2,829.66
Post-minor stroke	N/A	0.00	N/A	Expert clinical opinion	0.00
Major stroke	Stroke: acute treatment	2,829.66	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined: non-elective inpatient[70]	AA22Z: Non-transient Stroke OR Cerebrovascular Accident, Nervous system infections or Encephalopathy	12,350.77
	Stroke: acute treatment. Excess bed days	210.53			
	Rehabilitation cost per day	308.94	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined[70]	VC04Z: rehabilitation for stroke (weighted average)	
Post-major stroke	Follow-on care costs per quarter	1,206.50	Nice Clinical Guideline CG92[76]	Taken from the annual cost of stroke care in subsequent years following an index event (£4,826.00)	1,206.50
Intracranial bleed	Intracranial bleeding	2,072.72	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined[70]	AA23Z: Haemorrhagic Cerebrovascular Disorders (weighted average)	6,397.87
	Rehabilitation cost per day	308.94		VC04Z: rehabilitation for stroke (weighted average)	
Post-intracranial bleed	Follow-on care costs per quarter	1,206.50	Nice Clinical Guideline CG92[76]	Taken from the annual cost of stroke care in subsequent years following an index event (£4,826.00)	1,206.50

MI	MI: acute treatment	4,448.00	NICE Clinical guideline CG48[75]	Taken from the annual unit cost per patient (£4,448)	5,277.77
	Rehabilitation	829.77	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined[70]	VC38Z: rehabilitation for acute myocardial infarction and other cardiac disorders	
Post-MI	Follow-on care costs per quarter	140.88	NICE clinical guideline CG48[75]	Taken from the annual unit cost of subsequent care per patient (£500)	140.88
Abbreviations used in table: MI, myocardial infarction; N/A, not available; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PCT, Primary Care Trust.					

The resource use associated with major stroke was supplemented with evidence from the literature and clinical opinion. The manufacturer used the average length of hospital stay after a major stroke reported in Saka *et al.*[77] of 34.4 days to calculate the number of excess bed days required for acute treatment:

No. of excess bed days for acute treatment = 34.4 – 9.72* = 24.68

* 9.72 days is the length of acute treatment accounted for by HRG code AA22Z for acute treatment of stroke.

In addition, based on clinical opinion, the manufacturer assumed that the number of days required for rehabilitation post-major stroke was 14 days (MS; pg 193).

5.3.10 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS and PSS in England and Wales. The manufacturer used a lifetime time horizon, and both costs and benefits were discounted at 3.5% per annum.

5.3.11 Model validation

The manufacturer reports that the NICE Scientific Advice Consultancy Service was consulted during development of the model. The structure and parameters of the developed model were assessed for validity by two clinical experts, one internal and one external. No declaration of interest was sought from either clinical expert. Furthermore, the methodological approach was validated by two external reviewers, who undertook extensive analysis to assess the model for internal and external validity and a further model audit was performed by an external health economist.

5.3.12 Results included in manufacturer's submission

The MS presented the results of the manufacturer's base case analysis; rivaroxaban versus warfarin using significant only data from the ROCKET AF safety-on-treatment population. Also presented were the results of four subgroup analyses, as follows:

- Rivaroxaban versus warfarin in patients poorly controlled on warfarin;
- Rivaroxaban versus warfarin in patients naïve to warfarin;
- Rivaroxaban versus aspirin and versus no treatment (placebo) – full incremental results;
- Rivaroxaban versus dabigatran.

The results of the manufacturer's base case and subgroup analyses are summarised in Table 39. The ERG notes that the manufacturer claims to have based the comparisons of rivaroxaban with aspirin, no treatment (placebo) and dabigatran on a theoretical patient population with baseline characteristics taken from Gallagher *et al*.[51] However, the results of the comparison between rivaroxaban and dabigatran reported by the manufacturer correspond with an analysis that uses the baseline characteristics of patients in the ROCKET AF clinical trial.[7] Furthermore, the ERG was unable to replicate the results of the manufacturer's comparison of rivaroxaban with aspirin and no treatment (placebo). The comparisons of rivaroxaban with aspirin and dabigatran based on the manufacturer's NMA are discussed further in Section 6. The MS presented the results of a fully incremental analysis between rivaroxaban, aspirin and no treatment (placebo) (Table 40). However, no treatment (placebo) was dominated by aspirin and is therefore not presented in the summary table.

Table 39. 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.

Table 40. 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.						

For the base case analysis, the MS presents a series of tables summarising the movement of patients through the model, the quality adjusted life years (QALYs) and costs accrued by health state and the life-years gained (LYG) and QALYs gained by clinical outcome. Tables 41 and 42 display the summary of LYG and QALYs gained by clinical outcome for rivaroxaban and warfarin, respectively.

Table 41. Summary of LYG and QALYs gained by clinical outcome for rivaroxaban (reproduced from MS; Table 79; pg 235)

Clinical outcome	LYG	QALYs gained
Total strokes	0.0623	0.0252
Total bleeds	0.2887	0.2126
Total MIs	0.0238	0.0154
Total systemic emboli	0.0051	0.0034
Abbreviations used in table: LYG, life-years gained; MI, myocardial infarction; MS, manufacturer's submission; QALY, quality adjusted life year.		

Table 42. Summary of LYG and QALYs gained by clinical outcome for warfarin (reproduced from MS; Table 80; pg 235)

Clinical outcome	LYG	QALYs gained
Total strokes	0.0618	0.0250
Total bleeds	0.2901	0.2131
Total MIs	0.0236	0.0153
Total systemic emboli	0.0071	0.0047
Abbreviations used in table: LYG, life-years gained; MI, myocardial infarction; MS, manufacturer's submission; QALY, quality adjusted life year.		

Figures 4 and 5 present the scatter plot and cost effectiveness acceptability curve (CEAC) for the manufacturer's base case analysis of rivaroxaban versus warfarin. The ERG notes that the probabilistic sensitivity analysis (PSA) accounts for the parameter uncertainty associated with all point estimates, regardless of statistical significance. The PSA conducted on the manufacturer's base case indicates that rivaroxaban was dominant in 13% of runs, dominated in 0.6% of runs and incurred more costs and QALYs in 86.6% of runs. No simulation runs reported rivaroxaban to be inferior to

warfarin. The CEAC indicates that the probability of rivaroxaban being cost effective at a willingness to pay of £20,000 and £30,000 per QALY gained is 75% and 88%, respectively.

Figure 4. Cost-effectiveness plane for rivaroxaban versus warfarin, 1,000 runs (reproduced from MS; pg 240)

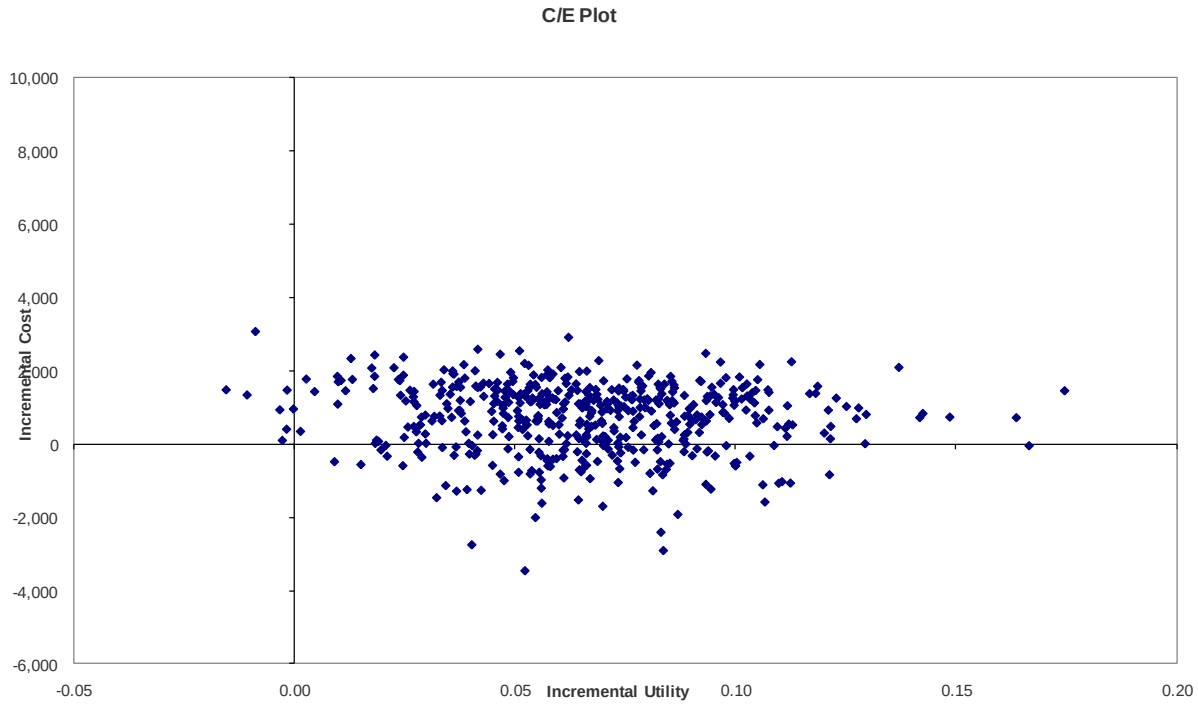
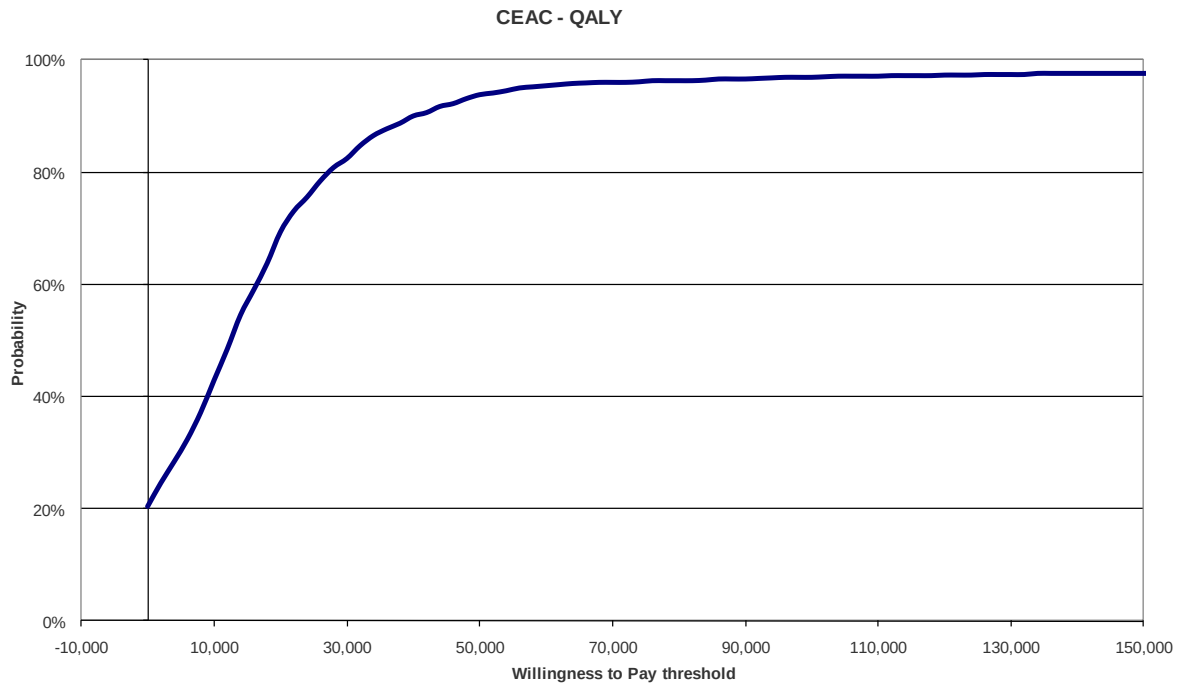


Figure 5. Cost-effectiveness acceptability curve for rivaroxaban versus warfarin, 1,000 runs (reproduced from MS; pg 240)



5.3.13 Sensitivity analyses

To assess the robustness of the ROCKET AF-based analysis; the manufacturer conducted two scenario analyses, as follows:

1. Scenario 1: Using all point estimates, regardless of statistical significance from the safety-on-treatment population analysis of ROCKET AF;
2. Scenario 2: Using only significant point estimates from the ITT population analysis of ROCKET AF.

The results of these analyses are displayed in Table 43, with the scatter plot of the ITT scenario analysis displayed in Figure 6. The ERG notes that the PSA for the point estimate analysis is identical to that of the manufacturer's base case. The results indicate robustness in the model to the choice of clinical effectiveness data.

Table 43. Base case and scenario analyses cost effectiveness results

Analysis	Technology	Total		Incremental		ICER (£)
		Costs (£)	QALYs	Costs (£)	QALYs	Incremental cost per QALY gained
ROCKET AF-based analyses						
Manufacturer's base-case	Warfarin	8,200	6.998	–	–	–
	Rivaroxaban	8,941	7.037	740	0.039	18,883
Scenario 1 (all safety-on-treatment point estimates)	Warfarin	8,200	6.998	–	–	–
	Rivaroxaban	8,834	7.071	633	0.073	8,732
Scenario 2 (ITT, significant only)	Warfarin	8,737	6.917	–	–	–
	Rivaroxaban	9,482	6.959	745	0.042	17,927
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality adjusted life year.						

