SUBMISSION TO

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA) of Rivaroxaban (Xarelto®)

Bayer Plc

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List of Abbreviations

AC	Anticoagulation
ACS	Acute Coronary Syndrome
ACTS	Anti-Clot Treatment Scale
AE(s)	Adverse events
AF	Atrial Fibrillation
AFNET	German Atrial Fibrillation Competence NETwork
ALT	Alanine Transaminase
ASA	Acetylsalicylic Acid (aspirin)
AST	Aspartate aminotransferase
BMI	Body Mass Index
BNF	British National Formulary
CABG	Coronary Artery Bypass Graft (surgery)
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
COPD	Chronic Obstructive Pulmonary Disease
CrCL	Creatinine Clearance
cTTR	Centre Time in Therapeutic Range
CV	Cardiovascular
DSMB	Data Safety and Monitoring Board
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
EM(E)A	European Medicines Agency
ESC	European Society of Cardiology
FAD	Final Appraisal Determination (in relation to NICE)
FDA	Food & Drug Administration
GCP	Good Clinical Practice
GP	General Practitioner
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRG	Healthcare Resource Groups
HRQoL	Health Related Quality of Life
IC	Intracranial
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICUR	Incremental Cost-Utility Ratio
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
ITT	Intention To Treat
IVRS	Interactive Voice Response System
LFT(s)	Liver Function Test(s)
LMWH	Low Molecular Weight Heparin
LOS	Length of Stay

LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LY	Life-Years
LYG	Life-Years Gained
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MI	Myocardial Infarction
min	minute
ml	millilitre
mmHg	millimeters Mercury
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network Meta-Analysis
NRAF	National Registry of Atrial Fibrillation
NVAF	Non-Valvular Atrial Fibrillation
NYHA	New York Heart Association
OAC	Oral Anticoagulation / Anticoagulant
Od	Once daily
OWSA	One Way Sensitivity Analysis
PbR	Payment by Results
PCI	Percutaneous Coronary Intervention
PCT	Primary Care Trust
PE	Pulmonary Embolism
PP	Per Protocol
PPI	Proton Pump Inhibitor
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTS	Patient Transport Service
QALY	Quality Adjusted Life Years
QOF	Quality and Outcomes Framework
RCT	Randomised Controlled Trial
RF	Risk Factor
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
SAE	Serious Adverse Event
SE	Systemic Embolism
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SOT	Safety On-Treatment (population)
SPAF	Stroke Prevention in Atrial Fibrillation
SPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis in Myocardial Infarction (in relation to bleeding)
TSQM	Treatment Satisfaction Questionnaire
TTR	Time in Therapeutic Range
Tx	Therapy / Treatment
UK	United Kingdom
ULN	Upper Limit of Normal
US(A)	United States (of America)

VKA	Vitamin K Antagonist
vs	versus
VTE	Venous Thromboembolism

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Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.

Rivaroxaban (Xarelto®) has been submitted for regulatory approval for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation via the EU centralised process. [redacted]

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.

Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.

Rivaroxaban will be available as 20mg film coated tablets. 15mg tablets will be available for those patients with moderate or severe renal impairment.

The tablets will be available in pack sizes of 28 and 100 tablets at a price of [redacted]

The indication(s) and any restriction(s).

The anticipated indication is:

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.

The recommended course of treatment.

Therapy with rivaroxaban should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding.

The main comparator(s).

Warfarin is the main comparator in England and Wales. In clinical practice, some patients eligible for warfarin are not prescribed it but instead receive aspirin or no treatment.

Dabigatran is currently undergoing evaluation by NICE.

Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.

The key clinical evidence comparing rivaroxaban with warfarin in the submission comes from a single head to head RCT - the Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study.

Network meta-analysis was used for comparing rivaroxaban to aspirin, no treatment and dabigatran.

The main results of the RCTs and any relevant non-RCT evidence.

The primary efficacy endpoint of the ROCKET AF trial (composite of stroke and non-central nervous system systemic embolism) demonstrated non-inferiority of rivaroxaban compared to warfarin for the pre-specified per protocol analysis. Superiority in the pre-specified safety on treatment was also then achieved.

The primary safety objective of ROCKET AF was assessed by the composite of major and non-major clinically relevant bleeding events. For the primary safety endpoint, results indicated a comparable safety profile of rivaroxaban to warfarin, with no statistically significant difference between the two treatments

There are no relevant non-RCTs included in this submission.

In relation to the economic evaluation, details of:

the type of economic evaluation and justification for the approach used

the pivotal assumptions underlying the model/analysis

the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.

Atrial fibrillation is a chronic disease with the risk of events over a prolonged period of time. As the potential events are associated with costs and health outcomes, a cost-utility evaluation was conducted.

A Markov model was developed to assess the long-term costs and health outcomes of rivaroxaban for the secondary prevention of stroke and non-CNS systemic embolism in non-valvular AF compared to the standard of care (warfarin).

The model used demographic data, event rates and relative risks from the ROCKET AF trial combined with UK specific epidemiology data to estimate the prognosis of patients experiencing stroke, IC haemorrhage and MI after treatment with warfarin, rivaroxaban and other comparators.

The main assumptions underlying the model were that: the ROCET AF data are applicable to a UK population with AF; that events prevented by therapy will have lasting consequences; and, that displacing warfarin will reduce the requirement for visitis and INR monitoring.

Tabulation of the base-case results as follows:

Table 1. Base-case cost-effectiveness results

	Rivaroxaban	**Warfarin**
Total costs	£8,941	£8,200
Difference in total costs	N/A	£740
LYG	9.272	9.221
LYG difference	N/A	0.051
QALYs	7.037	6.998
QALY difference	N/A	0.039
ICER	N/A	£18,883

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

Subgroup analyses considered and clinical- and cost-effectiveness results.

We expect a low likelihood of clinicians switching patients well controlled on warfarin to another oral anticoagulant. Therefore a number of subgroups have been evaluated in order to allow appropriate prioritisation of treatment with rivaroxaban:

- Patients who are poorly controlled on warfarin and therefore have a requirement for frequent INR monitoring.

Table 2 Cost effectiveness results – poorly controlled on warfarin

	Rivaroxaban	**Warfarin**
Total costs	£8,941	£10,423
Difference in total costs	N/A	-£1,482
LYG	9.272	9.221
LYG difference	N/A	0.051
QALYs	7.037	6.998
QALY difference	N/A	0.039
ICER	N/A	Rivaroxaban dominates

- Warfarin naive – patients who have not been previously treated with warfarin (consistent with the sub-group identified within the Final Scope for this Single Technology Appraisal)

Table 3 Cost effectiveness results – warfarin naive

	Rivaroxaban	**Warfarin**
Total costs	£8,941	£8,333
Difference in total costs	N/A	£607
LYG	9.272	9.221
LYG difference	N/A	0.051
QALYs	7.037	6.998
QALY difference	N/A	0.039
ICER	N/A	£15,494

- Warfarin unsuitable – specifically patients with atrial fibrillation who have previously discontinued warfarin for reasons other than bleeding or for whom the clinician anticipates the patients would not be able to manage regular INR monitoring and dose adjustments.

Table 4 Cost effectiveness results – warfarin unsuitable

	Rivaroxaban	No treatment	Aspirin
Total costs	£11,249	£10,753	£10,367
Difference in total costs	N/A	£496	£883
LYG	9.151	8.654	8.782
LYG difference	N/A	0.497	0.369
QALYs	6.833	6.285	6.409
QALY difference	N/A	0.548	0.424
ICER	N/A	£905	£2083

Table 5 Incremental cost effectiveness results – aspirin and no treatment

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aspirin based on data from NMA	10,367	6.409			
No therapy based on data from NMA	10,753	6.285	386	-0.124	Dominated
Rivaroxaban based on data from NMA	11,249	6.833	883	0.424	2,083

- Patients currently taking dabigatran 110mg bid or 150mg bid as their anti-thrombotic therapy. This population has been included in this as dabigatran was identified in the Final Scope as a potential comparator, but the Single Technology Appraisal for dabigatran etexilate is still ongoing at the time of this submission.

Table 6 Cost effectiveness results vs dabigatran

	Rivaroxaban	Dabigatran
Total costs	£12,397	£13,310
Difference in total costs	N/A	-£913
LYG	9.056	9.056
LYG difference	N/A	0
QALYs	6.712	6.712
QALY difference	N/A	0
ICER	N/A	Rivaroxaban dominant

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

Description of technology under assessment

Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

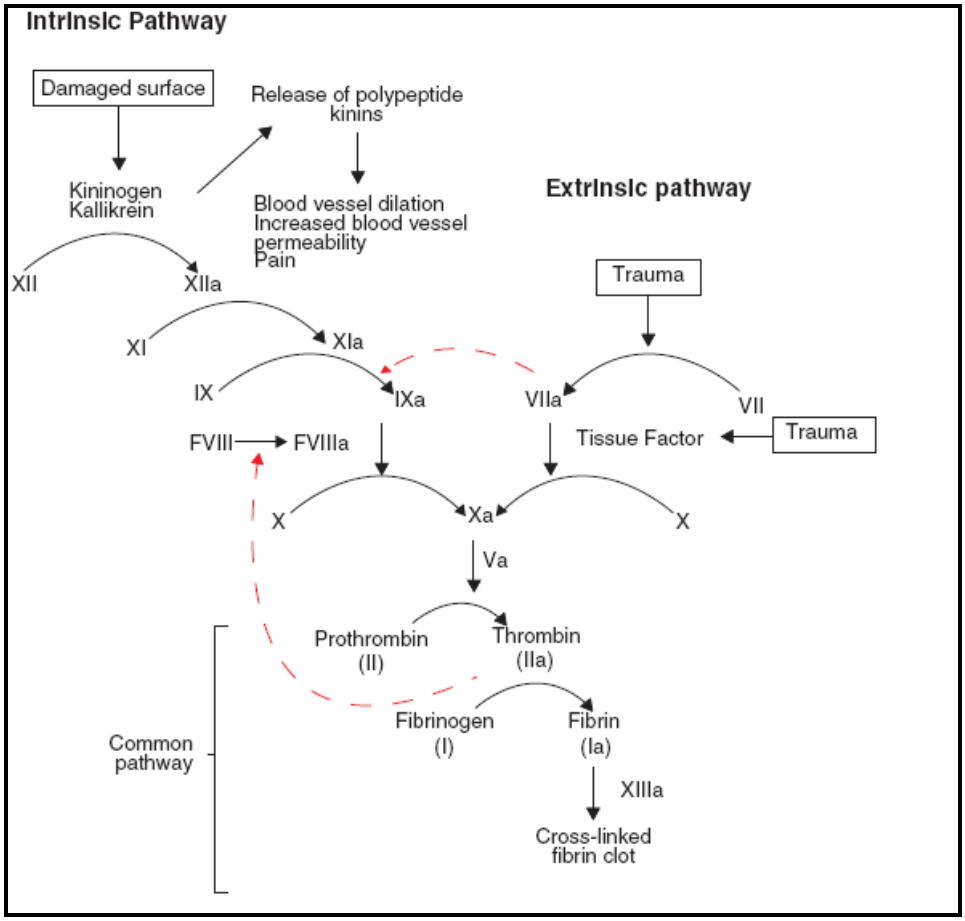
Brand name	Xarelto
Approved name	Rivaroxaban
Therapeutic class	Oral anticoagulant

What is the principal mechanism of action of the technology?

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi (see Figure 1 below).

Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Figure 1. Schematic representation of the clotting cascade



Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Rivaroxaban holds a UK marketing authorisation for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Rivaroxaban was submitted for regulatory approval for the indication under appraisal in December 2010 via the EU centralised process. [redacted]

Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

This information is not available at this time.

What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The anticipated indication is:

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.

Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

ROCKET AF (NCT00403767) – completed

A Prospective, Randomised, Double-Blind, Parallel-Group, Multicenter, Non-inferiority Study Comparing the Efficacy and Safety of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Non-Valvular Atrial Fibrillation.

J-ROCKET AF (NCT00494871) – completed [Japanese population]

Evaluation of the Efficacy and Safety of Rivaroxaban for the Prevention of Stroke and Non-central Nervous System Systemic Embolism in Subjects With Non-valvular Atrial Fibrillation.

If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that rivaroxaban will be available in the UK for this indication in [redacted]

Does the technology have regulatory approval outside the UK? If so, please provide details.

Rivaroxaban is yet to gain regulatory approval for this indication in other countries outside the UK.

Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Rivaroxaban will be assessed by SMC for this indication. We intend to submit by January 2012.