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 fairly consistent across analyses, with the cost of warfarin monitoring in primary care having a major impact on all ROCKET AF-based analyses. Table 44 lists the main drivers of each analysis discovered by the manufacturer's one-way sensitivity analysis.

Figure 6. Cost-effectiveness plane for rivaroxaban versus warfarin using data from the ITT analysis of ROCKET AF, 1,000 runs (reproduced from MS; pg 243)

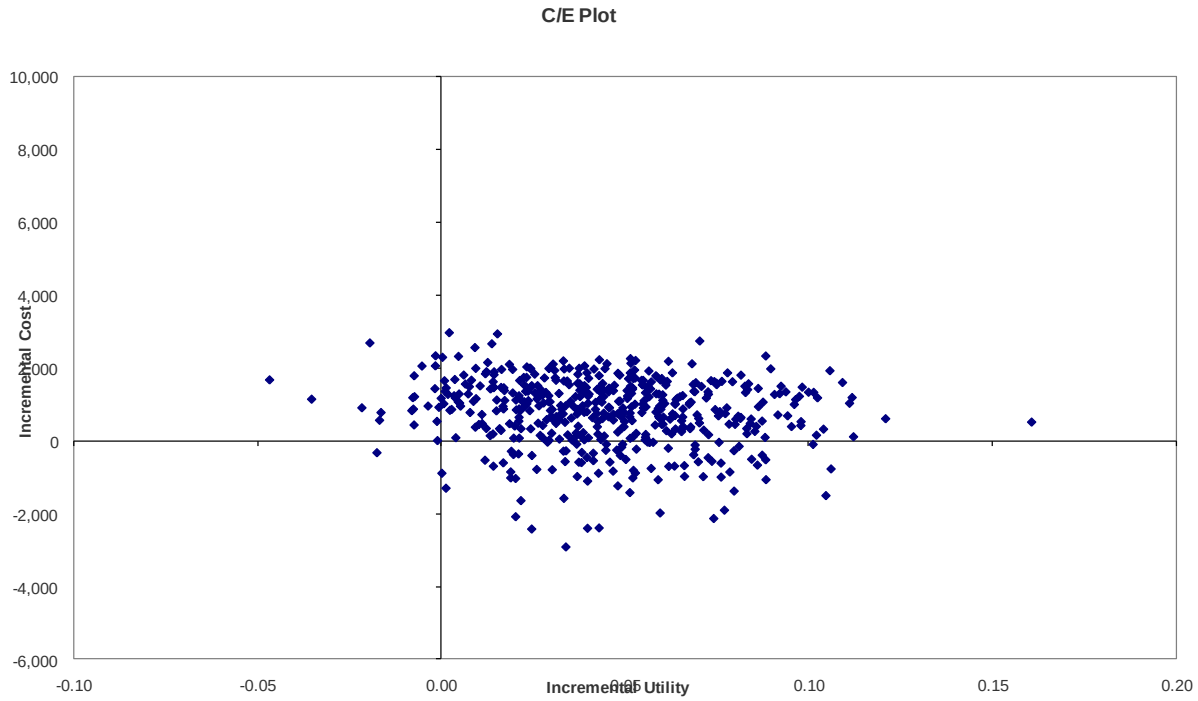


Table 44. Main cost-effectiveness drivers in each analysis

Model parameter	Base case	Scenario analyses		Subgroup analyses		
		All point estimates from safety-on-treatment population	ITT, significant only data	Poorly controlled warfarin patients	Warfarin -naïve patients	Warfarin unsuitable patients
Intracranial bleed RR for rivaroxaban	✓	–	✓	✓	✓	✓
Discontinuation rate for rivaroxaban	✓	–	–	–	✓	–
Cost of warfarin monitoring in primary care	✓	✓	✓	✓	✓	–
RR of stroke with rivaroxaban	✓	–	✓	✓	–	✓
Subsequent discontinuation rate for rivaroxaban	–	✓	–	–	–	–
No. of warfarin visits required during the maintenance monitoring phase	–	✓	–	–	✓	–
Subsequent discontinuation rate for warfarin	–	✓	–	–	–	–
RR of mortality following stroke	–	–	–	–	–	✓
Abbreviations used in table: ITT, intention-to-treat; RR, relative risk.						

5.4 Critique of the manufacturer's economic evaluation

The manufacturer provided an economic model constructed in Microsoft© EXCEL with Visual Basic for Applications, along with a written submission of the economic evaluation. In addition to these, following the clarification requests of the ERG, the manufacturer provided two revised models. The first revised model incorporated:

- An age adjustment of bleeding risk;
- An age adjustment of utility;
- A comparison of rivaroxaban with the dabigatran sequence regimen;
- Lower monitoring costs for warfarin.

The second revised model implemented a ROCKET AF-based analysis of rivaroxaban versus warfarin, with treatment effect disaggregated by INR levels.

The ERG considers the manufacturer's original model to be generally well constructed, highly transparent and easy to navigate. The manufacturer's revised models are of similar quality, with the data inputs used for each aspect of the analysis clearly labelled and named. However, the ERG notes that the comparison of rivaroxaban with the dabigatran sequence regimen, received as part of the clarification response, returned error messages when run (due to the presence of an error in the dabigatran transition matrices).

5.4.1 NICE reference case checklist

Tables 45 and 46 summarise the ERG's assessment of the manufacturer's economic evaluation. The manufacturer's base case economic evaluation satisfies most of the requirements set out in the reference case 'Guide to the Methods of Technology Appraisal'[10] (Table 45). However, the MS did not fully address the decision problem outlined in the NICE final scope.[8] The scope specified the inclusion of moderate to high risk patients; however, despite estimates of treatment effectiveness in patients considered to be moderate to high risk being available from the manufacturer's NMA, the manufacturer did not present a comparison of rivaroxaban with warfarin in this population. Furthermore, the scope specified an assessment of rivaroxaban versus aspirin in the subgroup of patients unsuitable for warfarin. However, the trials used to inform the NMA included trials comparing aspirin with warfarin, suggesting that the patient population examined would be eligible for therapy with warfarin. The scope also listed transient ischaemic attack (TIA) as an outcome of interest, which the manufacturer did not include in their economic evaluation.

Table 45. NICE reference case

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by the National Institute for Health and Clinical Excellence	Broadly yes, but did not adequately address the following: • The comparison of rivaroxaban and warfarin in moderate to high risk patients as 87% of patients included in ROCKET AF had a $CHADS_2$ score of 3 or more; • Aspirin in the warfarin unsuitable population as the data used for the aspirin comparison were sought from trials that compared warfarin with aspirin, the patient populations of which are likely to have been suitable for therapy with warfarin; • TIA is a listed outcome in the scope but was excluded from the analysis.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	The manufacturer used evidence from a systematic review for the base case analysis comparing rivaroxaban and warfarin in patients suitable for anticoagulation, those poorly controlled and those who are warfarin naïve; The manufacturer also performed a network meta-analysis for those patients who were suitable for anticoagulation.
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, the sources were derived from published literature which used standardised and validated instruments.
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	No A variety of literature sources were used to identify health state utilities values, some used patients preferences whilst others used a representative sample of the public.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

Sensitivity analysis	Probabilistic sensitivity analysis	Yes The manufacturer carried out sensitivity analysis, scenario analysis and probabilistic sensitivity analysis.
Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); NHS, National Health Service; QALY, quality adjusted life year; TIA, transient ischaemic attack.		

Table 46. Phillips checklist[78]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2:Statement of scope/perspective	The ERG notes that: • TIA was not included as a model event; • The high risk population of the ROCKET AF trial (87% had a $CHADS_2$ score of 3 or more) was used to inform the comparison between rivaroxaban and warfarin; • The subgroup of patients unsuitable for therapy with warfarin was not addressed in the MS. The manufacturer used data from trials that assessed warfarin versus aspirin, and the ERG considers that the patient population of these trials are likely to be suitable for therapy with warfarin.
S3: Rationale for structure	The ERG considers the model to be well constructed and the manufacturer justified why they adopted the approach they took for modelling the decision problem.
S4: Structural assumptions	The ERG considers the model to be well constructed. However the ERG considers it important to note: • Post-MI mortality was sourced from an old study that does not reflect the advances made in treating post MI patients; • The exclusion of a post-systemic embolism health state does not fully account for the increased risk of stroke after an embolic event; • The aggregation of major bleeding with gastrointestinal bleeding may bias the model in favour of rivaroxaban; • The number of visits required by patients who were within recommended INR levels was not disaggregated from the number of visits required by those who were outside recommended INR levels; • The monitoring costs of re-initiation with warfarin were double-counted; • The suspension of the risk of further events for the subsequent model cycle following an event may bias the model towards the least effective treatment.
S5: Strategies/comparators	All relevant comparators were included; However, the ERG does not agree with the cost minimisation approach taken by the manufacturer when comparing rivaroxaban with dabigatran.
S6: Model type	Correct, cost utility analysis.
S7: Time horizon	30 years is sufficient.
S8: Disease states/pathways	The ERG agrees with the pathways/health states modelled. However, the ERG notes that TIA, dyspepsia and a post-systemic embolism health state were not included and gastrointestinal bleeding was aggregated with all major bleeding.
S9: Cycle length	The ERG considers three months to be a reasonable cycle length to capture the consequences of model events.
Data	
D1: Data identification	Data were systematically sourced, clearly described and justified by the manufacturer.
D2: Premodel data analysis	Conversion of yearly rates to quarterly probabilities conducted using standard formulae[68].

D2a: Baseline data	Baseline data were taken from the warfarin arm of the ROCKET AF trial for the ROCKET AF-based analysis and from placebo data from the literature for the NMA-based analysis. A half cycle correction was not included, because of the short cycle length (three months) used.
D2b: Treatment effects	For the ROCKET AF-based analysis, RRs of rivaroxaban compared with warfarin were applied in the model; only statistically significant outcomes were used in the base case, and an RR of 1 was assumed for non-significant treatment effects For NMA-based analysis, odds ratios from the Manufacturer's NMA were converted into RRs for use in the model.
D2d: Quality of life weights (utilities)	Derived from literature and clearly referenced.
D3: Data incorporation	With the exception of the incorporation of aspirin treatment effects in the ROCKET AF-based analysis, the manufacturer clearly described how data were used in the model.
D4: Assessment of uncertainty	The assessment of sensitivity was thorough and robust.
D4a: Methodological	The ERG suggested that the manufacturer adjust utilities and bleeding risk by age. The manufacturer carried out the requested analysis and reported the result of these adjustments to the safety-on-treatment point estimate analysis. However, the manufacturer did not adjust the model to include a post-systemic embolism health state and dyspepsia, as requested.
D4b: Structural	The manufacturer described deterministic sensitivity analysis and scenario analysis in detail.
D4c: Heterogeneity	Heterogeneity was partially addressed by the analysis of different subgroups of patients (i.e., poorly controlled warfarin and warfarin naïve patients). Ideally, the disaggregation of patients by level of INR control in the model should be implemented to fully account for the heterogeneity across patients treated with warfarin.
D4d: Parameter	Probabilistic sensitivity analysis was done to the satisfaction of the ERG.
Consistency	
C1: Internal consistency	The model seems to be mathematically sound with no obvious inconsistencies.
C2: External consistency	The results of the model are applicable to high-risk patients mainly for the ROCKET AF data and moderate to high-risk patients if different baseline characteristics are used. However, no conclusions can be drawn for those that are unsuitable for warfarin based on the current model. No comparisons were made with other studies.
Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; INR, International Normalised Ratio; NMA, network meta-analysis; MI, myocardial infarction; MS, manufacturer's submission; RR, relative risk; TIA, transient ischaemic attack.	

5.4.2 Interventions and comparators

The ERG is satisfied that all comparators specified in the final scope issued by NICE[8] have been included in the manufacturer's economic evaluation. However, the ERG notes that the manufacturer's economic evaluation does not account for sequential treatment with rivaroxaban and warfarin or dabigatran and warfarin. As discussed in Section 4.2.6, based on expert opinion, the ERG believes that patients who discontinue therapy with rivaroxaban or dabigatran may be treated with warfarin.

The NICE final scope[8] specifies that aspirin be considered as a comparator for rivaroxaban in patients who are not suitable for therapy with warfarin. The ERG notes that the clinical effectiveness data for aspirin used in the manufacturer's NMA are based on randomised controlled trials of warfarin versus aspirin (MS; pg 85). Therefore, the patient population of these trials are likely to be suitable for

therapy with warfarin. Consequently, the ERG considers that the question of rivaroxaban versus aspirin in a patient population unsuitable for warfarin has not been addressed in the MS.

5.4.3 Population

The proposed indication for rivaroxaban is the "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack". As discussed in Section 3.1, the ERG notes that the population of ROCKET AF is generally at a higher risk of stroke than the population specified in the NICE final scope.[8] The largest proportion of patients enrolled in the ROCKET AF trial had a $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA [doubled]) score of 3+ (87% of patients enrolled), whereas only three (0.02%) patients had a $CHADS_2$ score of 1. The ERG notes there is an absence of direct evidence regarding the efficacy of rivaroxaban in the lower risk AF population. However, the manufacturer argues that there is evidence that the relative effect of treatment will be consistent across baseline risk of stroke or systemic embolism. The manufacturer refers to the subgroup analyses of patients grouped by $CHADS_2$ scores carried out in ACTIVE A,[79] BAFTA,[80] AMADEUS,[81] and RE-LY.[9] These analyses revealed a consistent relative effect of the antithrombotic treatments considered in each trial, across populations of patients with different $CHADS_2$ scores. The ERG agrees with the manufacturer's proposition that relative treatment effect will in all likelihood be consistent across patient populations of different risk. However, the economic impact of treatment will vary across populations because of the extended period of treatment and the number of events avoided. Furthermore, the ERG considers that the manufacturer's proposition of consistent relative treatment effect would extend to allow an adjusted indirect comparison between ROCKET AF[7] and RE-LY.[9]

As discussed in Section 4.3.1 the ERG notes that the time in therapeutic range (TTR) seen in ROCKET AF is lower than that which would expected of a UK population. The ERG is concerned that this disparity in TTR may bias the ROCKET AF-based analysis against warfarin. As part of the clarification process, the ERG requested [redacted]. The manufacturer provided the requested data (Table 13, Section 4.3.3) and the ERG has used these data to perform an exploratory subgroup analysis into the impact of using [redacted] data to inform a comparison of rivaroxaban and warfarin, the results of which are displayed in Section 6.

5.4.4 Model structure

The ERG considers a Markov model to be an appropriate choice for modelling the chronic condition of AF. The manufacturer chose a cycle length of three months "To enable the capture of short-term events (e.g. treatment related adverse events) and their acute impact on costs and clinical outcomes" (MS; pg 141). Therefore, only one event per three month cycle would be permitted due to the

Markovian nature of the model. The manufacturer acknowledged that, in reality, patients may experience more than one event in three months, but clinical opinion considered that the probability of experiencing more than one event in three months would be low. The ERG agrees that the assumption of one event per model cycle is a necessary and reasonable assumption. However, the ERG notes 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.

In addition to this, the ERG considers it important to note the following aspects of the model structure (each point is subsequently discussed in more detail):

- The omission of TIA as an outcome;
- The aggregation of gastrointestinal bleeding with any major extracranial bleeding;
- The exclusion of gastrointestinal adverse effects, such as dyspepsia;
- The absence of a post-systemic embolism health state;
- The age adjustment of event risks;
- The re-initiation of primary therapy;
- Treatment discontinuation.

TIA

The final scope issued by NICE[8] listed TIA as an outcome of interest. However, the manufacturer omitted this outcome from the economic analysis. The ERG requested clarification regarding the rationale for omission of TIA. The manufacturer stated that TIA was excluded from the analysis because of the low event rate observed in ROCKET AF. The number of events in each arm of ROCKET AF, which were provided in the clarification response, were [redacted] and [redacted] in the rivaroxaban and warfarin arms, respectively. The ERG notes that the event rate for systemic embolism is lower than that of TIA and yet systemic embolism was accounted for in the economic model. However, given that the TIA event rate is higher with warfarin than rivaroxaban, the omission of this outcome is likely to be conservative in the base case analysis. Moreover, results from the manufacturer's NMA indicate that rivaroxaban is associated with a lower risk of TIA than warfarin, aspirin or placebo, although none of the differences between treatments reach statistical significance (Table 47).

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 provided no rationale for the difference between rivaroxaban and warfarin in gastrointestinal bleeding. 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 to include dyspepsia on the basis that dyspepsia is not an adverse event associated

with rivaroxaban. As discussed in Section 4.3.4, the ERG accepts that dyspepsia is unlikely to be an issue with rivaroxaban, as it is with dabigatran, because rivaroxaban does not require the active drug coating used in dabigatran. Therefore, in the comparison of rivaroxaban with dabigatran, the exclusion of dyspepsia from the manufacturer's model may be considered to bias the analysis against rivaroxaban. However, the ERG expects the impact of this bias to be low, since the disutility and costs associated with dyspepsia are expected to be small.

Post-systemic embolism health state

As discussed in Section 5.3.3, systemic embolism is classified as a temporary event and as such does not have an associated post-event health state. The ERG notes that the inclusion of a post-systemic embolism health state may more accurately capture the costs and consequences of a systemic embolism. The ERG is particularly concerned that the increased risk of further embolic events, such as stroke, would not be captured. The ERG accepts that the costs associated with a post-systemic embolism state would be difficult to capture due to the highly variable consequences associated with systemic embolism. However, based on expert opinion, the ERG notes that the higher risk of stroke should be accounted for following a systemic embolism. In the ROCKET AF-based analyses, the ERG notes that patients are not exposed to a higher risk of ischaemic stroke following an embolic event (i.e., minor/major stroke), as these patients are considered high risk at baseline. However, in the NMA-based analyses, patients who experience a minor or major stroke are then exposed to a higher risk of ischaemic stroke (discussed in more detail in Section 5.3.3). The ERG considered that the post-minor stroke health state would make a suitable approximation of a post-systemic embolism health state, as no additional stroke-related costs are applied to patients in the post-minor stroke health state and the utility value seemed reasonably akin to what would be expected of patients after a systemic embolism. Therefore, the ERG adapted the manufacturer's model to transition patients into post-minor stroke health state following a systemic embolism. The influence of this change on the ICERs of the NMA-based analyses is displayed in Section 6 and Appendix 9.3.

Age adjustment of event risks

The manufacturer has adjusted the risk of stroke and systemic embolism by age, using the Framingham risk equations.[52] The ERG notes that the Framingham risk equations may underestimate cardiovascular risk, particularly in patients with type 2 diabetes;[83] 40% of patients in ROCKET AF were diabetic. However, the ERG notes that the alternative RISK scores: QRISK and ASSIGN have not been validated.[84]

The manufacturer has assumed that the risk of bleeding is independent of time and as such has not adjusted the baseline risk of bleeding by age. It is unclear what evidence this assumption is based on. As part of the clarification process, the ERG requested that bleeding risk be adjusted by age, based on the evidence presented in the SAFE study.[85] The manufacturer amended the model to incorporate

adjustment for patients aged 65 and over (Table 48), normalised to a 73-year-old population and assuming that the relative rate of gastrointestinal bleed is applicable to all bleed types.

Table 48. Relative rate of gastrointestinal bleed by age[85]

Age	Gastrointestinal bleed (rate at age)	Normalised rate
65	1.0	0.83
70	1.2	1.00
80	1.6	1.30
90	1.9	1.60

The result of this adjustment, based on the safety-on-treatment point estimate analysis, was presented in the manufacturer's clarification response. The ICER decreased by £473 (unadjusted ICER £8,732, adjusted ICER £8,259). The ERG conducted a parallel analysis using the relative rate of gastrointestinal bleeding and the relative rate of intracranial bleeding, also available from Hobbs *et al*.[85] (converted into risks for use in the model). The ERG's analysis yielded a decrease in the ICER of £396, which is largely in agreement with the manufacturer's analysis. The impact of the adjustment of bleeding risk by age on the manufacturer's base case and other analyses is presented in Section 6 and Appendices 9.2 and 9.3.

Re-initiation of primary therapy

The MS states that "AF patients who experience an embolic event and come under the care of a physician will be placed back on to anti-thrombotic therapy" (MS; pg 161). However, the manufacturer's model does not allow patients experiencing a systemic embolic event to re-initiate primary therapy. The ERG accepts the manufacturer's rationale for re-initiating patients on antithrombotic therapy following a bleeding event. However, the ERG considers that, as a systemic embolism is an embolic event that will result in a higher risk of stroke, patients would be more likely to be re-initiated on antithrombotic therapy after a systemic embolism. As discussed above, the ERG used the post-minor stroke health state as a proxy for a post-systemic embolism health state. The ERG notes that all patients in the post-minor stroke health state are re-initiated onto their primary therapy, regardless of their therapy status prior to the event.

Treatment discontinuation

In the model, the manufacturer assumed that aspirin, dabigatran and placebo have the same probability of discontinuation as that observed in ROCKET AF for rivaroxaban. Assuming equivalent rates of discontinuation led to the initial discontinuation rate of aspirin being higher than that of warfarin, which contradicts evidence from the BAFTA trial.[80] As discussed in Section 4.5, the ERG's NMA also incorporated discontinuation as an outcome. The ERG calculated RRs (relative to warfarin) of discontinuation in the first three months of treatment of 0.59, 1.32 and 1.04 for aspirin, dabigatran and rivaroxaban, respectively. Similarly, the ERG calculated the quarterly RRs of subsequent discontinuation to be 0.58, 1.34 and 1.04 for aspirin, dabigatran and rivaroxaban,

respectively. For the NMA-based analyses, these RRs were applied to the initial and subsequent risks of discontinuation with warfarin to give initial and subsequent discontinuation risks for aspirin, dabigatran and rivaroxaban (Table 49). The impact of employing discontinuation rates derived from the ERG's NMA on analyses based either on the manufacturer's NMA or on the ERG's NMA is presented in Section 6 and Appendix 9.3.

Table 49. Discontinuation rates derived from the ERG's NMA

Intervention	Initial discontinuation rate	Subsequent discontinuation rate
ASA (aspirin)	4.7%	2.6%
Dabigatran	10.6%	6.0%
Rivaroxaban	9.2%	4.6%
Abbreviation used in table: ASA, acetylsalicylic acid.		

5.4.5 Treatment effects

The ERG has identified the following points for consideration relating to the manufacturer's approach to the implementation of treatment effects in the economic model and incorporation of the treatment effects estimated by the ERG's NMA (each of which is discussed in detail below):

1. The use of data from the safety-on-treatment population in the ROCKET AF-based analysis;
2. The lack of differentiation in the treatment effect of warfarin based on level of INR control;
3. The risk of MI associated with aspirin in the ROCKET AF-based analysis;
4. Incorporation of the ERG's NMA/adjusted indirect comparison results;
5. The cost minimisation approach used for the comparison of rivaroxaban with dabigatran.

Use of data from the safety-on-treatment population in the ROCKET AF-based analysis

The manufacturer has used data from the safety-on-treatment population rather than the ITT population to inform the efficacy estimates used in the base case analysis. In the clarification response, the manufacturer stated that the ITT population of ROCKET AF includes a prolonged "off treatment" period during which patients receive open-label antithrombotic therapy and so data from the ITT population of ROCKET AF is not comparable with ITT data from other trials. The ERG notes that [redacted] of rivaroxaban patients moved onto open-label VKA and were followed for a median of 117 days off randomised treatment. Therefore, the ERG accepts that data from the safety-on-treatment population of ROCKET AF provides an unbiased estimate of the relative efficacy of rivaroxaban compared with warfarin. However, the ERG notes that it is likely in clinical practice that patients discontinuing therapy with rivaroxaban would be treated with warfarin. Therefore, the ITT population may provide results that reflect clinical effectiveness in real-life clinical practice.

No differentiation between treatment effects by INR control

In the ROCKET AF-based analysis, the treatment effect associated with warfarin is implemented as the baseline risk of events. The manufacturer's model does not adjust the treatment effect of warfarin based on a patient's level of INR control. Instead, the overall event rates observed in ROCKET AF, which are from a patient population with differing levels of INR control, are applied. As part of the clarification process, the ERG requested that the manufacturer conduct a scenario analysis incorporating different treatment effects for patients within, above and below TTR, as outlined in the model. The manufacturer conducted two scenario analyses based on the safety-on-treatment point estimate analysis. The first analysis adjusted for treatment effect by TTR observed in ROCKET AF with 55.16% of patients within range, [redacted]% below and [redacted]% above range. The second analysis assumed that patients were poorly controlled on warfarin, with different distributions among within (40%), below (37%) and above (23%) range; distributions based on data from Gallagher *et al*.[86] The results of these analyses, as supplied by the manufacturer, are presented in Tables 50 and 51.

Table 50. Results of manufacturer's adjusted base case analysis

Trial population (safety-on-treatment – point estimates)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Warfarin based on the ROCKET AF trial safety-on-treatment data (point estimates)	8,200	9.221	6.998	–	–	–	–
Rivaroxaban based on the ROCKET AF trial safety-on-treatment data (point estimates)	8,834	9.308	7.071	633	0.087	0.073	8,732
TTR distribution taken from ROCKET AF							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]							

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality adjusted life year; TTR, time in therapeutic range; vs, versus.

Table 51. Results of manufacturer's adjusted analysis of patients poorly controlled on warfarin

Patients poorly controlled (safety-on-treatment – point estimates)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Warfarin based on the ROCKET AF trial safety-on-treatment data – poor control	10,423	9.221	6.998	–	–	–	–
Rivaroxaban based on the ROCKET AF trial safety-on-treatment – poor control	8,834	9.308	7.071	–1,589	0.087	0.073	Rivaroxaban dominates
TTR distribution taken from Gallagher *et al*.[86]							
[redacted]							
[redacted]							

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality adjusted life year; TTR, time in therapeutic range; vs, versus.