For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 7. Unit costs of technology being appraised

Pharmaceutical formulation	15mg and 20mg film-coated tablets
Acquisition cost (excluding VAT)	The provisional price is [redacted]
Method of administration	Oral
Doses	15mg and 20mg
Dosing frequency	Once daily
Average length of a course of treatment	Therapy should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding
Average cost of a course of treatment	The provisional annual cost will be [redacted]
Anticipated average interval between courses of treatments	Treatment is continuous unless interruption is required e.g. surgical intervention
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 -29 ml/min) renal impairment the recommended dose is 15 mg once daily

For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

It is not anticipated that there will be any additional tests or investigations required for selection of patients appropriate for rivaroxaban.

There are no particular administration requirements for rivaroxaban.

Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Rivaroxaban is administered at a fixed dose once daily and there is no requirement for routine monitoring of coagulation parameters during treatment.

Warfarin, the oral anticoagulant used most frequently in current clinical practice has a narrow therapeutic index with a need to balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage. As a result, warfarin requires dose adjustment using frequent, inconvenient and costly INR monitoring.

What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Whilst patients with atrial fibrillation may be prescribed other medication for their condition, rivaroxaban would be used alone as prophylactic anticoagulant therapy.

Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

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). Trends of increasing AF prevalence over time have been observed(5) and as the prevalence of the condition increases with age, atrial fibrillation will become increasingly common due to the aging population.

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).

AF is associated with a prothrombotic state leading to a predisposition to thrombus formation(1). Thromboembolic stroke occurs when stagnant blood in the fibrillating atrium forms a thrombus that then embolises to the cerebral circulation, blocking arterial blood flow and causing ischaemic injury(10).

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).

Additionally, AF is associated with an increased risk of systemic embolism (SE) which may result in major damage to limbs and organs(11).

Therefore, effective prevention of stroke and non-CNS embolism in atrial fibrillation is important to reduce this burden and improve health and socioeconomic outcomes.

How many patients are assumed to be eligible? How is this figure derived?

The total number of patients in England and Wales on the disease register associated with QOF with a diagnosis of AF is 822,825(8;12). Of these, 93% have non-valvular AF(3), which equates to 765,228 patients.

As highlighted above in section 2.1, the underlying risk of stroke in patients with non-valvular AF (NVAF) is dependent on the presence or absence of a number of different risk factors. The level of risk influences the choice of thromboprophylaxis.

It is anticipated that the licence for rivaroxaban will be:

"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."

This equates to a $CHADS_2$ score (see below in section 2.4) of ≥1. The proportion of patients with a $CHADS_2$ score of zero is 12.6% of the AF population(13). The remaining patients have a $CHADS_2$ score of ≥1 (87.4%). The estimated number of patients eligible for rivaroxaban in England and Wales is therefore 662,747.

Table 8. Eligible population

	% of all AF patients	**Patient numbers**
All AF	100%	822,825
NVAF	93%	765,228
$CHADS_2$ ≥1	87%	669,003

Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE guideline

CG36 The management of atrial fibrillation. June 2006.

NICE technology appraisals addressing the management of atrial fibrillation:

TA197 Dronedarone for the treatment of non-permanent atrial fibrillation. August 2010

NICE appraisals in development:

Dabigatran etexilate for the prevention of stroke or systemic embolism in people with atrial fibrillation.

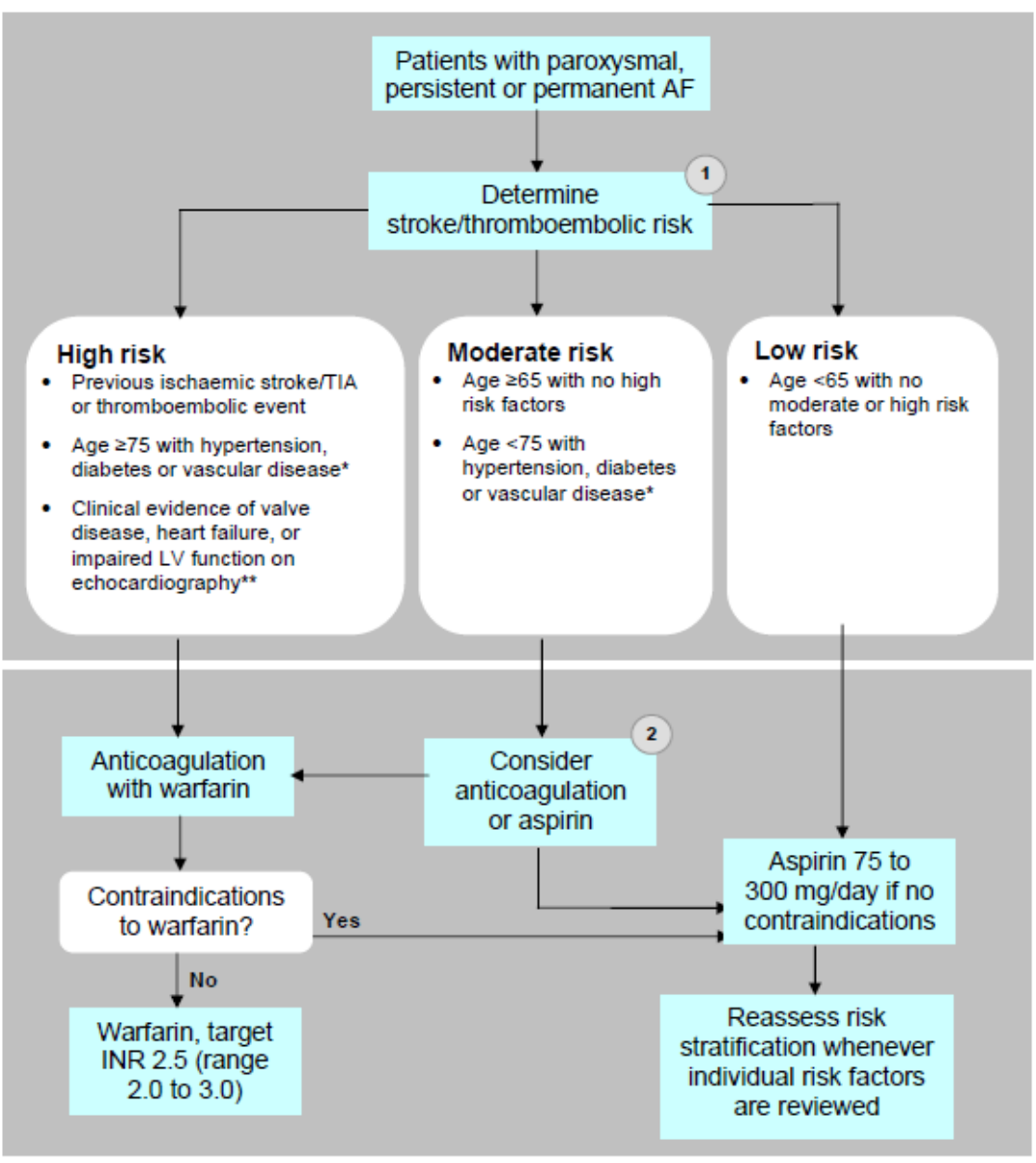
Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

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

Recommended place of oral anticoagulants – stroke risk assessment

There are a number of different tools for assessing stroke risk. NICE CG36(1) from 2006 uses the algorithm on the following page (Figure 2), although it should be noted that this guideline may be updated, with the review decision due in August 2011.

Figure 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.

ROCKET AF enrolled patients for whom guidelines(14) recommended anticoagulation. Recruitment was based on the $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] risk index(15) classification system. This is also 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).

Current management of oral anticoagulants in the UK

Warfarin, the oral anticoagulant used most frequently in clinical practice has a number of well reported limitations, including:

- A narrow therapeutic index with a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage
- Response that is significantly influenced by genetic polymorphisms, diet, concomitant medications (which may be of particular concern in a co-morbid elderly population), herbal supplements and intercurrent illness
- The requirement for dose adjustment using frequent, inconvenient and costly INR monitoring. The frequency of monitoring varies depending on individual patient characteristics.

Warfarin management therefore has an infrastructure around it – for blood sampling, testing and dose adjustment. Anticoagulant services are managed in a number of settings in the UK depending on the locally commissioned arrangements, including:

- Secondary care
- Secondary care satellite clinics
- Primary care – GP led, nurse led, community pharmacy led
- "Hybrid" – where there is a mixture of the different settings involved at different stages of the care pathway or for different patient types

Clinical pathway for rivaroxaban

The clinical pathway for rivaroxaban will still require stroke risk assessment but will not involve the infrastructure that is required for warfarin management.

Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

It is reported that there is underuse of warfarin in eligible AF patients within the UK. The costing report associated with NICE CG36 state that a number of studies of routine clinical practice have suggested that prophylaxis is generally underused. The report estimated that approximately 46% of patients eligible for warfarin were untreated(16;17). This represents a significant number of patients remaining exposed to the risk of stroke and other embolic events.

It is likely that under-treatment with warfarin is due to concerns from both patients and clinicians about the implications of the narrow therapeutic index with warfarin. Maintaining optimal INR control is necessary to avoid the risk of over- or under-anticoagulation and for some patients this may be more difficult due to factors such as poor compliance, multiple changes in prescribed medication, lifestyle or confusion/ failing memory.

Please identify the main comparator(s) and justify their selection.

Warfarin is the oral anticoagulant most commonly used in practice in the UK and is therefore the main comparator. However, as there is significant under-treatment in warfarin eligible patients, aspirin and “no treatment” are also considered within the economic modelling.

Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

For clinically significant bleeding, usual treatment measures should be considered, including fluid replacement and hemodynamic support, blood transfusion, and fresh frozen plasma.

If bleeding cannot be controlled, consideration should be given to the administration of a procoagulant.

Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

It is anticipated that in the majority of cases, rivaroxaban will be initiated during a secondary care outpatient consultation with follow up in primary care by the GP. Costs for these consultations are sourced from National Schedule of Reference Costs 2009/10 for NHS Trusts(18) and the PSSRU(19), respectively. There are no administration costs associated with use of rivaroxaban and there is no requirement for routine monitoring of coagulation parameters. This is in contrast to warfarin, the main comparator, which is managed within

an established infrastructure in the NHS, required for blood sampling, testing and dose adjustment.

As mentioned in section 2.4, anticoagulant services for warfarin are managed in a number of settings in the UK depending on the locally commissioned arrangements, including:

- Secondary care
- Secondary care satellite clinics
- Primary care – GP led, nurse led, community pharmacy led
- "Hybrid" – where there is a mixture of the different settings involved at different stages of the care pathway or for different patient types

The prevalence of different models of anticoagulation service in the UK was identified via a UK survey conducted in 2011(20).

Resource use associated with warfarin management in terms of the annual number of clinic appointments was sourced from NICE CG 36 costing report(17), NHS evidence clinical knowledge summaries(21) and a real world evaluation conducted in the UK in 2010(22).

The cost associated with managing patients on warfarin in different care settings were taken from National Schedule of Reference Costs 2009/10 for NHS Trusts(18) and NICE CG36 costing report(17). The cost associated with primary care GP consultations was taken from the PSSRU(19) and costs associated with patient transport services, for those who required it, from National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined(18).

Does the technology require additional infrastructure to be put in place?

Rivaroxaban does not require additional infrastructure to be put in place. Indeed, over time, the availability of rivaroxaban will allow for rationalisation of existing costly anticoagulation services. It will also assist with managing demand for such services in the future, which will inevitably rise with the ageing population.

Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

Identification of equity and equalities issues

Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

We are not aware of any equity or equality issues.

Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

We are not aware of any equity or equality issues.

How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable.

Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with non-valvular atrial fibrillation who are at moderate to high risk of stroke and non-CNS systemic embolism	Adults with non-valvular atrial fibrillation with one or more risk factors for stroke and systemic embolism, such as congestive heart failure, hypertension, age ≥ 75 years, 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. This is in line with the proposed indication.
Intervention	Rivaroxaban	Rivaroxaban	
Comparator(s)	• Warfarin • Dabigatran 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	The outcome measures to be considered include: • stroke • non-CNS systemic embolism • myocardial infarction • mortality • transient ischaemic attacks • adverse effects of treatment including haemorrhage • health-related quality of life	The outcome measures to be considered include: • 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 reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies	• 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	

	being compared. Costs will be considered from an NHS and Personal Social Services perspective.	perspective of the NHS and PSS	
Subgroups to be considered	If evidence allows, the following subgroups should be considered: • people who have not been previously treated with warfarin	If evidence allows, the following subgroups should be considered: • 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.	

Section B – Clinical and cost effectiveness

Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

Identification of studies

Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A systematic search of the literature was undertaken to identify randomised, placebo or active-controlled, comparative studies investigating the efficacy and safety of rivaroxaban for stroke prevention in non-valvular atrial fibrillation (AF) was undertaken on February 2nd 2011 using Medline, Medline in process, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL). The search formed part of a broader search for any evidence to support indirect comparisons or network meta-analysis (NMA) of rivaroxaban versus any other relevant treatments in stroke prevention in patients with AF, in the event that this was required for the submission. Within the broader search, studies comparing long-term treatment (≥12 weeks), with any of the following drugs as interventions, were included: vitamin K antagonists (VKAs), aspirin, antiplatelet agents, idraparinux, rivaroxaban, ximelagatran, dabigatran and apixaban.