The manufacturer has expressed concern that the data used to inform these scenario analyses are not based on randomised cohorts and recommends that the results are treated with caution. Clinical advice received by the ERG suggested that poor INR control can be considered a proxy for poor compliance. Consequently, the results of an analysis comparing poorly controlled warfarin patients with all rivaroxaban patients would be biased towards rivaroxaban. Conversely, an analysis comparing well-controlled warfarin patients with all rivaroxaban patients would be biased against rivaroxaban. The ERG notes that, as the results of both analyses are used in the manufacturer's scenario analyses, it is not possible to establish a definite direction of bias.

The ERG notes that in the manufacturer's revised model, on which these analyses are based, the effect of treatment differs for patients who are above and below the recommended INR. The data used to inform these analyses have not been provided to the ERG in any other form, and the ERG was, therefore, unable to validate the derivation of these treatment effects. However, the ERG agrees with

the manufacturer that the results of the above scenario analyses should be treated with caution, due to the unquantifiable bias associated with any analysis upon which these treatment effects are based.

MI risk associated with aspirin in the ROCKET AF-based analysis

As discussed in Section 5.3.5, aspirin is the second-line therapy for rivaroxaban and warfarin in the ROCKET AF-based analyses. Analyses based on ROCKET AF use a baseline risk of events with warfarin and apply the relative effect of treatment (compared to warfarin) to this baseline risk. The ERG notes that, with the exception of MI, the risk of any event for patients treated with aspirin in the ROCKET AF-based analysis is relative to warfarin. The risk of MI for patients receiving aspirin is relative to placebo, as it is taken from the manufacturer's NMA. The ERG considers that for analysis based on ROCKET AF it would be more consistent to apply a risk of MI in aspirin patients that is relative to warfarin. The ERG calculated this risk to be 1.34, using the placebo-based RRs of the manufacturer's NMA for warfarin and aspirin, as follows:

$$\frac{RR_{MI\_aspirin\_vs\_placebo}}{RR_{MI\_warfarin\_vs\_placebo}} = \frac{p_{MI\_aspirin} / p_{MI\_placebo}}{p_{MI\_warfarin} / p_{MI\_placebo}} = \frac{p_{MI\_aspirin}}{p_{MI\_warfarin}} = RR_{MI\_aspirin\_vs\_warfarin}$$

The influence of this adjustment is presented in Section 6.

Incorporation of the ERG's NMA/adjusted indirect comparison results

As discussed in Section 4.5, the ERG considers the heterogeneity present in the manufacturer's NMA to be substantial. The ERG conducted an exploratory NMA, based on a network of trials exclusively considering the treatments of interest listed in the NICE final scope.[8] The results of this exploratory analysis and the results of the manufacturer's NMA for outcomes required by the economic model are displayed in Table 52. Dabigatran 110 mg (twice daily) was not assessed in the ERG's NMA, as this dose would only be used as part of the sequential regimen specified by the European Medicines Agency[81] and the manufacturer's original model was not set up to incorporate the sequential regimen. The effect of using the ERG's NMA results to inform the comparison of rivaroxaban with dabigatran and with aspirin is discussed further in Section 6 and Appendix 9.3.

Table 52. Comparison of results from the manufacturer's NMA and the ERG's NMA

Technology	Event					
	Ischaemic stroke	Systemic embolism	Minor extracranial bleed	Major extracranial bleed	Intracranial bleed	MI
Manufacturer's NMA: OR (95% CI) vs placebo						
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

150 mg	[redacted]	[redacted]	[redacted]			
ERG's NMA: OR (95% CI) vs placebo						
Rivaroxaban	0.28 (0.13 to 0.49)	0.18 (0.02 to 0.73)	1.75 (1.23 to 2.47)	2.42 (0.76 to 6.16)	6.25 (0.25 to 40.19)	0.29 (0.01 to 1.49)
Aspirin	0.49 (0.19 to 0.96)	0.76 (0.04 to 3.67)	0.95 (0.50 to 1.65)	1.45 (0.39 to 3.95)	4.28 (0.12 to 27.50)	0.46 (0.01 to 2.39)
Dabigatran 150 mg	0.24 (0.11 to 0.43)	0.49 (0.05 to 1.78)	1.49 (1.05 to 2.08)	2.31 (0.73 to 5.85)	3.90 (0.15 to 25.61)	0.51 (0.01 to 2.63)
Abbreviations used in table: 95% CI, 95% Confidence Interval; ERG, Evidence Review Group; MI, myocardial infarction; NMA, network meta-analysis; OR, odds ratio; vs, versus.						

As highlighted in Section 4.5, the results of the ERG's NMA display a general trend in favour of dabigatran for the outcomes of ischaemic stroke, minor/major extracranial bleeding and intracranial bleeding, whereas rivaroxaban appears to be better at preventing systemic embolism and MI. This is in agreement with the results of the manufacturer's NMA, as discussed in Section 4.4.7. However, as discussed in section 4.5, there is a statistically significant ($p < 0.05$) imbalance in the number of patients with prior MI at baseline; with 16.6% and 18.0% of rivaroxaban and warfarin patients respectively, having prior MI at baseline (MS; pgs 46-47). The ERG considers that this may bias the treatment effect in MI reduction estimated from the indirect comparison in favour of rivaroxaban. The ERG has conducted an exploratory analysis to investigate the effect of assuming equivalence in MI prevention between dabigatran and rivaroxaban on the ICER; the treatment effect estimated for dabigatran in the prevention of MI is also applied to rivaroxaban. The result of this exploratory analysis on the NMA-based analysis is further discussed in section 6.

The manufacturer presented the argument that the substantial heterogeneity between the ROCKET AF and RE-LY trials prohibited a meaningful indirect comparison. However, the ERG notes that the manufacturer's case for extending the results of the ROCKET AF-based analysis to a broader, lower risk population is founded on the proposition that the relative effect of treatment will not significantly differ across populations of different risk. The ERG considers that this argument would extend to the comparison of the relative effect of treatment between ROCKET AF and RE-LY. As discussed in Section 4.5, the ERG used an adjusted indirect comparison to estimate the relative treatment effect of rivaroxaban versus dabigatran 150 mg (twice daily). The results of this exploratory analysis agree with those seen in the manufacturer's and ERG's NMA.

Cost minimisation approach used for the comparison with dabigatran

The comparison of rivaroxaban and dabigatran is based on the results of the manufacturer's NMA and uses a cost minimisation approach. The manufacturer's rationale for assuming equal efficacy of rivaroxaban and dabigatran is that no significant difference was observed for any of the outcomes assessed in the manufacturer's NMA. The ERG notes that both significant and non-significant outcomes of the NMA are used to inform the comparison of rivaroxaban with aspirin and with no

treatment. The ERG does not accept that significance is a prerequisite for the use of point estimates in the model and considers that non-significant point estimates may be used provided the uncertainty associated with such estimates is accounted for with full PSA. Hence, for consistency between comparisons, the ERG requested that the manufacturer provide an analysis, and accompanying PSA, based on the point estimates obtained from the manufacturer's NMA. The manufacturer provided the results of the requested analysis (Table 53) using the sequential regimen for dabigatran (switch from dose of 150 mg twice daily to 110 mg twice daily at age 80) specified in the European Medicines Agency licence.[81] The manufacturer's analysis also incorporated age-adjusted bleeding risk and utility. The ERG notes that the revised model provided by the manufacturer that incorporated the comparison with the dabigatran sequential regimen was not operational (i.e., returned error messages when the dabigatran sequential analysis was run). Moreover, the use of a sequential treatment regimen for dabigatran was not available in the manufacturer's original model. However, the ERG conducted a parallel analysis using the point estimates of dabigatran 150 mg (twice daily) obtained from the manufacturer's NMA. The results of this analysis are presented in Section 6.

Table 53. Results of manufacturer's analysis of rivaroxaban versus dabigatran using point estimates obtained from the manufacturer's NMA

Manufacturer's analysis (includes age-adjusted bleeding risk and utility)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Dabigatran (sequential) based on NMA data	13,241	9.048	6.461	–	–	–	–
Rivaroxaban based on NMA data	12,430	9.049	6.463	–811	0.001	0.001	Rivaroxaban dominates

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

5.4.6 Mortality

The ERG considers that all events associated with an immediate and long-term higher risk of death have been accounted for in the manufacturer's model. The ERG agrees with the manufacturer that the risk of death is independent of treatment. However, the ERG notes that the manufacturer has used the long-term risk of death associated with MI reported in a paper from 1986.[59] Hoit *et al.*[59] report the post-discharge one-year risk of death in young (<45 years), middle-aged (46 to 70 years) and elderly (>70 years) patients who have previously experienced an MI. Given advances in available treatments, the ERG considers that the risk of death reported in the study by Hoit *et al.*[59] may no longer be representative of the risk of death for MI patients in today's settings. Moreover, the manufacturer has

used the risk of death associated with middle-aged patients (annual risk of 10.3%), rather than elderly patients (annual risk 24.4%), despite an average age of 73 years being used in the manufacturer's model.

The ERG identified a randomised controlled trial comparing high dose atorvastatin verses usual-dose simvastatin in secondary prevention following MI; the IDEAL study by Pedersen *et al*.[87] This study was conducted in Northern Europe and reported an annual post-MI mortality rate of 1.07%; there was no difference in mortality between treatments. Therefore, the ERG converted the annual mortality rate into a quarterly probability of 0.268% for use in the model. The effect of this adjustment is discussed in Section 6.

5.4.7 Health-related quality of life

The ERG considers the manufacturer's literature searches around HRQoL to be comprehensive and is confident that no studies have been missed. The manufacturer has assumed that the utility of patients does not vary with treatment and regards this assumption as conservative, particularly in the comparisons of rivaroxaban with warfarin and with dabigatran. Clinical advice received by the ERG considered the assumption of no disutility associated with treatment to be reasonable, due to an absence of evidence on the disutility associated with rivaroxaban. However, the ERG's clinical advisor did not agree with the manufacturer that this was a conservative assumption when comparing rivaroxaban with warfarin. Furthermore, the ERG notes that treatment discontinuation in ROCKET AF as a result of treatment-related side effects is higher in patients randomised to rivaroxaban than in those randomised to warfarin (8.33% with rivaroxaban vs 6.98% with warfarin; MS; pg 60).

As part of the clarification process, the ERG asked the manufacturer to incorporate age-adjusted utilities into the main analysis. The manufacturer provided the results of the age adjustment to the scenario analysis of the safety-on-treatment population using point estimates regardless of significance. The ICER increased by £688. The ERG conducted a parallel analysis that adjusted the manufacturer's model for age at baseline; the effect of this adjustment on the ICERs of the ROCKET AF-based and NMA-based analyses is displayed in Section 6 and Appendices 9.2 and 9.3.

5.4.8 Resources and costs

The manufacturer presented a thorough and accurate calculation of all costs required for the economic model. The majority of costs were sourced from NHS reference costs 2009/10[70] and the ERG is confident that the appropriate HRG codes were used throughout. Where there was insufficient information provided in the NHS reference costs or the PSSRU, the manufacturer used evidence from a systematic review of the resource and cost literature, conducted in support of the submission. The

ERG agrees that the manufacturer used the most appropriate literature sources to supplement the resource and cost information required for the economic model.

The information provided by the NHS reference costs,[70] PSSRU[71] and the manufacturer's literature review did not provide sufficient information of the management of anticoagulation in the UK. However, the manufacturer had commissioned a survey to investigate the current anticoagulation management practices of PCTs across the UK.[88] The results of this survey were used to inform the ratio of management in primary and secondary care and the proportion of patients using the NHS-sponsored PTS.

However, the ERG considers it important to note the following points in relation to the manufacturer's implementation of resources and costs (each point is subsequently discussed in more detail):

- Double counting of re-initiation costs;
- Inclusion of fixed costs of monitoring;
- No disaggregation of costs by INR control.

Double counting of re-initiation costs

As discussed in Section 5.3.8, the monitoring of warfarin is categorised into three phases: initiation; maintenance; and re-initiation. For the base case analysis, the manufacturer calculated the quarterly cost of each of these phases to be £181, £136 and £190, respectively. The type of warfarin monitoring a patient receives depends on the patient's current health state. The ERG notes that patients who experience a minor bleed or major bleed are assumed to incur a re-initiation phase monitoring cost of £190. This is because patients are assumed to temporarily discontinue antithrombotic therapy and then resume therapy within the same cycle. However, the ERG notes that the majority of patients in the minor/major bleed health states transition to the initiation of anticoagulant health state in the subsequent model cycle. Therefore, most patients who experience a minor or major extracranial bleeding event incur both the cost of re-initiation and the cost of initiation. Similarly, patients who experience an intracranial bleed incur the cost of initiation plus the cost of re-initiation applied in the post-intracranial bleed health state. The ERG has corrected the double counting of re-initiation cost by applying maintenance rather than a re-initiation cost to the health states of minor bleed, major bleed and intracranial bleed. The effect of this adjustment on the comparisons of rivaroxaban with warfarin is presented in Section 6 and Appendices 9.2 and 9.3.