Full details of the literature search strategy including search terms employed are provided in Section 9.2, Appendix 2. In addition, the reference lists from any Cochrane reviews were checked for other relevant studies and a search of the Bayer in-house database was also undertaken for non-published literature.

When designing the search strategies several pilot searches were performed including broader terms for anticoagulants and antithrombotics. The inclusion of free text and controlled vocabulary terms for "anticoagulants" and "antithrombotics" (and all variations of these terms) reduced the specificity of the search significantly, therefore these terms were not included in the final search strategy.

Study selection

Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.

All the records retrieved from the search strategies were screened and assessed for inclusion according to the eligibility criteria (described in section 5.2.1). Two reviewers independently assessed all the potential studies identified. A flow diagram of the numbers of studies included and excluded at each stage is provided in section 5.2.2

Randomised controlled trials comparing long-term rivaroxaban treatment (≥12 weeks), with antithrombotic therapies in patients with chronic non-valvular atrial fibrillation (AF) were included, as were any rivaroxaban studies that reported results for sub-group of patients with non-valvular AF.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were as wide as possible to reflect the relevant patient population. Patients with prosthetic cardiac valves were excluded as they are managed within a different INR range.

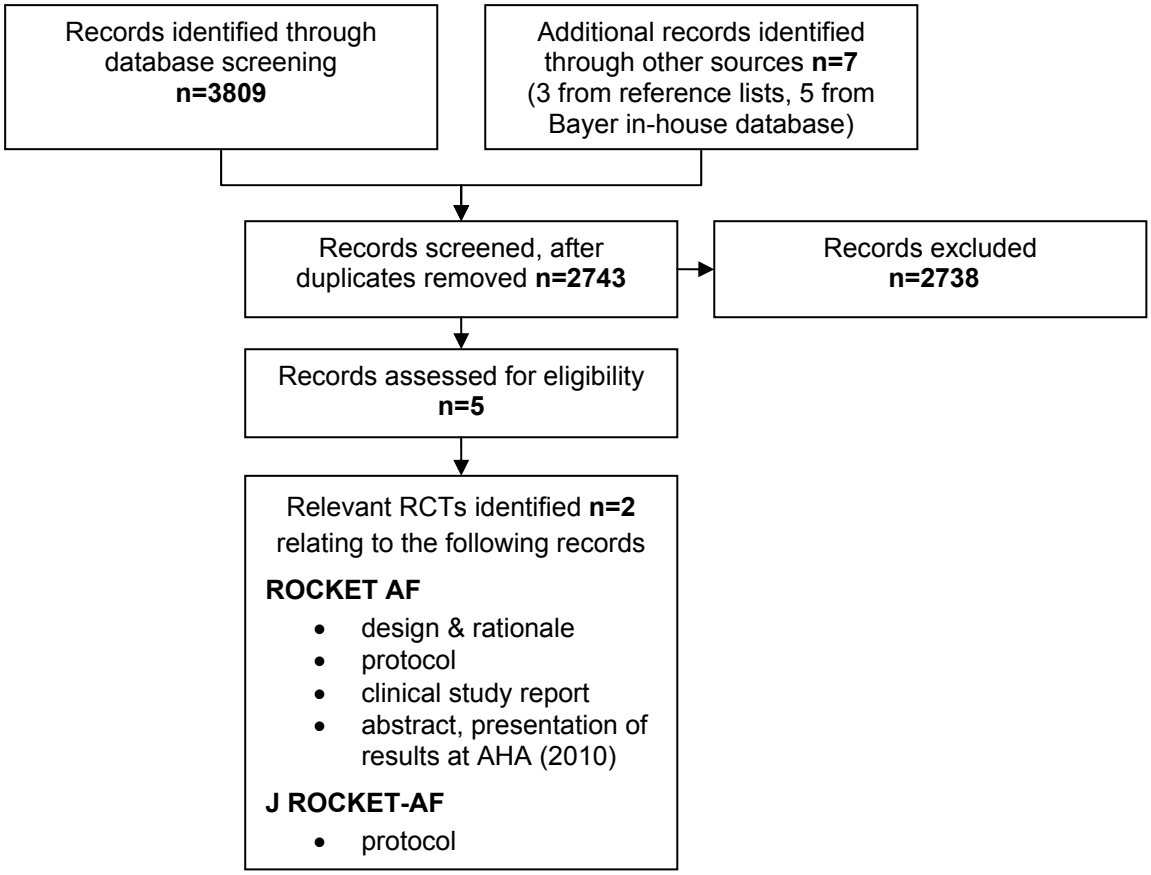
Table 9. Eligibility criteria used in search strategy

	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 (TIA); 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

Only studies reported in full were included in the review; studies that were only reported in abstract form were not included. Studies that reported results for sub-groups of patients with non-valvular AF were also included.

A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure 3. Prisma Flow diagram



When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Multiple publications

The systematic review identified multiple reports of one comparative study - the Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) involving rivaroxaban. In addition, during the writing of the submission, results of the ROCKET AF study were published in full in the New England Journal of Medicine (NEJM)(23). The following sources of information on ROCKET AF have been used throughout this section:

- Study design and methodology of the ROCKET AF study(24)
- ROCKET AF protocol(25)
- Clinical Study Report(26)

- Results presented at American Heart Association, Chicago, 2010 (Patel, 2010)(27)
- ROCKET AF study – full publication and supplementary appendix (NEJM)(23;28)

Where multiple reports of the same study were identified, data were extracted and reported as a single study.

Complete list of relevant RCTs

Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form.

Table 10. List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
ROCKET AF(23-27)	**Rivaroxaban** 20mg 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 M et al 2011(23;28)
NCT00494871 J-ROCKET AF	**Rivaroxaban** 15mg 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	Masatsugu H et al. 2011(29)

†Defined as calculated creatinine clearance [CrCl] between 30-49ml/min, inclusive

Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Selected: The ROCKET AF study compares rivaroxaban with dose-adjusted warfarin in a relevant population and at a relevant target INR for warfarin (target INR of 2.5 (range 2.0 to 3.0, inclusive), applicable to the UK population and the current decision problem in this submission.

When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For

example, when studies have been identified but there is no access to the level of trial data required, this should be indicated

Excluded: The other Phase III study listed in section 5.2.4, J-ROCKET AF (NCT00494871)(29), was conducted as a supportive safety study in the Japanese population. Clinical practice of anticoagulation management is different in Japan, with lower target INR levels than the rest of the world. Efficacy results from J-ROCKET AF provided supportive evidence to the efficacy conclusions from the ROCKET AF study but as the dose and clinical practice used in this study was different to the main ROCKET AF study and the ethnic origin was not considered representative of the UK population, no further reference to this study is made in this submission.

List of relevant non-RCTs.

Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table**.**

No studies of this nature were considered relevant to the decision problem.

Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

ROCKET AF: Rivaroxaban – Once daily, oral, direct factor Xa Inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation(23-28)

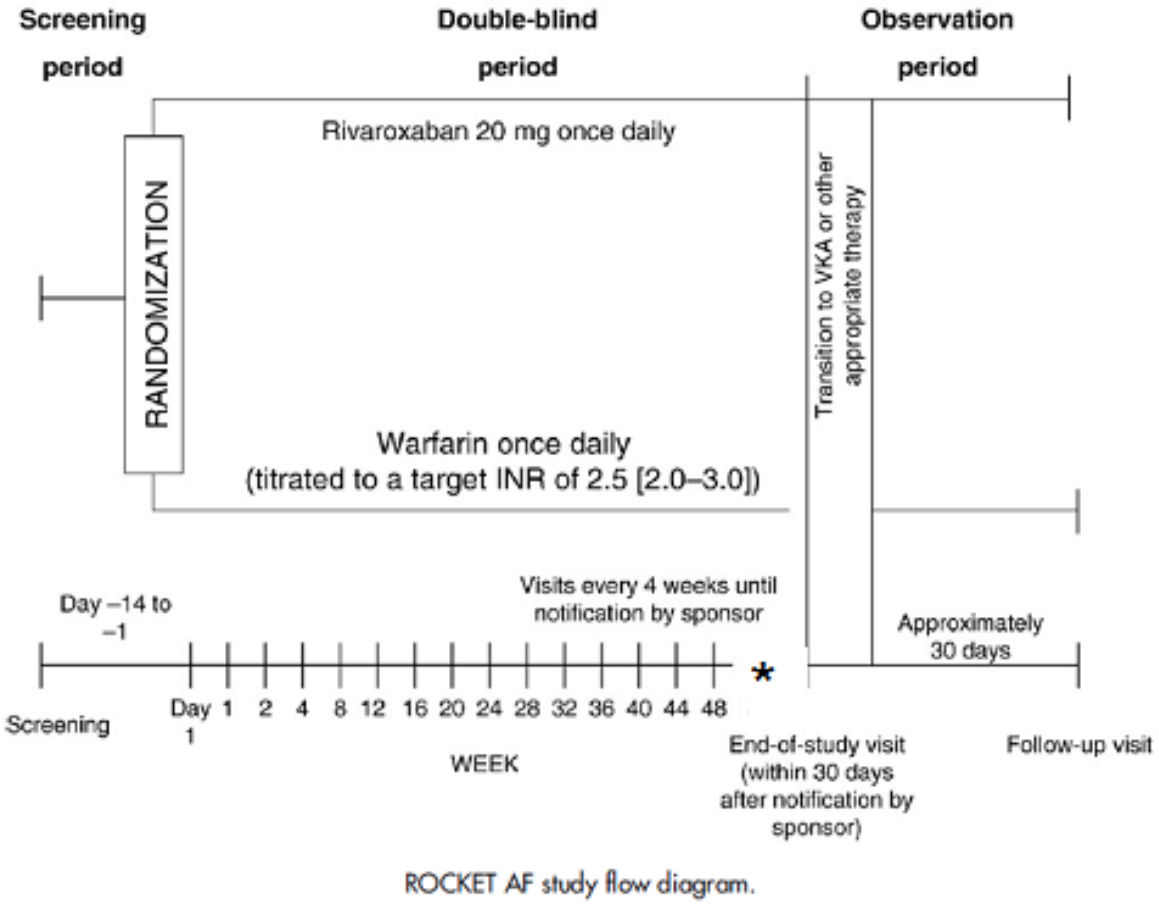
The **ROCKET AF study**, involving over 14,000 participants worldwide, had a primary study objective (using per-protocol, on treatment analysis) to demonstrate that the efficacy of rivaroxaban is non-inferior to that of dose-adjusted warfarin titrated to a target INR of 2.5 (range 2.0-3.0 inclusive) for the prevention of thromboembolic events in patients with non-valvular AF(23). The principal safety objective of ROCKET AF was assessed by the composite of major and non-major clinically relevant bleeding events(23).

Key features of the ROCKET AF study are summarised in Table 11 and Figure 4.

Table 11. Key features of rivaroxaban phase III RCT in the prevention of stroke and thromboembolism in AF(23-28)

	Treatments (number of patients)	Countries	Patient type	Primary endpoints
ROCKET AF	Rivaroxaban (n=7131) 20mg once daily (*patients with a calculated creatinine clearance of 30 to 49 mL/min received a reduced dose of rivaroxaban of 15 mg od*) vs. Dose-adjusted warfarin (to maintain a therapeutic INR (target 2.5, range 2.0-3.0)) (n=7133)	1178 sites across 45 countries. Each country was assigned to 1 of 5 regions as follows: ▪ **Asia Pacific:** Australia, China, Hong Kong, India, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand ▪ **East Europe:** Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Turkey, Ukraine ▪ **Latin America:** Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru, Venezuela ▪ **North America:** Canada, United States ▪ **West Europe:** Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, United Kingdom.	Non-valvular Atrial Fibrillation with a history of stroke/ TIA or systemic embolism or ≥2 additional independent risk factors for stroke	**Efficacy** Composite of all-cause stroke and non-central nervous system (non-CNS) systemic embolism **Safety** Composite of major & clinically relevant non-major bleeding For further details of the definitions and timings of assessments see section 5.3.2

Figure 4. ROCKET AF study design. Adapted from reference(24)



*Patients attended follow-up visits every 4 weeks after week 4 until site notification by sponsor. The duration of the treatment period depended on the time required to accrue approximately 405 adjudicated primary efficacy endpoint events in the per protocol population/on treatment. As a result, the time on study drug varied from patient to patient depending upon the time of the patient's enrolment. The expected study duration rate was approximately 40 months from first patient enrolled to the occurrence of the last event.

Methods

Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

Design

ROCKET AF was an international, multicentre, prospective, randomised, double-blind, double-dummy, event-driven, phase III non-inferiority study designed to compare the efficacy and safety of rivaroxaban with standard therapy vitamin K antagonist (warfarin) in the prevention of stroke and thromboembolic events in patients with non-valvular AF at risk of future thromboembolic events. This kind of rigorous study design is generally considered the 'gold standard'. The study design(24) and results(23;28) have been fully published.

Study enrolment started in December 2006 and was completed in June 2009, during which time 14,264 patients were randomised to treatment (n=7,131 rivaroxaban; n=7,133 warfarin).

The study was divided into a screening period, a double-blind treatment period (closing with an end of study visit) and a 30 day post-treatment observation period (closing with a follow-up visit). Treatment continued until the pre-specified number of on-treatment primary clinical efficacy endpoint 'events' had occurred (site notification). The site notification date refers to the date sites were notified by the Executive Committee that the required number of primary endpoint events, as deemed by the clinical events committee (CEC), had been reached. Site notification date was 28th May 2010.

At the end of study visit (or earlier if patients discontinued study drugs prematurely), patients were transitioned from study drug to an open-label VKA or other appropriate regimen (VKA, aspirin or no therapy) as determined by the investigator (rivaroxaban was not available for use in an open-label extension study). The end-of-study transition from blinded study drug to open-label warfarin (or other VKA or antithrombotic therapy) was to be done without breaking the study blind.

Discontinuation of study treatment or withdrawal from the study occurred upon safety concerns, pregnancy, stroke or systemic embolism, diagnosis of HIV, abnormal liver function, creatinine clearance <25mL/min on two consecutive measurements, noncompliance, or a need for an excluded medication.

Duration

The duration of the treatment period depended on the time required to accrue approximately 405 adjudicated primary efficacy endpoint events in the per protocol population/on-treatment. As a result, the time on study drug varied from patient to patient depending upon the time of the patient's enrolment. The expected study duration rate was approximately 40 months from first patient enrolled to the occurrence of the last event.

The median duration of treatment exposure was 590 days. Over 50% of patients received treatment for at least 18 months.

Method of randomisation

Patients from 45 countries (1178 trial sites(23)), including the UK, were randomised in a ratio of 1:1 to either the 'Rivaroxaban group' or the 'Warfarin group'. Randomisation was performed with the use of a central 24-hour, computerised, automated voice-response system (Interactive Voice Response System – IVRS). Regimen allocation was balanced according to country, prior use of vitamin K antagonists, and a history of stroke, transient ischaemic attack (TIA) or non-CNS systemic embolism. Stratification by country was performed to ensure balance across potential local differences in anticoagulation treatment practices. Stratification by prior VKA use and prior stroke, TIA or non-CNS systemic embolism events was performed since these factors are predictors of future events. 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 IVRS assigned a unique patient number and treatment code and corresponding medication kits for the duration of study. Investigators were not provided with randomisation codes and the blind was not to be broken except in emergency situations, for which the investigator had to contact the sponsor.

Blinding

A double-blind, double-dummy design was chosen to minimise bias in co-interventions and interpretation of clinical events.

Rivaroxaban was administered once-daily as a fixed dose that did not require titration. As warfarin did require titration and modification over time depending on the INR, to maintain the study blind, sham INR results were provided for patients in the rivaroxaban arm. A point-of-care coagulation testing device displayed a code number that when entered into the Interactive Voice Response System (IVRS) with the patient's study identification number, generates either the subject's real INR or a sham INR depending on the assigned treatment.

All suspected outcome events were classified and adjudicated by an independent clinical events committee (CEC) whose members were unaware of the treatment assignments.

To maintain the integrity of the blind, local unblinded INR measurements (i.e., not using the study point-of-care device) were discouraged for at least 3 days after the start of open-label VKA therapy (i.e. after discontinuing study drugs). After 3 days, VKA dosing was managed at the discretion of the treating physician using local unblinded INR measurements. If necessary, for patients with high risk of thromboembolism, bridging (e.g., low molecular weight heparin; LMWH) therapy could be administered at the discretion of the investigator during this transition period. In patients who were transitioned to open-label VKA treatment,

dosing was initiated only after discontinuation of study drug dosing in order to prevent those already receiving warfarin from receiving overlapping and excessive VKA treatment.

Intervention and comparator

Enrolled patients were randomised to one of two treatment regimens containing rivaroxaban or warfarin. Study drug and placebo tablets were taken in the evening with food:

1. '**Rivaroxaban group**' (n=7131) were given 20mg rivaroxaban once daily (no titration required) plus matching oral warfarin placebo once daily titrated to a sham INR of 2.5 (range 2.0-3.0 inclusive). Patients randomly assigned to rivaroxaban who had moderate renal impairment (CrCL 30-49 ml/min) at the time of randomisation received a reduced dose of rivaroxaban (15mg once daily) [redacted]

2. '**Warfarin group**' (n=7133) received oral warfarin once daily, titrated to a target INR of 2.5 (range 2.0-3.0 inclusive), plus matching oral rivaroxaban placebo once daily. Patients randomly assigned to warfarin with a baseline Creatinine Clearance 30-49ml/min [redacted]

Table 12. Treatment Assignments

Treatment Assignment	Rivaroxaban (20mg)[a]	Matching placebo (for rivaroxaban 20mg)	Warfarin (1,2.5 or 5mg)	Matching placebo (for warfarin 1,2.5 or 5mg)
Rivaroxaban	X			X
Warfarin		X	X	

[a] Patients with moderate renal impairment at screening had a dose adaptation to rivaroxaban 15mg p.o. once daily

Follow up

Patients were seen at fixed intervals that were identical for rivaroxaban and warfarin groups: week 1, week 2 and week 4 and every month thereafter, the 'End of Study visit', and a 'follow-up' visit 30 days later at the end of the observation period. At each visit a standardised questionnaire and examination took place 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 occurred as clinically indicated but at least every 4 weeks.

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

Participants

Provide details of the eligibility criteria (inclusion and exclusion) for the trial.

Inclusion and Exclusion criteria(23-28)

The inclusion/ exclusion criteria were designed to recruit patients considered representative of the majority of subjects with non-valvular atrial fibrillation for whom oral anticoagulant therapy is indicated.

Table 13. Eligibility criteria in the ROCKET AF study(24)

Trial no. (acronym): ROCKET- AF	
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 enrollment) ▪ 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.*	**Cardiovascular-related conditions** ▪ Prosthetic heart valve ▪ Planned cardioversion ▪ AF secondary to reversible disorders (ie, thyrotoxicosis) ▪ Known presence of atrial myxoma or left ventricular thrombus ▪ Active endocarditis ▪ Hemodynamically significant mitral stenosis ▪ **Haemorrhage risk-related criteria** ▪ 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 ▪ **Concomitant conditions and therapies** ▪ 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 >100 mg 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

Describe the patient characteristics at baseline. Highlight any differences between study groups.

Baseline Characteristics(23;26;27)

[redacted]. Results described here are for the ITT population (see Table 14).

Of the 14,264 patients randomised and valid for inclusion in the ITT population 8,604 (60%) were men (n=4,301 rivaroxaban; n=4,303 warfarin) and 11,879 patients (83%) were 'White' (n=5,922 rivaroxaban; n=5,957 warfarin).

The median age (25th, 75th) was 73 years (65,78).

The population recruited had substantial rates of co-existing illnesses.

Risk factors of prior stroke, TIA, or non-CNS systemic embolism were well balanced between the 2 treatment groups. Overall, 54.8% of subjects had a history of stroke, TIA, or non-CNS systemic embolism, with prior strokes occurring in [redacted] of the study population, TIAs in [redacted] of the study population, and non-CNS systemic emboli occurring in [redacted] of the study population. At baseline, 62% of subjects had congestive heart failure ([redacted] NYHA Class I, [redacted] NYHA Class II [redacted] NYHA Class III, [redacted] NYHA Class IV); 90.5% had hypertension; [redacted] had an age ≥ 75 years, and 40.0% had diabetes mellitus.

The mean CHADS2 score was 3.48 for the rivaroxaban group and 3.46 for the warfarin group. All but 3 subjects had baseline $CHADS_2$ of 2 or more (1 rivaroxaban and 2 warfarin patients).

The majority of patients (62.4%) received prior therapy with VKA and 36.49% of patients previously received acetylsalicylic acid therapy. Overall [redacted] had moderate renal impairment, defined as a baseline CrCL of 30 to 49 mL/min.

Table 14. Demographic and baseline data of ROCKET AF study participants (ITT population)

		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)
Race, n (%)	**White**	5,922 (83.05)	5,957 (83.51)	11,879 (83.28)
	Black	94 (1.32)	86 (1.21)	180 (1.26)
	Asian	897 (12.58)	889 (12.46)	1,786 (12.52)
	Other	218 (3.06)	201 (2.82)	419 (2.94)
Age in years	**Median (interquartile range)**	73 (65, 78)	73 (65, 78)	73 (65, 78)
	18 - <65	1,651 (23.15)	1,643 (23.03)	3,294 (23.09)
	65 - <75	2,360 (33.09)	2,381 (33.38)	4,741 (33.24)
	≥ 75	3,120 (43.75)	3,109 (43.59)	6,229 (43.67)
Baseline weight, (kg)	**Mean**	82.07	81.64	81.85
Baseline BMI (kg/m²)	**Median (interquartile range)**	28.3 (25.2-32.1)	28.1(25.1-31.8)	28.2 (25.1-32.0)
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)	2514 (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				
CHADS2, 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 (%) Yes		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 (MI), n (%)‡		1,182 (16.58)	1,286 (18.03)	2,468 (17.30)
Creatinine Clearance, median,		67.00 (52.00,	67.00 (52.00,	67 (52.00, 87.00)

		Rivaroxaban (n=7,131)	Warfarin (n=7,133)	Total (n=14,264)
(interquartile range) ml/min, n (%)		88.00)	86.00)	
Peripheral vascular disease, n (%)		401 (5.62)	438 (6.14)	839 (5.88)
Chronic obstructive pulmonary disease (COPD), 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)
Regions (%)	North America	1,339 (19)	1,342 (19)	2,681 (19)
	Latin America	940 (13)	938 (13)	1,878 (13)
	Asia-Pacific	1,055 (15)	1,054 (15)	2,109 (15)
	Eastern Europe	2,751 (38)	2,749 (38)	5,500 (39)
	Western Europe	1,046 (15)	1,050 (15)	2,096 (15)
*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 arm and n=7,125 in the warfarin arm. ‡ P<0.05 for the between-group comparison				

Median duration of treatment exposure was 590 days(23).

Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

Outcomes(23-27)

The **primary efficacy endpoint** in ROCKET AF was the composite of:

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

Stroke is defined as a sudden, focal neurologic deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily

identifiable cause, such as tumour or seizure. An event matching this definition that lasts less than 24 hours is considered a TIA. Advanced brain imaging helped distinguish haemorrhagic from ischaemic stroke. The outcome of all strokes was classified according to the Rankin scale (see Figure 5) at hospital discharge. Any death within 30 days of the onset of stroke was regarded as 'fatal stroke'.

Figure 5. Rankin Scale

Modified Rankin scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention
6	Patient death

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 **primary safety endpoint** was defined as the 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 the haemoglobin concentration of $\geq$2g/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), 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 are classified as minor bleeding.

Secondary endpoints were:

1. Major Secondary Endpoint 1 (Composite of stroke, non-CNS systemic embolism, and vascular death)(23;27)
2. Major Secondary Endpoint 2 (Composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death)(23;27)
3. All-cause mortality(27)
4. Individual components of the composite primary and major secondary endpoints(23)
5. Stroke outcome(28)
6. Individual bleeding event categories(23)
7. Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0(25)

The adjudication of MI as a clinical end point considers the occurrence relative to PCI or coronary artery bypass surgery (CABG). In the absence of PCI or CABG, MI is defined by clinical symptoms consistent with MI and cardiac biomarker elevation (troponin I or T, creatine kinase-muscle and brain subunit) greater than the upper limit of normal (ULN), the development of new pathologic Q waves in $\geq$2 contiguous electrocardiographic leads, or confirmed by autopsy.

For all suspected events (stroke, systemic embolism, MI, death, and major bleeding events), an independent, blinded, Clinical Events Committee (CEC) provided adjudication based on event specific forms and data collected from individual sites. Adjudication decisions were the basis for the final analyses.

Note - All intracranial haemorrhages were reviewed by CEC to determine if each event met the criteria of a stroke and / or a bleed event.

Reliability/ validity/ current use in clinical practice

All assessments, including clinical laboratory tests, and adverse events, were standard validated tests and evaluations were in accordance with GCP to ensure safety of patients participating in research. The definition and assessment of outcome parameters of 'death' and 'stroke' and systemic embolic events are as recommended in a consensus conference organised by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA)(30). Stroke and non-CNS embolism have been used in previous studies examining the effect of warfarin in non-valvular atrial fibrillation(31-34). By the very nature of these drugs, there is also an associated risk of bleeding. Bleeding outcomes are also recommended to be incorporated into trials to ensure that the studied drugs can be used safely in clinical practice with a good benefit-risk profile(30). For further discussion regarding the reliability/ validity/ current use in clinical practice of these outcomes, please see Section 0.