Inclusion of fixed costs of monitoring

The appropriateness of including fixed costs in an analysis of cost-effectiveness in the AF population was discussed by the ERG responsible for reviewing Boehringer Ingelheim's submission to NICE for

dabigatran in the prevention of stroke and systemic embolism in AF.[19] The argument presented against the inclusion of fixed costs was that fixed costs do not depend on patient numbers and as such "will only be eliminated if anticoagulation clinics are shut down and clinicians diverted to other activities".[19] As part of the clarification process, the ERG asked the manufacturer to conduct a scenario analysis that incorporated a cost of INR monitoring of £279.36 as suggested by the appraisal committee undertaking the appraisal of dabigatran.[50] The manufacturer argued that according to Drummond *et al*.[89] the inclusion of only variable costs in costing is not standard practice. However, the manufacturer conducted the requested scenario analysis on their original point estimate scenario analysis of the safety-on-treatment population. The resultant ICER was £22,645.

No disaggregation of costs by INR control

As discussed in Section 5.4.5, the ERG agrees with the manufacturer that analysis of patients based on differing treatment effects for patients within, below and above recommended INR range should be treated with caution. However, the ERG considers that, whilst it is difficult to account for differing treatment effects without a randomised comparison, it is possible to account for the differing costs of patients within, below and above the recommended range. The ERG adjusted the manufacturer's model to apply a frequency of three and five visits in the calculation of the maintenance costs of warfarin for patients within and outside the recommended INR control, respectively. The effect of this is discussed further in Section 6.

6 ADDITIONAL WORK UNDERTAKEN BY ERG

Following a detailed critique of the manufacturer's model and the literature used to inform the model parameters, the ERG has identified several adjustments and some alternative model inputs. The ERG's recommended adjustments vary between the ROCKET AF-based and NMA-based analyses.

6.1 ROCKET AF-based analyses

The following analyses based on data from ROCKET AF are considered here:

- Manufacturer's base case (safety-on-treatment population, significant only data);
- Safety-on-treatment point estimate analysis;
- Poorly controlled warfarin patients (safety-on-treatment population, significant only data);
- Poorly controlled warfarin patients (safety-on-treatment point estimate analysis);
- Warfarin-naïve patients (safety-on-treatment population, significant only);
- Warfarin-naïve patients (safety-on-treatment point estimate analysis);
- [redacted].

As detailed in section 5.4, each of the ROCKET AF-based analyses is subject to the adjustment of:

- The cost of maintenance monitoring by INR level;
- Bleeding risk by age;
- Utility by age;
- Risk of MI with aspirin;
- Risk of mortality from MI;
- The cost of monitoring applied to minor/major bleed and intracranial bleed health states.

In addition to these adjustments, the ERG also identified some issues with the model structure that could not be addressed. Namely, the suspension of event risk following any event for a further model cycle and the exclusion of TIA as an event.

As discussed in Sections 5.4.4 and 5.4.8, the ERG conducted exploratory analysis into the effect of: the aggregation of gastrointestinal bleeding with all major bleeding; and the inclusion of fixed costs in the analysis.

The ICERs obtained for each ROCKET AF-based analysis following the ERG's recommended adjustments and exploratory analyses are displayed in Table 54. The full details of the effect of each adjustment on the manufacturer's base case analysis, safety-on-treatment point estimate analysis and

the [redacted] are displayed in Tables 55, 56 and 57, respectively. Full details of the analysis of poorly controlled and warfarin naïve patients are given in Appendix 9.2.

Table 54. Summary of the impact of the ERG's adjustments and exploratory analyses on the ICER of each ROCKET AF-based analysis

Adjustment	Analysis						
	Base case	**Safety-on-treatment point estimate**	**Poorly controlled (significant only)**	**Poorly controlled (point estimates)**	**Warfarin-naïve (significant only)**	**Warfarin-naïve (point estimates)**	[redacted]
None	**£18,883**	**£8,732**	**Dominant**	**Dominant**	**£15,494**	**£6,900**	[redacted]
INR cost adjustment	£27,281	£13,271	Dominant	Dominant	£23,892	£11,439	[redacted]
Age-adjusted bleeding risk	£17,599	£8,336	Dominant	Dominant	£14,365	£6,543	[redacted]
Age-adjusted utilities	£24,262	£11,214	Dominant	Dominant	£19,907	£8,861	[redacted]
Aspirin MI risk	£19,721	£9,160	Dominant	Dominant	£16,282	£7,302	[redacted]
MI mortality	£18,751	£10,300	Dominant	Dominant	£15,491	£8,088	[redacted]
Monitoring cost of bleeding health states	£19,715	£9,181	Dominant	Dominant	£16,383	£7,380	[redacted]
Removal of risk suspension	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease ICER)						
Inclusion of TIA	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease ICER)						
ERG's base case	**£33,758**	**£20,444**	**Dominant**	**Dominant**	**£29,894**	**£17,765**	[redacted]
Exploratory analysis applied to the ERG's alternative base case							
Replacement of major bleeding with gastrointestinal bleeding	£37,268	£20,975	Dominant	Dominant	£33,243	£18,351	[redacted]
Removal of fixed costs	£62,568	£40,419	£15,965	£8,107	£59,894	£38,565	[redacted]

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; TIA, transient ischaemic attack.

Accounting for the different costs associated with treating patients who are within and outside the recommended INR range had the largest effect on the ICER, increasing the manufacturer's base case ICER by over £8,000. However, the effect of suspending the risk of further events for six months following any temporary or permanent event is likely to have a significant impact on the ICER. The period following an event is the time when, in reality, patients would be more at risk of further events. However, the manufacturer's model does not capture this extra risk and in fact delays any risk for 6 months. To address this issue would require substantial adjustment of the manufacturer's model. As discussed in Section 5.4.4, the ERG considers that this suspension of risk is most likely to favour the least effective treatment; the absolute number of events will be lower and therefore the potential to demonstrate clinical and economic benefits will also be lower.

Table 55. Results of the ERG's adjustments to manufacturer's base-case analysis

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**8,200**	**7.00**	**–**	**–**	**–**
	Rivaroxaban	**8,941**	**7.04**	**740**	**0.039**	**18,883**
INR cost adjustment	Warfarin	7,871	7.00	–	–	–
	Rivaroxaban	8,941	7.04	1,069	0.039	27,281
Age-adjusted bleeding risk	Warfarin	8,275	6.99	–	–	–
	Rivaroxaban	9,001	7.03	726	0.041	17,599
Age-adjusted utilities	Warfarin	8,200	5.45	–	–	–
	Rivaroxaban	8,941	5.48	740	0.031	24,262
Aspirin MI risk	Warfarin	8,423	6.92	–	–	–
	Rivaroxaban	9,178	6.96	755	0.038	19,721
MI mortality	Warfarin	8,430	7.10	–	–	–
	Rivaroxaban	9,194	7.14	764	0.041	18,751
Monitoring cost of bleeding health states	Warfarin	8,168	7.00	–	–	–
	Rivaroxaban	8,941	7.04	773	0.039	19,715
Removal of risk suspension	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG's alternative base case	**Warfarin**	**8,460**	**5.49**	**–**	**–**	**–**
	Rivaroxaban	**9,594**	**5.52**	**1,134**	**0.034**	**33,758**
Exploratory analysis applied to the ERG's alternative base case						
Exploratory analysis of gastrointestinal bleeding	Warfarin	8,354	5.50	**–**	**–**	**–**
	Rivaroxaban	9,503	5.53	1,149	0.031	37,263
Exploratory analysis of removal of fixed costs	Warfarin	7,493	5.49	**–**	**–**	**–**
	Rivaroxaban	9,594	5.52	2,102	0.034	62,568

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 56. Results of the ERG's adjustments to safety-on-treatment point estimate analysis

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**8,200**	**7.00**	**–**	**–**	**–**
	Rivaroxaban	**8,834**	**7.07**	**633**	**0.073**	**8,732**
INR cost adjustment	Warfarin	7,871	7.00	–	–	–
	Rivaroxaban	8,834	7.07	962	0.073	13,271
Age-adjusted bleeding risk	Warfarin	8,275	6.99	–	–	–
	Rivaroxaban	8,895	7.06	620	0.074	8,336
Age-adjusted utilities	Warfarin	8,200	5.45	–	–	–
	Rivaroxaban	8,834	5.51	633	0.056	11,214
Aspirin MI risk	Warfarin	8,423	6.92	–	–	–

	Rivaroxaban	9,072	6.99	649	0.071	9,160
MI mortality	Warfarin	8,430	7.10	–	–	–
	Rivaroxaban	9,049	7.16	619	0.060	10,300
Monitoring cost of bleeding health states	Warfarin	8,168	7.00	–	–	–
	Rivaroxaban	8,834	7.07	666	0.073	9,181
Removal of risk suspension	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG's alternative base case	**Warfarin**	**8,460**	**5.49**	**–**	**–**	**–**
	Rivaroxaban	**9,451**	**5.54**	**990**	**0.048**	**20,444**
Exploratory analysis applied to the ERG's alternative base case						
Exploratory analysis of gastrointestinal bleeding	Warfarin	8,354	5.50	–	–	–
	Rivaroxaban	9,344	5.54	991	0.047	20,975
Exploratory analysis of removal of fixed costs	Warfarin	7,493	5.49	–	–	–
	Rivaroxaban	9,451	5.54	1,958	0.048	40,419
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; QALY, quality adjusted life year; TIA, transient ischaemic attack.						

Table 57. [redacted]

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**8,200**	**6.998**	**–**	**–**	**–**
	Rivaroxaban	**8,834**	**7.071**	**633**	**0.073**	**8,732**
[redacted]	Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INR cost adjustment	Warfarin	7,813	6.998	–	–	–
	Rivaroxaban	8,880	7.101	1,067	0.103	10,361
Age-adjusted bleeding risk	Warfarin	8,275	6.987	–	–	–
	Rivaroxaban	8,941	7.092	666	0.105	6,343
Age-adjusted utilities	Warfarin	8,200	5.450	–	–	–
	Rivaroxaban	8,880	5.531	679	0.080	8,446
Aspirin MI risk	Warfarin	8,423	6.921	–	–	–
	Rivaroxaban	9,120	7.022	697	0.101	6,904
MI mortality	Warfarin	8,430	7.095	–	–	–
	Rivaroxaban	9,035	7.162	605	0.067	9,060

Monitoring cost of bleeding health states	Warfarin	8,168	6.998	–	–	–
	Rivaroxaban	8,880	7.101	712	0.103	6,913
Removal of risk suspension	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG's alternative base case	**Warfarin**	**8,402**	**5.487**	**–**	**–**	**–**
	Rivaroxaban	**9,438**	**5.541**	**1,036**	**0.054**	**19,258**
Exploratory analysis applied to the ERG's alternative base case						
Exploratory analysis of gastrointestinal bleeding	Warfarin	8,296	5.495	–	–	–
	Rivaroxaban	9,339	5.547	1,042	0.052	20,103
Exploratory analysis of removal of fixed costs	Warfarin	7,451	5.487	–	–	–
	Rivaroxaban	9,438	5.541	1,988	0.054	36,942
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; QALY, quality adjusted life year; TIA, transient ischaemic attack.						

6.2 Manufacturer's NMA-based analyses

The manufacturer's NMA was used to inform comparisons between rivaroxaban and: aspirin; no treatment (placebo); and dabigatran. The manufacturer claimed that the comparisons of rivaroxaban with aspirin and with no treatment (placebo) were carried out in the warfarin-unsuitable population, including patients who:

- Have discontinued from previous OAC use;
- Are contraindicated to warfarin;
- Are deemed unable to keep track of warfarin intake and keep up with monitoring requirements, due to physical or mental impairments (MS; pg 250).

However, as discussed in Section 5.4.2, the ERG notes that the trials used to inform the comparison of rivaroxaban with aspirin and with no treatment (placebo) include warfarin as a comparator suggesting that the patient population is suitable for warfarin. The comparison between rivaroxaban and dabigatran adopts a cost minimisation approach. The manufacturer argues that this is reasonable because of the absence of a significant difference in any outcome, estimated by the manufacturer's NMA. As discussed in Section 5.4.5, the ERG does not accept the manufacturer's rationale for adopting a cost minimisation approach to the comparison of rivaroxaban with dabigatran. Furthermore, the ERG notes that the manufacturer has not used the outcomes estimated by the manufacturer's NMA to inform a comparison between rivaroxaban and warfarin.

The ERG considers that a fully incremental analysis of rivaroxaban, dabigatran, warfarin, aspirin and no treatment (placebo) is both possible and desirable. Therefore, the ERG conducted such an analysis (Table 58), using point estimates obtained from the manufacturer's NMA applied to a population of patients with baseline characteristics from the UK observational study by Gallagher *et al*.[51] The baseline distribution by $CHADS_2$ score used by the ERG was as follows:

- 13% of patients with $CHADS_2$ score of 0;
- 61% of patients with $CHADS_2$ score of 1 or 2;
- 26% of patients with $CHADS_2$ score of 3 or more.

Table 58. Results of fully incremental analysis based on manufacturer's NMA, using baseline characteristics from a UK observational study[51]

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£)
ASA (aspirin)	9,546	6.48	–	–	–
No therapy	9,777	6.39	231	–0.088	Dominated
Warfarin	9,816	6.85	270	0.374	721
Rivaroxaban	10,476	6.91	660	0.059	11,114
Dabigatran	11,061	6.92	585	0.004	131,003
Abbreviations used in table: ASA, acetylsalicylic acid; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.					

Following examination of the results of the incremental analysis the ERG considers the relevant comparison to be that of rivaroxaban and dabigatran (for details of analysis of rivaroxaban versus aspirin and versus warfarin see Appendix 9.3, also presented in Appendix 9.3 are the results of analysis of rivaroxaban versus dabigatran based on the manufacturer's NMA and ROCKET AF baseline characteristics). As discussed above, the ERG recommends several adjustments to the assumptions and parameters of the manufacturer's model. The result of the comparison between rivaroxaban and dabigatran is displayed in Table 59, following adjustment of:

- The risk of stroke post-systemic embolism;
- Bleeding risk by age;
- Utility by age;
- Risk of mortality from MI;
- Treatment discontinuation rates.

In addition to these adjustments, the structural issues of the suspension of event risk, the exclusion of TIA and the exclusion of dyspepsia would have an impact on the ICER. However, the ERG is not able to fully quantify the effect of these structural assumptions. Furthermore, as discussed in section 5.4.5 the ERG has conducted exploratory analysis into the effect of assuming equivalence between rivaroxaban and dabigatran in MI prevention.

Generally, there is little difference in the costs and QALYs obtained from treatment with rivaroxaban or dabigatran. However, the adjustments that had the largest impact on the QALY difference between these two treatments were the adjustment of the mortality rate associated with MI and the discontinuation rates associated with dabigatran. Increasing the rate of discontinuation with dabigatran reduced the number of QALYs gained with this treatment. Conversely, decreasing the mortality rate associated with MI reduced the number of QALYs gained with rivaroxaban. This is because, based on the manufacturer's NMA, rivaroxaban is more effective at preventing MI than dabigatran (RR [relative to placebo]: 0.26 for rivaroxaban, 0.44 for dabigatran). Therefore, applying a lower risk of mortality associated with an MI reduces the potential QALY gain available to rivaroxaban by reducing the absolute number of deaths from MI. Although, once all the adjustments have been accounted for in the ERG's alternative base case, there remains little difference in the costs and QALYs associated with each treatment. However, the exploratory analysis assuming equivalence in MI prevention between dabigatran and rivaroxaban indicates that the model is very sensitive to the relative effect of MI prevention.

Table 59. Results of the ERG's adjustments to the comparison of rivaroxaban and dabigatran, based on the results of the manufacturer's NMA, using baseline characteristics from a UK observational survey[51]

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Rivaroxaban**	**12,397**	**6.71**	**–**	**–**	**–**
	Dabigatran	**13,310**	**6.71**	**913**	**0.000**	**Dominated**
Manufacturer's NMA point estimates applied to Gallagher[51] $CHADS_2$ score distribution	Rivaroxaban	10,476	6.91	**–**	**–**	**–**
	Dabigatran	11,061	6.92	585	0.004	131,003
Post-systemic embolism health state	Rivaroxaban	10,538	6.91	**–**	**–**	**–**
	Dabigatran	11,143	6.91	605	0.004	170,625
Age-adjusted bleeding risk	Rivaroxaban	10,507	6.91	**–**	**–**	**–**
	Dabigatran	11,087	6.91	580	0.006	105,381
Age-adjusted utilities	Rivaroxaban	10,476	5.38	**–**	**–**	**–**
	Dabigatran	11,061	5.39	585	0.004	152,203
MI mortality	Rivaroxaban	10,660	6.99	**–**	**–**	**–**
	Dabigatran	11,328	7.02	668	0.031	21,428
Discontinuation rates from the ERG's NMA	Rivaroxaban	10,461	6.91	**–**	**–**	**–**
	Dabigatran	10,868	6.88	408	–0.029	Dominated
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour dabigatran (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., increase the ICER)					
Inclusion of dyspepsia	Impact on ICER undeterminable but likely to favour rivaroxaban (i.e., increase the ICER)					

ERG's alternative base case	**Rivaroxaban**	**10,739**	**5.43**	**–**	**–**	**–**
	Dabigatran	**11,251**	**5.42**	**512**	**-0.002**	**Dominated**
Exploratory analysis of assuming equivalent MI prevention	Rivaroxaban	10,851	5.41	**–**	**–**	**–**
	Dabigatran	11,251	5.42	400	0.011	37,912
Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; NMA, network meta-analysis; QALY, quality adjusted life year; TIA, transient ischaemic attack.						

The ERG notes that inclusion of TIA and dyspepsia are likely to favour rivaroxaban, because of the lower occurrence of these events estimated with rivaroxaban. However, the elimination of risk suspension would be more likely to favour dabigatran. This is because, according to the manufacturer's NMA, dabigatran is more effective at preventing ischaemic stroke and is associated with fewer minor/major extracranial and intracranial bleeding events.

6.3 ERG's NMA-based analyses

As discussed in Section 4.5, the ERG conducted an NMA based on a simplified network of trials, the results of this were implemented in the manufacturer's model and a fully incremental analysis of rivaroxaban, dabigatran, warfarin and aspirin was conducted, using baseline characteristics from Gallagher *et al*.[51] The results of this analysis are displayed in Table 60.

Table 60. Results of fully incremental analysis based on ERG's NMA, using baseline characteristics from a UK observational survey[51]

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£)
ASA (aspirin)	7,800	6.633	**–**	**–**	**–**
No therapy	8,928	6.423	1,128	–0.209	Dominated
Warfarin	8,757	6.875	957	0.243	3,943
Rivaroxaban	9,234	6.960	477	0.085	5,616
Dabigatran	9,749	6.975	516	0.015	34,680
Abbreviations used in table: ASA, acetylsalicylic acid; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.					

As with the results obtained from the manufacturer's NMA, the ERG considers these results to indicate that the relevant comparison is between rivaroxaban and dabigatran (detailed results of rivaroxaban versus aspirin and versus warfarin are available in Appendix 9.3, also presented in Appendix 9.3 are the results of analysis of rivaroxaban versus dabigatran based on the ERG's NMA and ROCKET AF baseline characteristics). The results of this analysis after incorporation of the ERG's recommended adjustments are displayed in Table 61.

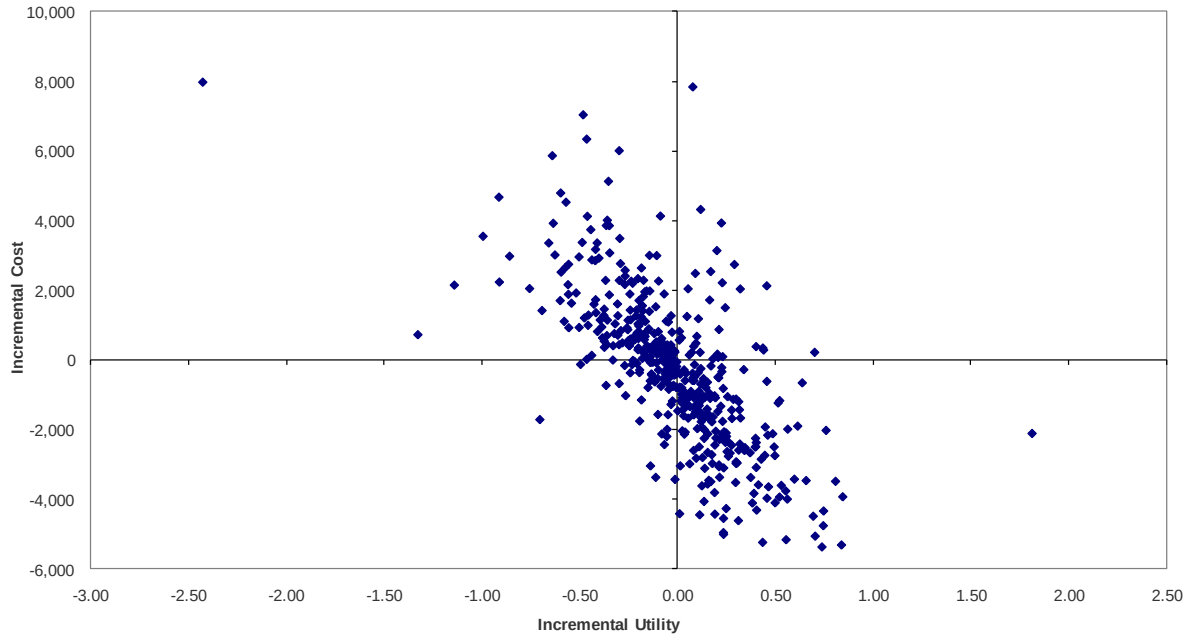
The results of the comparison between rivaroxaban and dabigatran, based on point estimates from the ERG's NMA indicate that dabigatran is the more effective treatment, with an ICER of £34,680 per QALY gained. Following incorporation of the ERG's recommended adjustments the ICER decreases to £12,701, with the exploratory analysis assuming equivalence of MI prevention between treatments yielding an ICER of £3,578. However, the ERG notes that the model is highly sensitive to changes in the discontinuation rates used and advises that the ICER of £12,701 per QALY gained, be considered in the context of the associated uncertainty. Figure 7 displays the scatter plot of the CE plane derived from the ERG's alternative base case.

Table 61. Results of the ERG's adjustments to the comparison of rivaroxaban and dabigatran, based on the results of the ERG's NMA

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
ERG's NMA point estimates	**Rivaroxaban**	**9,234**	**6.960**	**–**	**–**	**–**
	Dabigatran	**9,749**	**6.975**	**516**	**0.015**	**34,680**
Post-systemic embolism health state	Rivaroxaban	9,323	6.952	–	–	–
	Dabigatran	9,870	6.965	548	0.012	43,844
Age-adjusted bleeding risk	Rivaroxaban	9,304	6.948	–	–	–
	Dabigatran	9,810	6.965	506	0.017	30,004
Age-adjusted utilities	Rivaroxaban	9,234	5.421	–	–	–
	Dabigatran	9,749	5.433	516	0.012	43,820
MI mortality	Rivaroxaban	9,438	7.039	–	–	–
	Dabigatran	10,048	7.085	610	0.045	13,469
Discontinuation rates from the ERG's NMA	Rivaroxaban	9,193	6.958	–	–	–
	Dabigatran	9,354	6.958	161	0.005	338,706
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour dabigatran (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., increase the ICER)					
Inclusion of dyspepsia	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., increase the ICER)					
ERG's alternative base case	**Rivaroxaban**	**9,559**	**5.464**	**–**	**–**	**–**
	Dabigatran	**9,843**	**5.486**	**284**	**0.022**	**12,701**
Exploratory analysis of assuming equivalent MI prevention	Rivaroxaban	9,706	5.448	–	–	–
	Dabigatran	9,843	5.486	137	0.038	3,578

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; NMA, network meta-analysis; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Figure 7. Cost-effectiveness plane for dabigatran versus rivaroxaban based on ERG's alternative base case, 1,000 runs



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 scope8 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[50] 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.[8]

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 (overall adverse event rate: 20.7% with rivaroxaban vs 20.3% with warfarin). 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. The ERG undertook a detailed investigation of the manufacturer's model and has identified the following limitations to the model's structural assumptions and parameter sources:

- The lack of disaggregation of the number of visits required by patients who were within and outside recommended International Normalised Ratio (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 (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 transient ischaemic attack (TIA) as a potential event.

The ERG has presented an alternative base case in which, where possible, adjustments have been made to account for the limitations identified. The alternative base case ICER is £33,758 per QALY gained. Similarly, for warfarin-naïve patients, 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 patients 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 TIA as a potential event. Consequently, the ERG was unable to fully quantify the impact of these limitations on the ICERs. However, the ERG considers that the suspension of risk and exclusion of TIA as an event would favour warfarin (i.e., 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).

The ERG considers 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. 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 (suggested by the Appraisal Committee in the dabigatran STA[50]) increased the ICER to £62,568 per QALY gained.

7.1 NMA-based analysis

The ERG is concerned that the NMA presented by the manufacturer has high levels of heterogeneity, which was not the case when the ERG conducted its own NMA restricting the network to the comparators specified in the final scope issued by NICE.[8] This is illustrated by the results presented by the manufacturer predominantly being based on a random effects model compared with the ERG's NMA in which the underlying trials were sufficiently coherent for a fixed effects model to be universally used.

The ERG notes that the clinical effectiveness data for aspirin compared with rivaroxaban were 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. Consequently, the ERG considers that the question of rivaroxaban versus aspirin in a patient population unsuitable for warfarin has not been addressed in the manufacturer's submission (MS).

Application of the treatment effects estimated by the ERG's NMA to the manufacturer's model yielded an ICER of £34,680 per QALY gained for dabigatran versus rivaroxaban. After further adjustments to account for the limitations listed below, the ICER reduced to £12,701. The ERG adjusted for:

- 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;
- The assumption of equivalent discontinuation rates.

Exploratory analysis, assuming an equivalent ability of rivaroxaban and dabigatran to prevent MI further decreased the ICER to £3,578. The ERG notes that the presence of conflicting bias in the model limitations of: risk suspension and the absence of TIA and dyspepsia as adverse events. The removal of risk suspension is likely to favour dabigatran (i.e. reduce the ICER), whereas the inclusion of TIA and dyspepsia is likely to increase the ICER. Furthermore, the ERG notes that there is a large amount of uncertainty present in the model and that the model is highly sensitive to even small changes to the discontinuation rates. Therefore, the ERG considers that the results of the PSA should be taken into account when considering the ERG's alternative ICER for dabigatran versus rivaroxaban. The PSA indicated that dabigatran was dominant in 45% of the 1,000 runs and dominated in 35% of runs.