Other analyses

Additional exploratory measures included the evaluation of pharmacokinetics and pharmacodynamics of rivaroxaban and identification of any genetic factors which may influence the safety and tolerability of rivaroxaban. Data on healthcare resource use (all patients) and treatment satisfaction with anticoagulant therapy was also collected(24).

Treatment Compliance(25-27)

A log was kept, by patient number, of the date, quantity and batch numbers of medication dispensed and returned.

Compliance was measured by a rivaroxaban/rivaroxaban placebo pill count. Pill counts were performed for rivaroxaban and rivaroxaban placebo only as warfarin and warfarin placebo dosage changed based on INR monitoring, whether actual or sham(26).

For subjects randomly assigned to warfarin therapy, the Time in Therapeutic Range (TTR; i.e., 2.0 to 3.0) was measured using a conservative interpretation of the Rosendaal method(23;35), including values during the first week and after re-initiation of study therapy following interruptions(36). This TTR can also be used as a surrogate for or indirect measure of treatment compliance.

Statistical analysis plan and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a

description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

Statistical analysis plan and definition of study groups(23;24;26;27)

Table 15. Definitions of observation periods and study populations for statistical analysis(26)

Observation period	Definition
On-treatment	All events after the first study drug intake during which the patient was receiving study drug (including temporary interruptions) plus two days
Off treatment	All events occurring more than two days after permanent study drug discontinuation until the observation period ends
Site Notification	All events after randomisation up to the date of site notification (date when sites were informed to schedule the end of treatment visits). This period included "on-treatment" as well as off-treatment events up to the date of site notification
Regardless of treatment exposure	Included data up to and including the Follow-up Visit for subjects who completed the study and data up to and including the last study contact (i.e., after site notification) for those who prematurely discontinued.
Study Population	
Intention-to-treat (ITT)	All patients uniquely randomised
Safety	All ITT patients who had taken at least one dose of study medication
Per-Protocol (PP)	All ITT patients excluding those who have major pre-defined protocol deviations (e.g. no informed consent, no evidence of AF, prosthetic heart valve, endocarditis, left ventricular thrombus, atrial myxoma or $CHADS_2$ score of 0 or 1 at time of study enrolment, or less than 60% compliance with study treatment).

Hypothesis objective

Since the primary goal of the trial was to establish non-inferiority of rivaroxaban versus warfarin for prevention of stroke or systemic embolism [redacted] The literature on this topic is substantial, and guidance from regulatory agencies (e.g., ICH Guideline E9: Statistical Principles for Clinical Trials)(37) has indicated that for this type of determination an per-protocol analysis, which usually only includes on-treatment data, is preferred over an intention-to-treat (ITT) approach in an evaluation of non-inferiority.

If non-inferiority was achieved in the primary analysis, a closed hierarchical testing procedure (see Figure 6) was to be conducted for superiority on the primary efficacy endpoint in the 'on-treatment' safety population i.e. all randomised patients who had taken at least one dose of study drug and were followed for events, regardless of adherence to the protocol, while they were receiving the assigned study drug or within 2 days after discontinuation.

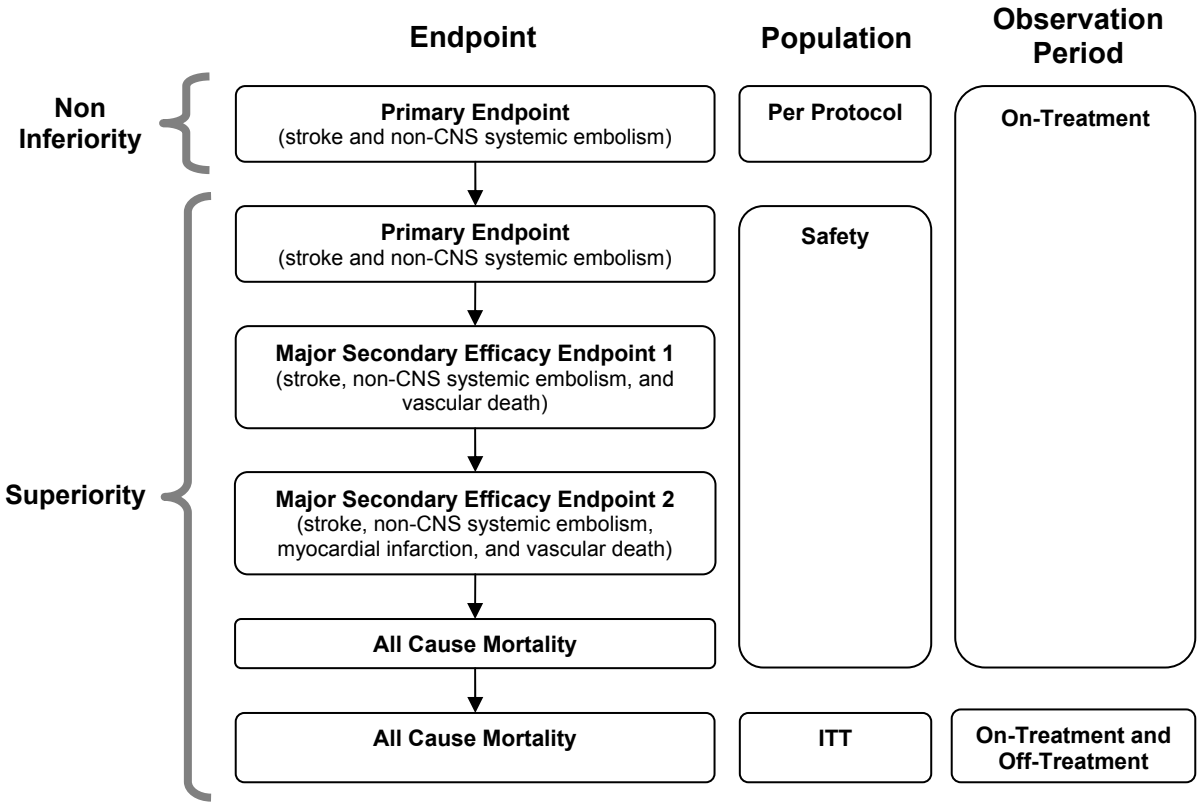
The ROCKET AF Executive Committee pre-specified the evaluation of superiority to be assessed within the period of time when research participants were on study medication. The “on-treatment” analysis was the most appropriate for assessing superiority, given that rivaroxaban would not be expected to have a durable effect beyond the period of its pharmacodynamic activity: i.e., anticoagulation is not disease-modifying and does not cure the underlying pro-thrombotic potential central to the mechanism of stroke in AF, namely the low flow conditions in the left atrial appendage.

This was followed by superiority testing of key secondary endpoints using the same population. If an individual test during any step did not reach statistical significance, later tests would not be declared statistically significant.

In order to test robustness of the pre-specified “on-treatment” analysis, sensitivity testing for non-inferiority and superiority was also performed in the intention-to-treat (ITT) population – this analysis was not part of the hierarchical closed testing procedure. This sensitivity analysis in the ITT population to site notification is presented alongside the results from the pre-specified primary analyses.

Furthermore, post hoc analyses of events in the ITT population while on and off treatment, up to the time of site-notification, and events occurring during transition at the end of the study to open-label treatment with conventional anticoagulant agents were conducted as a sensitivity analysis. This analysis was not part of the hierarchical closed testing procedure.

Figure 6. Pre-specified statistical testing procedures in the ROCKET AF study(25)



Note: On treatment is the period between the date of the first double-blind study medication to the date of the last double-blind study medication administration plus 2 days

All of the efficacy analyses excluded data from one site in the Czech Republic, from which data was deemed unreliable due to violations in good clinical practice guidelines (GCP). The site had recruited 50 rivaroxaban and 43 warfarin patients. This site exclusion altered the numbers of patients in the ITT, safety and per protocol populations for the efficacy analysis as shown in Figure 7. All safety analyses included safety data from this site.

Of note, the intent-to-treat and the safety populations were the same with the exception of 28 subjects (20 rivaroxaban, 8 warfarin) who were randomised but never received a dose of study drug(28).

A scheduled interim analysis was performed when 50% of the primary efficacy events, as reported by the investigators, had occurred. The recommendation from the interim analysis was to continue with the study as planned. Ongoing safety and efficacy monitoring was performed by the Independent Data Monitoring Committee (IDMC). During the closed sessions of the IDMC review meetings, unblinded data were reviewed including the summary of bleeding events, summary of clinical outcomes, summary of serious adverse events, adverse events that led to discontinuation of the study drug, and drug-related adverse events by body system, discontinuation of double-blind study drug, laboratory tests at baseline, change from baseline, and abnormalities, blood pressure, and INR(26).

Discussion on analysis and study populations

Typically, studies with active controls are designed in order to show non-inferiority, therefore the choice of a non-inferiority design for ROCKET AF (novel treatment (rivaroxaban) vs. active control (warfarin) adheres to current thinking on trial design(38).

The likelihood of non-adherence, many dropouts on the study (due to extensive comorbidity, elderly patients) and the possible subsequent (diluting) impact on the study analyses, led the Study Executive Steering Committee to select the per-protocol 'as treated' population as the primary efficacy analysis with supporting ITT analyses as sensitivity analyses, testing the robustness of the results. This is in line with FDA draft recommendation that *both* ITT and 'as-treated' analyses are conducted in non-inferiority studies(38). When patients are not taking the assigned medication, no gradient in the effect of treatment compared with control will be seen as all patients in both groups are essentially taking the same treatment, and this circumstance biases towards non-inferiority - the 'on-treatment' analysis minimises this risk.

In designing ROCKET AF there was no prior large blinded trial experience to guide estimation of the impact of the periods when participants were not taking study medication. It was determined that the primary analysis should be 'on-treatment' (including, the additional 2 days after the stop of study drug) while the ITT analysis (including all events occurring off randomised treatment up to site notification) would be done to evaluate the robustness of the treatment effect seen in the 'on-treatment' population. This decision was based on several reasons:

- The mechanism of action, anticoagulation - the study drugs would not be expected to have a durable effect beyond the period of their pharmacodynamic activity: they were not disease modifying and did not eliminate the underlying pro-thrombotic potential central to the mechanism of stroke in AF, namely the low flow conditions in the left atrial appendage.
- The very different pharmacokinetic and pharmacodynamic properties mean that the longer acting warfarin would still be active for a greater duration after discontinuation of study drug and would confer an advantage for warfarin if the 'on and off treatment' dataset had been used.

Based on the decision to use the "on-treatment" data set, it was decided that the most appropriate population for the superiority analysis was the safety population, as a requirement for this population was administration of at least one dose of study drug. In actuality, the ITT population did not differ substantially in number from the Safety population (only 28 patients did not start study medication after randomisation) (see Figure 7). The ITT to site notification analyses remove the censoring of off-treatment time periods and thus expand the window in which events can be assigned to the two treatment arms. Patients who discontinued or completed the trial still had a need for anticoagulation because of the

continued presence of atrial fibrillation, and thus the background risk of stroke persisted into the post-treatment period. Patients were therefore transitioned to an open-label VKA, or other appropriate regimen at the discretion of their individual clinicians. In the full ITT (to site notification), there was a median of 117 days of follow-up assigned medication i.e. patients were off randomised treatment. See results section for details of the impact of the on treatment / off treatment study periods on the analysis.

- **Statistical analysis – primary outcomes(23;25-27)**

Primary Efficacy Endpoint (Composite of stroke and non-CNS systemic embolism)

The study was powered to determine non-inferiority of rivaroxaban compared with warfarin for prevention of the primary efficacy endpoint, with a non-inferiority margin of 1.46 in terms of risk (hazard) ratio.

The selection of the non-inferiority margin was based on a 2.3% warfarin event rate derived from meta-analysis of six warfarin trials(34) and regulatory guideline requirements that the non-inferiority margin would, at the very least, rule out the minimum warfarin effect versus placebo(39). The most conservative approach was chosen by selecting the lower limit of the confidence boundary.

To obtain a 95% power with a 1-sided α equal to 0.025 in this event-driven trial with a non-inferiority margin of 1.46 for the risk ratio (rivaroxaban / warfarin), 363 events were required from the per-protocol population. The number of events required was increased to 405 to provide robust evaluation across all subgroups. The total number of randomised patients required to observe 405 events was estimated to be 14,000 assuming a 14% dropout rate.

To assess the robustness of the non-inferiority conclusion from the primary efficacy analysis, supportive (sensitivity) analyses were performed using a stratified Cox proportional hazards model with 3 stratification factors; 1) region, 2) prior VKA use and 3) history of prior stroke, TIA or non-CNS systemic embolism.

Furthermore, cumulative event rates of the primary efficacy endpoint over time were estimated using the Kaplan-Meier method [redacted]

As specified in the statistical analysis plan, should the non-inferiority hypothesis be satisfied, the possibility of superiority was assessed. The primary efficacy endpoint analysis for superiority used a similar approach as the primary efficacy analysis of non-inferiority except

that the upper limit of the 2-sided confidence interval needed to be **below 1** for superiority of rivaroxaban over warfarin to be declared and the analysis was based on ‘on-treatment’ data from the safety population(26).

Statistical analysis – secondary and other endpoints(26)

The 2 major secondary efficacy endpoints formed part of the pre-specified hierarchical testing procedure (see Figure 6). The hypothesis of superiority on the Major secondary efficacy endpoints was tested and analysed using the same approach as described in the primary efficacy analysis of superiority i.e. based on on-treatment data from the safety population [redacted]

All secondary efficacy endpoints were analysed using the Cox proportional hazards model with treatment as covariate. This included separate analysis of the individual components of the composite primary efficacy and safety endpoints for the per protocol and ITT populations, in order to better understand the impact of component endpoints on the primary endpoint.

Cumulative event rates over time were estimated using the Kaplan-Meier method.

- **Missing data / Patient discontinuation**

For details of patient discontinuation and loss to follow up, see Figure 7 [redacted]

Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup Analyses – statistical plan

The homogeneity of treatment effects on the first occurrence of the primary [redacted] and safety endpoints across subgroups was pre-planned and examined (at a 2-sided significance level of 0.05) via a test for treatment-by-subgroup interaction by adding this term and the subgroup as covariates to the Primary Efficacy Cox Proportional Hazards model. Results were summarised by subgroup based on 'on-treatment' data from the [redacted] safety population. Lack of a significant interaction was taken to imply that the results were consistent across subgroups and that the overall response rates are the most appropriate estimates of treatment effect within each subgroup. If a significant interaction was observed, the results were examined to determine whether the interaction was quantitative or qualitative using the Gail-Simon test.

The following subgroups determined by baseline characteristics will be examined:

- Region
- Prior VKA use
- History of a prior stroke (ischaemic or unknown type), TIA or non-CNS systemic embolism
- $CHADS_2$
- 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)

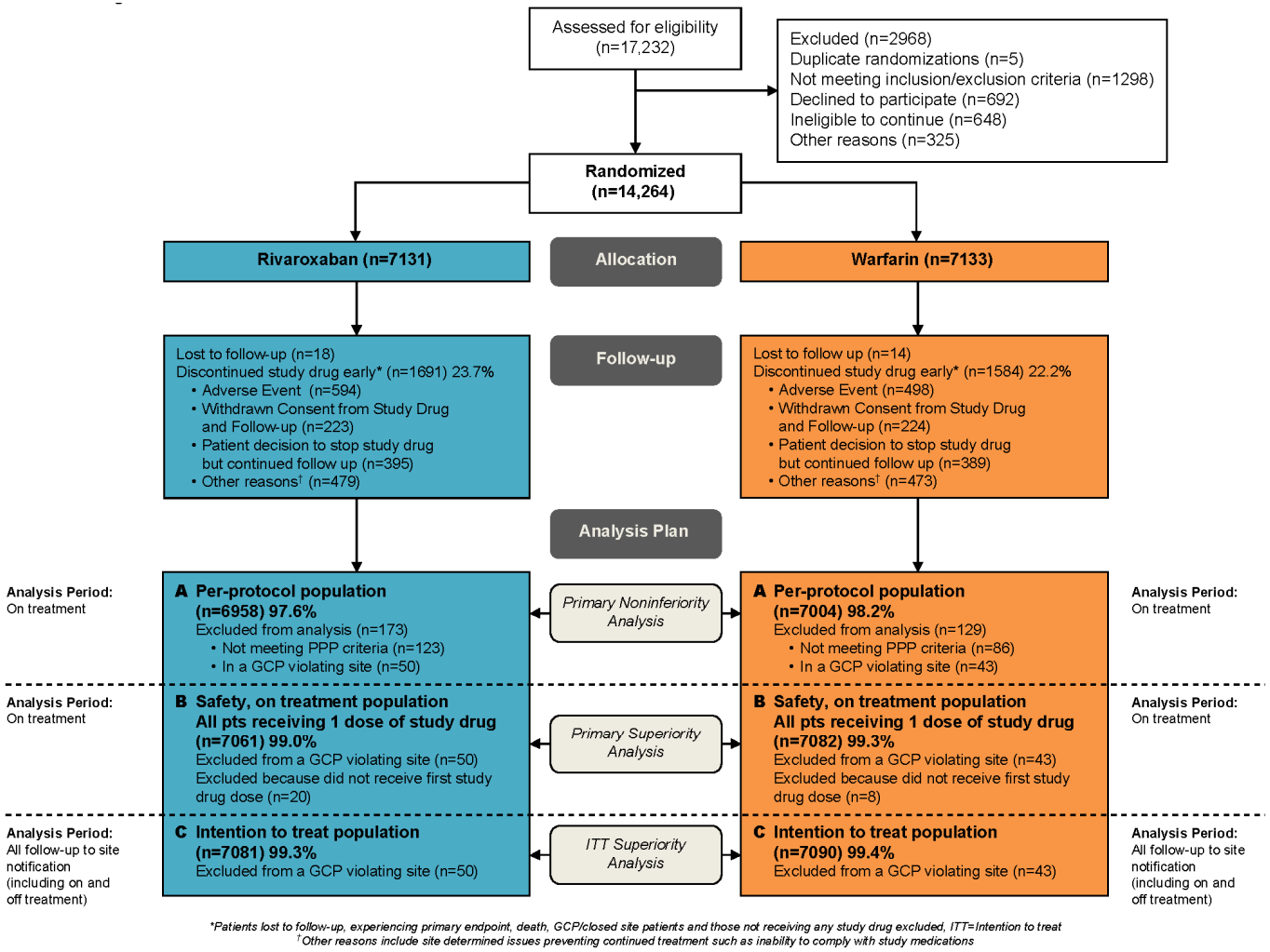
Comparative analyses of treatment efficacy were performed according to quartiles of time that INR values fell within the therapeutic range at the participating clinical sites.

Participant flow

Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Participant flow(28)[a]

Figure 7. Summary of study populations and analysis sets for ROCKET AF



Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT.

See section 9.3, appendix 3 for further details.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.

Table 16. Quality assessment of RCTs

	ROCKET AF(23-26)
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

Results of the relevant RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

For each outcome for each included RCT, the following information should be provided.

The unit of measurement.

The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.

A 95% confidence interval.

Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.

When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.

Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

Discuss and justify definitions of any clinically important differences.

Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

ROCKET AF

Primary Efficacy endpoint

Composite of stroke and non-CNS systemic embolism(23)

In the per protocol population 'as treated', stroke or non-CNS systemic embolism was confirmed in 188/6958 patients in the rivaroxaban group and 241/7004 patients receiving warfarin, with an event rate of 1.7 per 100 patient-years for rivaroxaban compared with 2.2

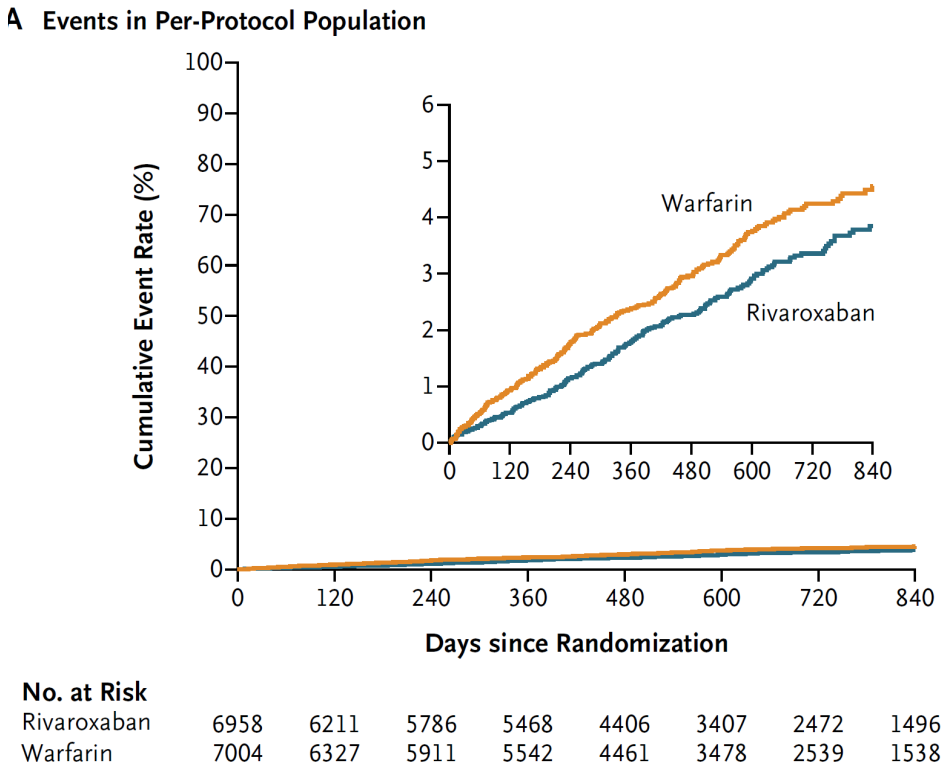
per 100 patient-years in the warfarin group (hazard ratio 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for non-inferiority) (see Table 17).

In the safety on treatment population, primary efficacy endpoint events were reported in 189 of the 7061 patients taking rivaroxaban, with an event rate of 1.7 per 100 patient-years, and 243 of the 7082 patients receiving warfarin (event rate 2.2 per 100 patient-years) (hazard ratio 0.79; 95% confidence interval[CI], 0.65 to 0.95; P=0.02 for superiority) (see Table 17).

In the ITT analysis, primary events occurred in 269 rivaroxaban patients (2.1% per year) and 306 patients on warfarin (2.4% per year) (HR 0.88; 95% CI, 0.75 – 1.03; P<0.001 for non-inferiority; P=0.12 for superiority) (see Table 17).

The primary efficacy endpoint was analysed based on time from randomisation to the first occurrence of the event. The Kaplan-Meier plots demonstrate the cumulative event rate for the per protocol / as treated population (Figure 8) and for the ITT group (Figure 9).

Figure 8. Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population



ɡure 9. Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) Intention-to-Treat Population.

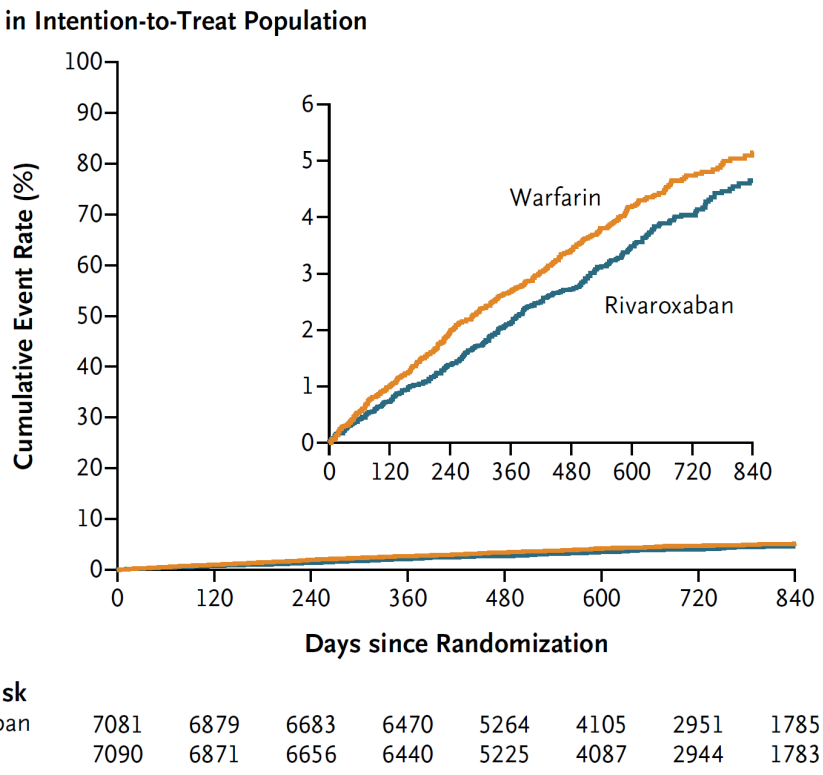


Table 17. Primary Trial Endpoint: Stroke and Non-CNS Embolism

	Rivaroxaban			Warfarin				Rivaroxaban vs. Warfarin	
	N	Total	Event Rate (100 pt-yr)	N	Total	Event Rate (100 pt-yr)	Hazard Ratio (95% CI)	p-value Non-inferiority	p-value Superiority
Per Protocol/as treated[#†]	6958	188	1.7	7004	241	2.2	0.79 (0.66, 0.96)	<0.001*	[redacted]
Safety on treatment [#]	7061	189	1.7	7082	243	2.2	0.79 (0.65, 0.95)	[redacted]	0.02*
ITT[#‡]	7081	269	2.1	7090	306	2.4	0.88 (0.75,1.03)	<0.001*	0.12
Events on-treatment		188	1.7		240	2.2	0.79 (0.66, 0.96)		0.02*
Events off-treatment		81	4.7		66	4.3	1.10 (0.79, 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
Those highlighted in teal are part of the pre-specified closed hierarchical testing procedure (see Figure 6)

These results confirm that rivaroxaban is non-inferior to warfarin in the prevention of stroke and non-CNS systemic embolism in patients with non-valvular AF(23). Individual components of the primary composite efficacy endpoint were numerically reduced by rivaroxaban compared with warfarin and are detailed separately in the analysis of secondary endpoints (see Table 18 & Table 19) (23;26;28).