7.2 Implications for research

The ERG considers anticoagulation monitoring an important issue when considering warfarin as a comparator. Independently funded studies that investigate the frequency of INR monitoring would be valuable in informing economic evaluations, such as the evaluation presented in this report that is driven by cost of anticoagulation monitoring rather than effectiveness. The ERG considers that there is a need for further research into the safety and clinical benefit of rivaroxaban compared with dabigatran etexilate and aspirin in patients who are not suitable for warfarin. There is a need for quality of life studies in people taking rivaroxaban as well as utility data in AF patients who develop MI or experience ischaemic or haemorrhagic stroke.

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9 APPENDICES

9.1 References for studies included in manufacturer's systematic review and/or network meta-analysis

Note that the studies excluded from the manufacturer's network meta-analysis are shaded grey.

ACTIVE A	Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al; The Active Steering Committee. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. New England Journal of Medicine 2009 May 14;360(20):2066-78.
ACTIVE W	Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al; ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial . Lancet 2006 Jun 10;367(9526):1903-12.
ACTIVE (design paper)	Connolly S, Yusuf S, Budaj A, Camm J, et al; The Active Steering Committee. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. American Heart Journal 2006 Jun;151(6):1187-93.
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AFASAK II	Koefoed BG, Gullov AL, Petersen P. Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study (AFASAK 2): Methods and Design. J Thromb Thrombolysis 1995;2(2):125-30.
	Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study . Archives of Internal Medicine 1998 Jul 27;158(14):1513-21.
AMADEUS	Amadeus I, Bousser MG, Bouthier J, Buller HR, Cohen AT, Crijns H, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial . Lancet 2008 Jan 26;371(9609):315-21.
AVERROES (not in SR)	Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011 Mar 3;364(9):806-17.
BAATAF	The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators . New England Journal of Medicine 1990 Nov 29;323(22):1505-11.
BAFTA	Mant JW, Richards SH, Hobbs FD, Fitzmaurice D, Lip GY, Murray E, et al. Protocol for Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA): a randomised controlled trial of warfarin versus aspirin for stroke prevention in the management of atrial fibrillation in an elderly primary care population [ISRCTN89345269]. BMC Cardiovascular Disorders 2003 Aug 26;3:9.
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CAFA	Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. Journal of the American College of Cardiology 1991 Aug;18(2):349-55.
CHARISMA (excl NMA)	Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Am Heart J 2004 Aug;148(2):263-8.
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EAFT	Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group . Lancet 1993 Nov 20;342(8882):1255-62.
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ESPS II (excl NMA)	Bertrand-Hardy JM, Cunha L, Forbes C, Hoeven C, Hogenhuis L, Lowenthal A, et al. European Stroke Prevention Study 2: Baseline data. Journal of the Neurological Sciences 1995 Aug;131:Suppl-58.
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ESTEEM (excl NMA)	Wallentin L, Wilcox RG, Weaver WD, Emanuelsson H, Goodvin A, Nystrom P, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet 2003 Sep 6;362(9386):789-97.
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FFAACS	Lechat P, Lardoux H, Mallet A, Sanchez P, Derumeaux G, Lecompte T, et al. [Study of combined anticoagulant (fluindione)-aspirin therapy in patients with atrial fibrillation at high risk for thromboembolic complications. A randomized trial (FFAACS)]. [French]. Therapie 2000 Nov;55(6):681-9.
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Hu 2006 (excl NMA)	Hu DY, Zhang HP, Sun YH, Jiang LQ. [The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin]. Zhonghua Xin Xue Guan Bing Za Zhi 2006 Apr;34(4):295-8.
JAST	Sato H, Ishikawa K, Kitabatake A, Ogawa S, Maruyama Y, Yokota Y, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial . Stroke 2006 Feb;37(2):447-51.
JNAFESP	Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation : a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Stroke 2000 Apr;31(4):817-21.
LASAF	Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation 1714. American Heart Journal 138(1 I)()(pp 137-143), 1999 Date of Publication: 1999 1999;(1 I):137-43.
Lu 2006 (excl NMA)	Lu Y, Zhang J. Anticoagulant treatment on chronic non-valvular atrial fibrillation in the elderly patients. [Chinese]. Chinese Journal of Emergency Medicine 15(1)()(pp 54-56), 2006 Date of Publication: Jan 2006 2006;(1):54-6.
MWNAF	Pengo V, Zasso A, Barbero F, Banzato A, Nante G, Parissenti L, et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. American Journal of Cardiology 1998 Aug 15;82(4):433-7.
NASPEAF	Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study . Journal of the American College of Cardiology 2004 Oct 19;44(8):1557-66.
PATAF	Hellemons BS, Langenberg M, Lodder J, Vermeer F, Schouten HJ, Lemmens T, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin . BMJ 1999 Oct 9;319(7215):958-64.
Pengo 2010	Pengo V, Cucchini U, Denas G, Davidson BL, Marzot F, Jose SP, et al. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. Thromb Haemost 2010 Feb;103(2):442-9.
PETRO	Wallentin LC, Ezekowitz M, Simmers TA, Pedersen KE, Stangier J, Nehmiz G, et al. Safety and efficacy of a new oral direct thrombin inhibitor dabigatran in atrial fibrillation - a dose finding trial with comparison to warfarin. Eu Heart J 2005;26:482-3.
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SAFT	Edvardsson N, Juul-Moller S, Omblus R, Pehrsson K. Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. Journal of Internal Medicine 2003 Jul;254(1):95-101.
SIFA	Amabile G, Matteoli S, Fattapposta F, Lavezzari M, Trappolini M, Heiman F, et al. [Italian Study on Atrial Fibrillation (SIFA): status report]. [Italian]. Cardiologia 1993 Dec;38(12:Suppl 1):327-32.
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SPAF (excl NMA)	Design of a multicenter randomized trial for the Stroke Prevention in Atrial Fibrillation Study. The Stroke Prevention in Atrial Fibrillation Investigators. Stroke 1990 Apr;21(4):538-45.
(excl NMA)	Prevention of stroke in atrial fibrillation.[comment]. New England Journal of Medicine 1990 Aug 16;323(7):481-4.
(excl NMA)	McBride R, Anderson DC, Asinger RW, Newburg SM, Farmer CC, Wang K, et al. Preliminary report of the stroke prevention in atrial fibrillation study 2190. New England Journal of Medicine 322(12)()(pp 863-868), 1990 Date of Publication: 1990 1990;(12):863-8.
(excl NMA)	Stroke Prevention in Atrial Fibrillation Study. Final results . Circulation 1991 Aug;84(2):527-39.
SPAF II	Warfarin Compared to Aspirin for Prevention of Arterial Thromboembolism in Atrial Fibrillation. Cerebrovasc Dis 1992;2(6):332-41.
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SPAF III	Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial . Lancet 1996 Sep 7;348(9028):633-8.
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SPINAF	Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators.[see comment][erratum appears in N Engl J Med 1993 Jan 14;328(2):148]. New England Journal of Medicine 1992 Nov 12;327(20):1406-12.
SPORTIF II (excl NMA)	Petersen P, Grind M, Adler J, SPORTIF II, I. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. Journal of the American College of Cardiology 2003 May 7;41(9):1445-51.
SPORTIF III	Olsson SB, Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial . Lancet 2003 Nov 22;362(9397):1691-8.
SPORTIF V	Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial . JAMA 2005 Feb 9;293(6):690-8.
SPORTIF III/V	Halperin JL, Executive Steering Committee. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). American Heart Journal 2003 Sep;146(3):431-8.
Vemmos 2006	Vemmos KN, Tsivgoulis G, Spengos K, Manios E, Xinos K, Vassilopoulou S, et al. Primary prevention of arterial thromboembolism in the oldest old with atrial fibrillation - A randomized pilot trial comparing adjusted-dose and fixed low-dose coumadin with aspirin 722. European Journal of Internal Medicine 17(1)()(pp 48-52), 2006 Date of Publication: Jan 2006 2006;(1):48-52.
WASPO	Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age & Ageing 2007 Mar;36(2):151-6.

9.2 Additional ROCKET AF-based analysis conducted by the ERG

Table 1. Results of ERG adjustments to manufacturer's analysis of poorly controlled warfarin patients, based on significant only data from the safety-on-treatment population

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**10,423**	**7.00**	**–**	**–**	**–**
	Rivaroxaban	**8,941**	**7.04**	**–1,482**	**0.039**	**Dominant**
INR cost adjustment	Warfarin	9,981	7.00	–	–	–
	Rivaroxaban	8,941	7.04	–1,040	0.039	Dominant
Age-adjusted bleeding risk	Warfarin	10,494	6.99	–	–	–
	Rivaroxaban	9,001	7.03	–1,492	0.041	Dominant
Age-adjusted utilities	Warfarin	10,423	5.45	–	–	–
	Rivaroxaban	8,941	5.48	–1,482	0.031	Dominant
Aspirin MI risk	Warfarin	10,679	6.92	–	–	–
	Rivaroxaban	9,178	6.96	–1,501	0.038	Dominant
MI mortality	Warfarin	10,713	7.10	–	–	–
	Rivaroxaban	9,194	7.14	–1,519	0.041	Dominant
Monitoring cost of bleeding health states	Warfarin	10,454	7.00	–	–	–
	Rivaroxaban	8,941	7.04	–1,513	0.039	Dominant
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	**Warfarin**	**10,748**	**5.49**	**–**	**–**	**–**
	Rivaroxaban	**9,594**	**5.52**	**–1,154**	**0.034**	**Dominant**
Exploratory analysis of gastrointestinal bleeding	Warfarin	10,620	5.50	–	–	–
	Rivaroxaban	9,503	5.53	–1,118	0.031	Dominant
Exploratory analysis of removal of fixed costs	Warfarin	9,058	5.49	–	–	–
	Rivaroxaban	9,594	5.52	536	0.034	15,965

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 2. Results of ERG adjustments to manufacturer's analysis of poorly controlled warfarin patients, based on safety-on-treatment point estimate analysis

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**10,423**	**7.00**	**–**	**–**	**–**
	Rivaroxaban	**8,834**	**7.07**	**–1,589**	**0.073**	**Dominant**
INR cost adjustment	Warfarin	9,981	7.00	–	–	–
	Rivaroxaban	8,834	7.07	–1,147	0.073	Dominant
Age-adjusted bleeding risk	Warfarin	10,494	6.99	–	–	–
	Rivaroxaban	8,895	7.06	–1,598	0.074	Dominant
Age-adjusted utilities	Warfarin	10,423	5.45	–	–	–
	Rivaroxaban	8,834	5.51	–1,589	0.056	Dominant
Aspirin MI risk	Warfarin	10,679	6.92	–	–	–
	Rivaroxaban	9,072	6.99	–1,607	0.071	Dominant
MI mortality	Warfarin	10,713	7.10	–	–	–
	Rivaroxaban	9,049	7.16	–1,664	0.060	Dominant
Monitoring cost of bleeding health states	Warfarin	10,454	7.00	–	–	–
	Rivaroxaban	8,834	7.07	–1,620	0.073	Dominant
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	**Warfarin**	**10,748**	**5.49**	**–**	**–**	–
	Rivaroxaban	**9,451**	**5.54**	**–1,297**	**0.048**	**Dominant**
Exploratory analysis of gastrointestinal bleeding	Warfarin	10,620	5.50	–	–	–
	Rivaroxaban	9,344	5.54	–1,276	0.047	Dominant
Exploratory analysis of removal of fixed costs	Warfarin	9,058	5.49	–	–	–
	Rivaroxaban	9,451	5.54	393	0.048	8,107

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 3. Results of ERG adjustments to manufacturer's analysis of warfarin-naïve patients, based on significant only data from the safety-on-treatment population

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**8,333**	**7.00**	**–**	**–**	**–**
	Rivaroxaban	**8,941**	**7.04**	**607**	**0.039**	**15,494**
INR cost adjustment	Warfarin	8,004	7.00	–	–	–
	Rivaroxaban	8,941	7.04	936	0.039	23,892
Age-adjusted bleeding risk	Warfarin	8,408	6.99	–	–	–
	Rivaroxaban	9,001	7.03	593	0.041	14,365
Age-adjusted utilities	Warfarin	8,333	5.45	–	–	–
	Rivaroxaban	8,941	5.48	607	0.031	19,907
Aspirin MI risk	Warfarin	8,555	6.92	–	–	–
	Rivaroxaban	9,178	6.96	623	0.038	16,282
MI mortality	Warfarin	8,563	7.10	–	–	–
	Rivaroxaban	9,194	7.14	631	0.041	15,491
Monitoring cost of bleeding health states	Warfarin	8,298	7.00	–	–	–
	Rivaroxaban	8,941	7.04	642	0.039	16,383
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	**Warfarin**	**8,590**	**5.49**	**–**	**–**	**–**
	Rivaroxaban	**9,594**	**5.52**	**1,004**	**0.034**	**29,894**
Exploratory analysis of gastrointestinal bleeding	Warfarin	8,478	5.50	–	–	–
	Rivaroxaban	9,503	5.53	1,025	0.031	33,243
Exploratory analysis of removal of fixed costs	Warfarin	7,582	5.49	–	–	–
	Rivaroxaban	9,594	5.52	2,012	0.034	59,894