Non-inferiority was consistently shown across subgroups (see Figure 11 & Figure 12) and for all other data scopes tested in the sensitivity analyses, including safety/on treatment, ITT – follow up visit, ITT – site notification, and ITT – regardless of treatment exposure, and when adjusted for region, prior VKA, and history of prior stroke, confirming the robustness of the primary analyses(23;26;28).

Since a statistically significant result for non-inferiority was achieved, the hierarchical testing (Figure 6) was initiated and the superiority of rivaroxaban versus warfarin was tested.

In the safety on treatment population, rivaroxaban was therefore shown to be statistically significantly superior to warfarin with respect to the pre-specified analysis of the primary efficacy endpoint(23). In the ITT analysis however, the numerically lower event rate in the rivaroxaban group (2.1/100 patient-years) compared with warfarin (2.4/100 patient-years) (HR 0.88, 95% CI 0.75,1.03) did not reach statistical significance for superiority (P=0.12). All analyses that extended the data scope more than 2 days after the last dose of study drug did not retain the statistical significance for superiority despite directional consistency in the treatment effect of rivaroxaban [redacted]

The post-hoc ITT “on-treatment” analysis shows that rivaroxaban is significantly superior to warfarin when taken (Table 17 & Figure 10) (188 vs 240 events; P=0.02). In patients stopping treatment prematurely (ITT ‘off-treatment’), primary events occurred in 81 patients randomised to rivaroxaban and 66 randomised to warfarin (P=0.58) (Table 17 & Figure 10). The “off-treatment” analysis looks at patients who had discontinued rivaroxaban and been transitioned to open-label therapy and compares them with warfarin-treated patients who had also discontinued to open label therapy. In the full ITT, there was a median of 117 days of follow-up assigned medication i.e. patients were off randomised treatment.

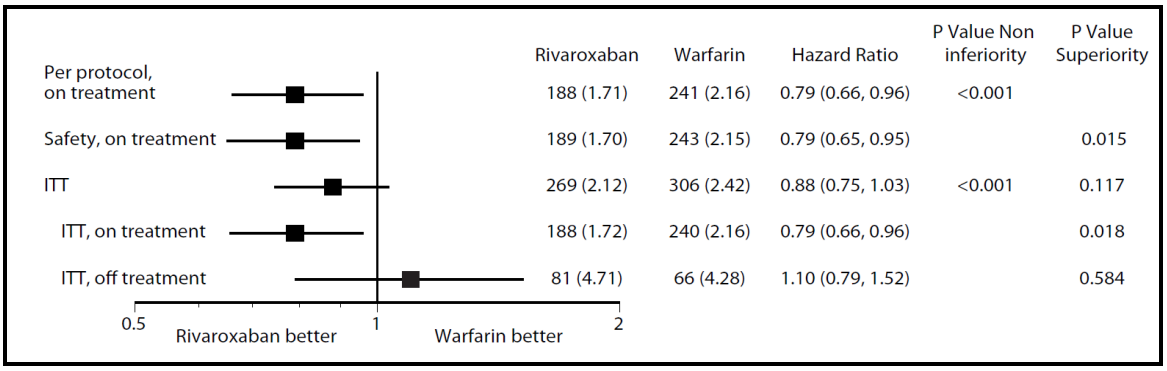
The events occurring primarily in the ‘off-treatment’ period, when patients had transitioned to open-label VKA or another appropriate treatment, dilute the observed ‘on treatment’ effect (Figure 10), especially as there was no difference in discontinuation rates between the two treatment arms. It is also of note that the treatment effect of rivaroxaban disappeared within a shorter time window than warfarin based on a shorter half life.

On further exploration, two concurrent factors are likely to have contributed to this:

1. Physicians prescribed post-study open-label VKA therapy at their discretion and to preserve the integrity of the study blind, were discouraged from performing INR measurements for at least 3 days.
2. For patients who had been treated with rivaroxaban, there was a period of vulnerability to thromboembolic events that resulted from the transition to a VKA.
    - For rivaroxaban patients, as they were warfarin naïve, dose finding and adjustment had to start from the beginning, and there was a period of 13 days on average after the end of double-blind therapy until open-label warfarin resulted in a therapeutic INR (2-3), versus 3 days for those originally assigned to warfarin. The timing and type of events in the rivaroxaban arm would suggest that these were associated with suboptimal anticoagulation over the transition period from rivaroxaban to a VKA. Such a transition could be more easily addressed in clinical practice.

In the Forest Plot below, the overall ITT analysis (including on and off-treatment events) shows that rivaroxaban consistently reduced the risk of stroke and systemic embolism compared with warfarin. The on-treatment events show that the benefits of Rivaroxaban are diluted when the off-treatment events are included in the analysis.

Figure 10. Primary efficacy outcome by analysis population



A dilution of the true treatment effect is expected given the design, and thus directional consistency alone in the sensitivity analyses in the ITT population is considered sufficient to support the pre-specified superiority analysis even though the ITT analysis did not itself reach statistical significance for superiority. An additional sensitivity analysis in the ITT on treatment population confirms superiority.

Subgroup Analyses (see Figure 11 & Figure 12)(23;28)

Treatment effects with regard to the primary efficacy endpoint were consistent across all pre-specified subgroups, including patients receiving a reduced dose of rivaroxaban (15mg once daily).

ROCKET AF sub-analysis investigating secondary prevention of stroke and non-CNS systemic embolism presented at ESC May 2011(40), showed that the efficacy and safety outcomes in patients with and without prior stroke/TIA taking rivaroxaban were consistent with the overall study results. Therefore, the conclusions from the overall study can be extended to the primary and secondary prevention subgroups.

Figure 11. Primary efficacy outcome by subgroup in the ROCKET AF study (ITT to site-notification)(28)

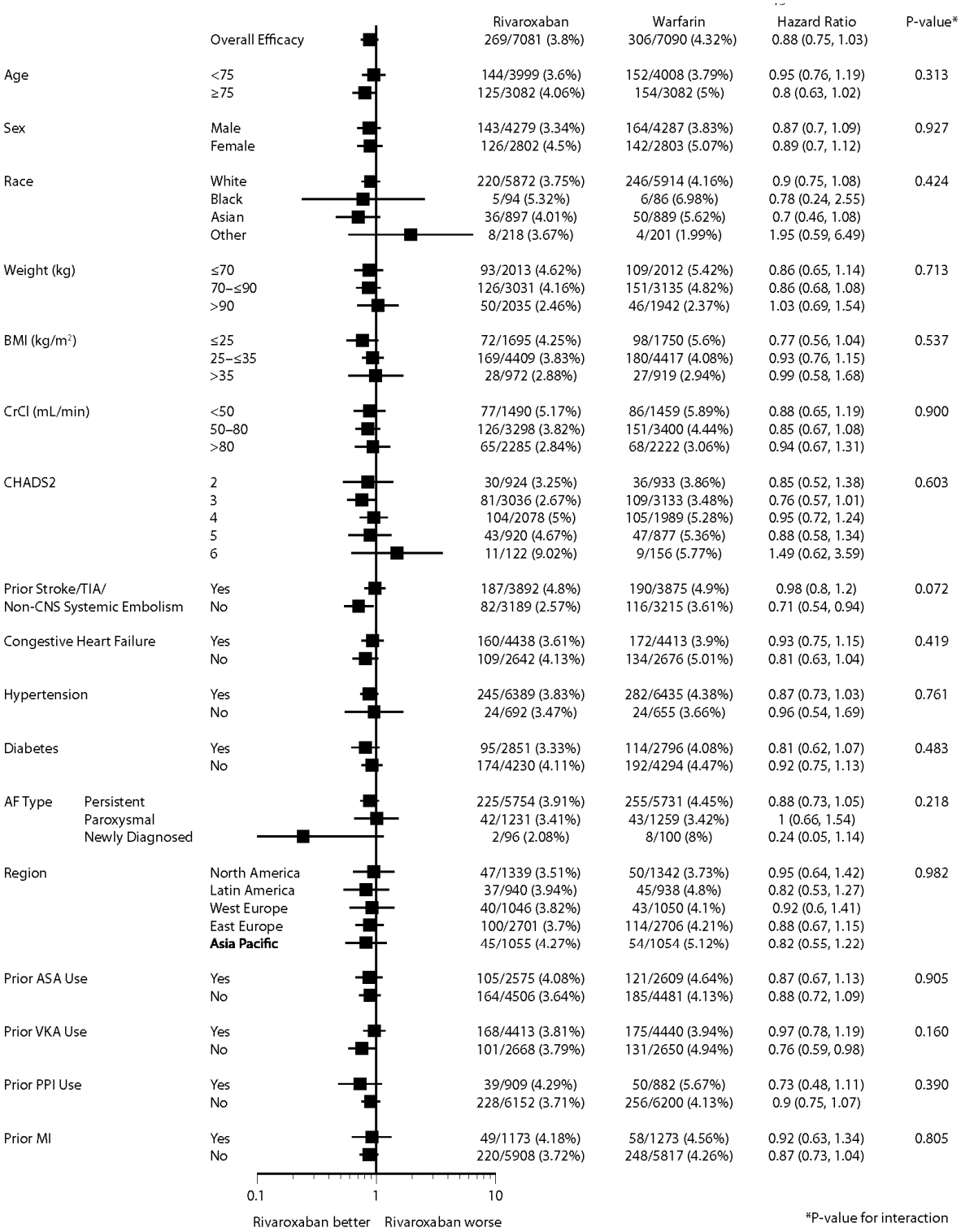
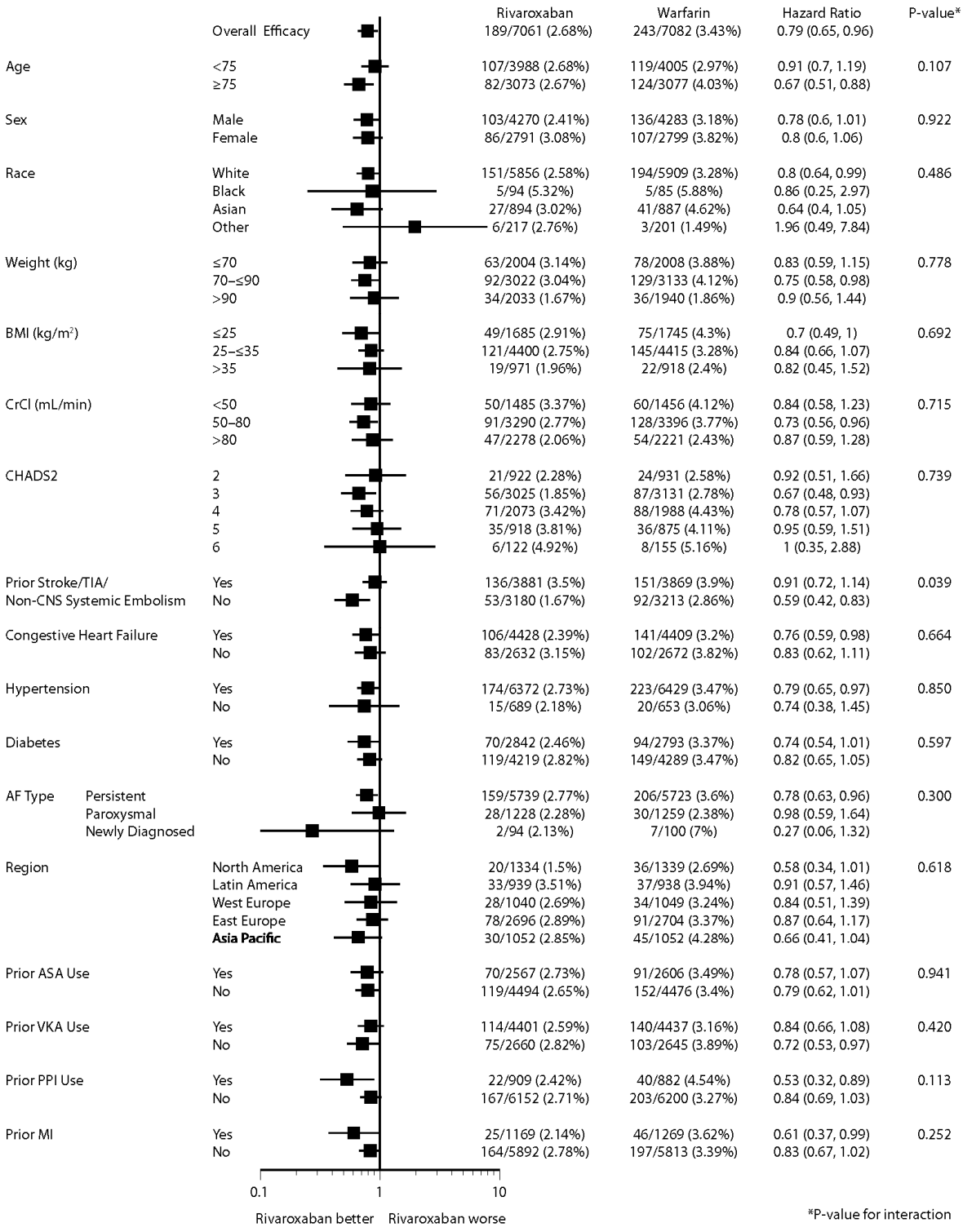


Figure 12. Primary efficacy outcome by subgroup in the ROCKET AF study (safety population/on-treatment)(28)



Primary Safety Endpoint (Composite of Major bleeding and Clinically relevant non-major bleeding) – safety endpoint data are reported in detail in Section 5.9 'Adverse Events'.