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 4. Results of ERG adjustments to manufacturer's analysis of warfarin-naïve patients, based on safety-on-treatment point estimate analysis

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**8,333**	**7.00**	**–**	**–**	**–**
	Rivaroxaban	**8,834**	**7.07**	**500**	**0.073**	**6,900**
INR cost adjustment	Warfarin	8,004	7.00	–	–	–
	Rivaroxaban	8,834	7.07	829	0.073	11,439
Age-adjusted bleeding risk	Warfarin	8,408	6.99	–	–	–
	Rivaroxaban	8,895	7.06	487	0.074	6,543
Age-adjusted utilities	Warfarin	8,333	5.45	–	–	–
	Rivaroxaban	8,834	5.51	500	0.056	8,861
Aspirin MI risk	Warfarin	8,555	6.92	–	–	–
	Rivaroxaban	9,072	7.00	517	0.071	7,302
MI mortality	Warfarin	8,563	7.10	–	–	–
	Rivaroxaban	9,049	7.16	486	0.060	8,088
Monitoring cost of bleeding health states	Warfarin	8,298	7.00	–	–	–
	Rivaroxaban	8,834	7.07	535	0.073	7,380
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	**Warfarin**	**8,590**	**5.49**	**–**	**–**	**–**
	Rivaroxaban	**9,451**	**5.54**	**861**	**0.048**	**17,765**
Exploratory analysis of gastrointestinal bleeding	Warfarin	8,478	5.50	–	–	–
	Rivaroxaban	9,344	5.55	867	0.047	18,351
Exploratory analysis of removal of fixed costs	Warfarin	7,582	5.49	–	–	–
	Rivaroxaban	9,451	5.54	1,868	0.048	38,565

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; QALY, quality adjusted life year; TIA, transient ischaemic attack.

9.3 Additional NMA-based analysis conducted by the ERG

Table 1. Results of fully incremental analysis based on manufacturer's NMA using ROCKET AF $CHADS_2$ distribution

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£)
Aspirin	11,782	6.248	–	–	–
No therapy	12,184	6.124	–	–	Dominated
Warfarin	11,739	6.648	–42	0.401	Dominant (over aspirin)
Rivaroxaban	12,397	6.712	658	0.063	10,392
Dabigatran	12,941	6.727	544	0.015	36,086

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality adjusted life year.

Table 2. Results of ERG adjustments to the comparison of rivaroxaban and dabigatran, based on the results of the manufacturer's NMA using ROCKET AF $CHADS_2$ distribution

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Rivaroxaban**	12,397	6.712	–	–	–
	Dabigatran	13,310	6.712	913	0.000	Dominated
Manufacturer's NMA point estimates applied to ROCKET AF $CHADS_2$ score distribution	Rivaroxaban	12,397	6.712	–	–	–
	Dabigatran	12,941	6.727	544	0.015	£36,086
Post-systemic embolism health state	Rivaroxaban	12,405	6.711	–	–	–
	Dabigatran	12,963	6.725	559	0.015	£38,201
Age-adjusted bleeding risk	Rivaroxaban	12,424	6.707	–	–	–
	Dabigatran	12,962	6.723	538	0.016	£33,332
Age-adjusted utilities	Rivaroxaban	12,397	5.221	–	–	–
	Dabigatran	12,941	5.233	544	0.012	£44,456
MI mortality	Rivaroxaban	12,582	6.779	–	–	–
	Dabigatran	13,212	6.821	630	0.042	14,878
Discontinuation rates from ERG's NMA	Rivaroxaban	12,395	6.706	–	–	–
	Dabigatran	12,873	6.678	478	–0.028	Dominated
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour dabigatran (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., increase the ICER)					
Inclusion of dyspepsia	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., increase the ICER)					
ERG alternative base case	**Rivaroxaban**	**12,615**	**5.263**	–	–	–
	Dabigatran	**13,191**	**5.263**	**576**	**–0.00005**	**Dominated**
Exploratory analysis of assuming equivalent MI	Rivaroxaban	12,715	5.252			
	Dabigatran	13,191	5.263	476	0.011	43,320

prevention						

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; NMA, network meta-analysis; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 3. Results of fully incremental analysis based on ERG's NMA using ROCKET AF $CHADS_2$ distribution

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£)
Aspirin	9,739	6.408	–	–	–
No therapy	11,139	6.160	1,400	–0.248	Dominated
Warfarin	10,381	6.710	642	0.303	2,120
Rivaroxaban	10,837	6.799	456	0.089	5,144
Dabigatran	11,313	6.823	477	0.024	19,834

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality adjusted life year.

Table 4. Results of ERG adjustments to the comparison of rivaroxaban and dabigatran, based on the results of the ERG's NMA using ROCKET AF $CHADS_2$ distribution

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
ERG's NMA point estimates	Rivaroxaban	**10,837**	**6.799**	–	–	–
	Dabigatran	**11,313**	**6.823**	**477**	**0.024**	**19,834**
Post-systemic embolism health state	Rivaroxaban	10,913	6.792	–	–	–
	Dabigatran	11,422	6.814	509	0.022	23,425
Age-adjusted bleeding risk	Rivaroxaban	10,901	6.788	–	–	–
	Dabigatran	11,367	6.814	466	0.026	17,840
Age-adjusted utilities	Rivaroxaban	10,837	5.293	–	–	–
	Dabigatran	11,313	5.312	477	0.019	25,086
MI mortality	Rivaroxaban	11,043	6.873	–	–	–
	Dabigatran	11,618	6.928	575	0.055	10,470
Discontinuation rates from ERG's NMA	Rivaroxaban	10,805	6.797	–	–	–
	Dabigatran	10,996	6.800	191	0.003	58,385
Removal of risk suspension	Impact on ICER undeterminable, but likely to favour dabigatran (i.e., decrease the ICER)					
Inclusion of TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., increase the ICER)					
Inclusion of dyspepsia	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., increase the ICER)					
ERG alternative base case	**Rivaroxaban**	**11,154**	**5.332**	–	–	–
	Dabigatran	**11,473**	**5.359**	**319**	**0.026**	**12,228**
Exploratory analysis of	Rivaroxaban	11,289	5.318			

assuming equivalent MI prevention	Dabigatran	11,473	5.359	184	0.041	4,540

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; NMA, network meta-analysis; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 5. Results of ERG adjustments to the comparison of rivaroxaban and warfarin, based on the results of the manufacturer's NMA and Gallagher's[51] $CHADS_2$ score distributions at baseline

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's base case	**Warfarin**	**11,739**	**6.648**	**–**	**–**	**–**
	Rivaroxaban	**12,397**	**6.712**	**658**	**0.063**	**10,392**
Manufacturer's base case using Gallagher [51] $CHADS_2$ distribution	**Warfarin**	**9,816**	**6.854**	**–**	**–**	**–**
	Rivaroxaban	**10,476**	**6.913**	**660**	**0.059**	**11,114**
INR cost adjustment	Warfarin	9,508	6.854	–	–	–
	Rivaroxaban	10,476	6.913	968	0.059	16,303
Post-systemic embolism health state	Warfarin	9,816	6.854	–	–	–
	Rivaroxaban	10,538	6.907	722	0.054	13,434
Age-adjusted bleeding risk	Warfarin	9,856	6.847	–	–	–
	Rivaroxaban	10,507	6,908	651	0.061	10,691
Age-adjusted utilities	Warfarin	9,816	5.335	–	–	–
	Rivaroxaban	10,476	5.381	660	0.046	14,236
MI mortality	Warfarin	10,003	6.932	–	–	–
	Rivaroxaban	10,660	6.985	657	0.053	12,353
Monitoring cost of bleeding health states	Warfarin	9,803	6.854	–	–	–
	Rivaroxaban	10,476	6.913	673	0.059	11,340
Risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No dyspepsia	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	**Warfarin**	**9,721**	**5.390**	**–**	**–**	**–**
	Rivaroxaban	**10,753**	**5.427**	**1.032**	**0.037**	**27,952**
Exploratory analysis of removal of fixed costs	Warfarin	8,785	5.390	–	–	–
	Rivaroxaban	10,753	5.427	1,969	0.037	53,331

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; INR, International Normalised Ratio; MI, myocardial infarction; NMA, network meta-analysis; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 6. Results of ERG adjustments to the comparison of rivaroxaban and aspirin, based on results of the manufacturer's NMA and Gallagher's[51] $CHADS_2$ score distributions at baseline

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's NMA point estimates	Aspirin	**9,385**	**6.519**	–	–	–
	Rivaroxaban	**10,476**	**6.913**	**1,091**	**0.394**	**2,769**
Post-systemic embolism health state	Aspirin	9,461	6.500	–	–	–
	Rivaroxaban	10,538	6.907	1,077	0.407	2,646
Age-adjusted bleeding risk	Aspirin	9,398	6.516	–	–	–
	Rivaroxaban	10,507	6.908	1,109	0.391	2,834
Age-adjusted utilities	Aspirin	9,385	5.070	–	–	–
	Rivaroxaban	10,476	5.381	1,091	0.311	3,508
MI mortality	Aspirin	9,644	6.635	–	–	–
	Rivaroxaban	10,660	6.985	1,016	0.351	2,899
ERG's discontinuation rates	Aspirin	9,232	6.554	–	–	–
	Rivaroxaban	10,461	6.909	1,229	0.355	3,462
Risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No dyspepsia	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	Aspirin	**9,566**	**5.159**	–	–	–
	Rivaroxaban	**10,739**	**5.424**	**1,173**	**0.265**	**4,418**

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; NMA, network meta-analysis; QALY, quality adjusted life year; TIA, transient ischaemic attack.

Table 7. Results of ERG adjustments to the comparison of rivaroxaban and warfarin, based on the results of the ERG's NMA and Gallagher's [51] $CHADS_2$ score distributions at baseline

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
ERG's NMA point estimates	**Warfarin**	**8,757**	**6.875**	**–**	**–**	**–**
	Rivaroxaban	**9,234**	**6.960**	**477**	**0.085**	**5,616**
INR cost adjustment	Warfarin	**8,458**	**6.875**	**–**	**–**	**–**
	Rivaroxaban	**9,234**	**6.960**	**776**	**0.085**	**9,136**
Post-systemic embolism health state	Warfarin	8,757	6.875	–	–	–
	Rivaroxaban	9,323	6.952	566	0.077	7,372
Age-adjusted bleeding risk	Warfarin	8,841	6.861	–	–	–
	Rivaroxaban	9,304	6.948	464	0.087	5,325
Age-adjusted utilities	Warfarin	8,757	5.355	–	–	–
	Rivaroxaban	9,234	5.421	477	0.066	7,193
MI mortality	Warfarin	8,964	6.960	–	–	–
	Rivaroxaban	9,438	7.039	474	0.080	5,956

Monitoring cost of bleeding health states	Warfarin	8,747	6.875	–	–	–
	Rivaroxaban	9,234	6.960	487	0.085	5,736
Risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No dyspepsia	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	**Warfarin**	**8,740**	**5.409**	**–**	**–**	**–**
	Rivaroxaban	**9,598**	**5.465**	**857**	**0.056**	**15,189**
Exploratory analysis of removal of fixed costs	Warfarin	7,891	5.409	–	–	–
	Rivaroxaban	9,598	5.465	1,707	0.056	30,244

Table 8. Results of ERG adjustments to the comparison of rivaroxaban and aspirin, based on results of the ERG's NMA and Gallagher's [51] $CHADS_2$ score distributions at baseline in warfarin suitable patients

Analysis	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
Manufacturer's NMA point estimates	Aspirin	**7,800**	**6.633**	**–**	**–**	**–**
	Rivaroxaban	**9,234**	**6.960**	**1,434**	**0.328**	**4,377**
Post-systemic embolism health state	Aspirin	7,789	6.623	–	–	–
	Rivaroxaban	9,323	6.952	1,533	0.329	4,655
Age-adjusted bleeding risk	Aspirin	7,832	6.628	–	–	–
	Rivaroxaban	9,304	6.948	1,472	0.320	4,601
Age-adjusted utilities	Aspirin	7,800	5.161	–	–	–
	Rivaroxaban	9,234	5.421	1,434	0.260	5,518
MI mortality	Aspirin	8,032	6.765	–	–	–
	Rivaroxaban	9,438	7.039	1,406	0.275	5,120
ERG's discontinuation rates	Aspirin	7,370	6.696	–	–	–
	Rivaroxaban	9,193	6.958	1,823	0.262	6,958
Risk suspension	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No TIA	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
No dyspepsia	Impact on ICER undeterminable, but likely to favour rivaroxaban (i.e., decrease the ICER)					
ERG alternative base case	Aspirin	**7,628**	**5.291**	**–**	**–**	**–**
	Rivaroxaban	**9,559**	**5.464**	**1,931**	**0.173**	**11,133**

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; NMA, network meta-analysis; QALY, quality adjusted life year; TIA, transient ischaemic attack.