In the primary safety analysis, there was no difference between rivaroxaban and warfarin with respect to major or non-major clinically relevant bleeding.

Secondary endpoints (Table 18 & Table 19)(23;26;28)

Since statistical significance was achieved for superiority of rivaroxaban over warfarin for the primary efficacy endpoint in the "safety, on treatment" population, analyses of secondary efficacy endpoints took place according to the pre-specified hierarchical testing procedure (see Figure 6). For results see Table 18 & Table 20. Alongside this, sensitivity analyses included use of ITT populations (see Table 19).

Table 18. Incidence and event rates of secondary efficacy endpoints as adjudicated by CEC (Safety / on-treatment population, excluding Czech site)(28)

Endpoints	Rivaroxaban (n=7061)		Warfarin (n=7082)		Rivaroxaban vs. Warfarin	
	n (%)	Event Rate (100 Pt-yr)	n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Major Secondary Endpoint 1 Composite of stroke, non-CNS embolism & vascular death	346 (4.90)	3.11	410 (5.79)	3.63	0.86 (0.74, 0.99)	0.034*
Major Secondary Endpoint 2 Composite of stroke, non-CNS embolism, vascular death & myocardial Infarction	433 (6.13)	3.91	519 (7.33)	4.62	0.85 (0.74, 0.96)	0.010*
Other Efficacy Endpoints						
Stroke Type	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.7, 1.03)	0.092
Primary Haemorrhagic Stroke	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37, 0.93)	0.024*
Primary Ischaemic Stroke	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75, 1.17)	0.581
Unknown Stroke Type	7 (0.10)	0.06	11 (0.16)	0.10	0.65 (0.25, 1.67)	0.366
Stroke Outcome						
Death	47 (0.67)	0.42	67 (0.95)	0.59	0.71 (0.49,1.03)	0.075
Disabling Stroke	43 (0.61)	0.39	57 (0.80)	0.50	0.77 (0.52, 1.14)	0.188
Non-disabling Stroke	88 (1.25)	0.79	87 (1.23)	0.77	1.03 (0.76, 1.38)	0.863
Unknown	7 (0.10)	0.06	12 (0.17)	0.11	0.59 (0.23, 1.50)	0.271
Non-CNS Systemic Embolism	5 (0.07)	0.04	22 (0.31)	0.19	0.23 (0.09, 0.61)	0.003*
Myocardial Infarction	101 (1.43)	0.91	126 (1.78)	1.12	0.81 (0.63, 1.06)	0.121
All Cause Mortality	208 (2.95)	1.87	250 (3.53)	2.21	0.85 (0.70, 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, 1.08)	0.094
Unknown Death	17 (0.24)	0.15	23 (0.32)	0.20	0.75 (0.40, 1.41)	0.370

Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score, 0-2 = nondisabling, 3-5 =disabling, 6=death.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at nominal 0.05 (two-sided)

Table 19. Incidence and event rates of secondary efficacy endpoints as adjudicated by CEC (ITT to Site Notification population, excluding Czech site)(26)

Endpoints	Rivaroxaban (n=7081)		Warfarin (n=7090)		Rivaroxaban vs. Warfarin	
	n (%)	Event Rate (100 Pt-yr)	n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Major Secondary Endpoint 1 Composite of stroke, non-CNS embolism & vascular death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major Secondary Endpoint 2 Composite of stroke, non-CNS embolism, vascular death & myocardial Infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Efficacy Endpoints	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke Type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary Haemorrhagic Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary Ischaemic Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown Stroke Type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke Outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disabling Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-disabling Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CNS Systemic Embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial Infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All Cause Mortality	582 (8.22)	4.5	632 (8.91)	4.9	0.92 (0.82, 1.03)	0.15
Vascular Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-vascular Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score, 0-2 = nondisabling, 3-5 =disabling, 6=death.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at nominal 0.05 (two-sided)

Major Secondary Endpoint 1 (Composite of stroke, non-CNS systemic embolism, and vascular death)(23;26;28)

The pre-specified analysis of 'major secondary endpoint 1' was to take place in the safety / on-treatment population. In this population, stroke, non-CNS embolism or vascular death occurred in 346 / 7061 (4.90%) patients receiving rivaroxaban and 410 / 7082 (5.79%) patients in the warfarin group. This translated to 3.11 events per 100 patient-years in the rivaroxaban group and 3.63 events per 100 patient-years in the warfarin group, which demonstrated the superiority of rivaroxaban over warfarin for 'major secondary endpoint 1' (hazard ratio 0.86; 95% confidence interval[CI], 0.74 to 0.99; P=0.034 for superiority), see Table 18.

Intention-to-treat population (to site notification [redacted] see Table 19.

Major Secondary Endpoint 2 (Composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death)(23;26;28)

In the safety / on-treatment population, the event rate in the rivaroxaban group was statistically lower (3.91 per 100 patient-years) compared with the warfarin group (4.62 per 100 patient-years); hazard ratio 0.85 (95% CI, 0.74 to 0.96; P=0.010 for superiority).

Intention-to-treat population (to site notification). [redacted] **All-cause mortality(23)**

Safety / on-treatment population All-cause mortality included vascular death, non-vascular death, and unknown death. A total of 458 deaths were adjudicated by the CEC (n=208 rivaroxaban; n=250 warfarin), the primary reason being 'vascular death'. Numerically, a better survival rate was shown for the rivaroxaban group (1.87 per 100 patient-years) compared with the warfarin group (2.21 per 100 patient-years); however, the superiority of rivaroxaban over warfarin for 'all-cause mortality' was not demonstrated (HR 0.85; 95% CI, 0.70, 1.02; P=0.073).

Intention-to-treat population There were 582 deaths in the rivaroxaban group and 632 deaths in the warfarin group (4.5% versus 4.9% per year; HR 0.92; 95% CI, 0.82, 1.03; P=0.15) from randomisation [redacted]

Individual components of the composite primary and major secondary endpoints

[redacted]

[redacted](see Table 19).

Stroke - Stroke types included primary ischaemic, primary haemorrhagic, and unknown type. For [redacted] and the Safety / on-treatment populations, overall, fewer strokes were reported in the rivaroxaban group compared with the warfarin group (Table 18 & Table 19).

The event rate for time to the first occurrence of a primary haemorrhagic stroke was significantly lower in the rivaroxaban group (0.26/100 patient-years) compared with the warfarin group (0.44/100 patient-years); hazard ratio of 0.59 (95% CI 0.37 to 0.93 p-value 0.024).

[redacted]

Fewer strokes in rivaroxaban-treated patients led to death and severe disability.

Disabling stroke (modified Rankin scale score of 3 to 5, inclusive)

Disabling strokes occurred more frequently in the warfarin-treated group than the rivaroxaban-treated group. This difference was not statistically significant (see Table 18 & Table 19).

Non-CNS Systemic Embolism was CEC -adjudicated in 5 patients in the rivaroxaban group and 22 patients from the warfarin group (safety / on-treatment). This resulted in event rates of 0.04 per 100 patient-years (rivaroxaban) and 0.19 per 100 patient-years (warfarin), a statistically significant difference (hazard ratio of 0.23 (95% CI 0.09 to 0.61, p-value 0.003).

[redacted]

Myocardial Infarction(23;26;28)

Safety / on-treatment population There were 101 patients in the rivaroxaban group and 126 patients in the warfarin group who had a myocardial infarction. Most myocardial infarctions were nonprocedural for both treatment groups. Based on the time to the first occurrence of a myocardial infarction, the event rate in the rivaroxaban group (0.91 per 100 patient-years) was numerically lower compared with the warfarin group (1.12 per 100 patient-years); hazard ratio of 0.81 (95% CI 0.63 to 1.06, p-value 0.121) (Table 18).

Intention-to-treat population [redacted] (Table 19).

Table 20 presents a summary of the results of the time to the first occurrence for the endpoints included in the hierarchical testing (see Figure 6).

Summary

The primary efficacy endpoint showed non-inferiority for the pre-specified per protocol analysis. Superiority in the pre-specified safety population on treatment was also then achieved. The pre-specified supportive efficacy analysis for superiority was the time from randomisation to the occurrence of the first primary efficacy endpoint in the intent-to-treat/up to follow-up visit analysis set. Results were numerically consistent (hazard ratio <1.0) for all analyses using broader censoring schemes [redacted] Non-inferiority was consistently shown for all analysis sets and was independent of censoring the duration of follow-up after the last dose of study drug.

Superiority was achieved for the first and second major secondary efficacy outcomes, consistent with the pre-specified primary efficacy outcome. Fewer strokes, non-CNS systemic embolisms, vascular deaths, and MIs were observed for the rivaroxaban group compared with warfarin group. With the exception of non-disabling stroke, the hazard ratios for the time to the first occurrence of all CEC-adjudicated efficacy endpoints while on treatment favoured rivaroxaban, lending further credence to the effectiveness of rivaroxaban.

Although the superiority of rivaroxaban over warfarin was not demonstrated for all cause mortality, the final analysis in the hierarchical testing procedure was performed [redacted]

Looking at the totality of pre-planned analyses a consistent picture is provided:

- Regardless of the population included, the pre-established non-inferiority criteria are met – rivaroxaban was non-inferior to warfarin.
- While on study medication, rivaroxaban is superior to warfarin for the primary efficacy outcome

Table 20. Hierarchical testing – Event rate, Hazard Ratio and 95% CI for Time to the first occurrence of Efficacy Endpoints (Adjudicated by CEC)(23;26;28)

Population / Observation Period - Analysis Endpoint	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	n / N	Event Rate (100 Pt-yr)	n / N	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Per Protocol / as treated – Non-inferiority						
Primary Efficacy Endpoint	188 / 6958	1.7	241 / 7004	2.2	0.79 (0.66, 0.96)	<0.001*a
Safety on treatment - Superiority						
Primary Efficacy Endpoint	189 / 7061	1.7	243 / 7082	2.2	0.79 (0.65, 0.95)	0.02*b
Major Secondary Efficacy Endpoint 1	346 / 7061	3.11	410 / 7082	3.63	0.86 (0.74, 0.99)	0.034*b
Major Secondary Efficacy Endpoint 2	433 / 7061	3.91	519 / 7082	4.62	0.85 (0.74, 0.96)	0.01*b
All Cause Mortality	208 / 7061	1.87	250 7082	2.21	0.85 (0.70, 1.02)	0.073b
ITT / regardless of treatment exposure - Superiority						
All Cause Mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Primary Efficacy Endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major Secondary Efficacy Endpoint 1 is the composite of stroke, non-CNS embolism, and vascular death.
Note: Major Secondary Efficacy Endpoint 2 is the composite of stroke, non-CNS embolism, myocardial infarction and vascular death
Note: Event Rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: On treatment is the period between the date of the first double-blind study medication to the date of the last double-blind study medication administration plus 2 days.
Note: Regardless of treatment exposure is the period of time from the date of the first double-blind study medication up to and including the Follow-up Visit for subjects who completed the study and data up to and including the last study contact for those who prematurely discontinued.
Note: Hazard Ratio (95% CI) and p-value from the Cox proportional hazard model with treatment as a covariate.
a p-value (one-sided) for non-inferiority of rivaroxaban versus warfarin by a non-inferiority margin of 1.46 in hazard ratio.
b p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
* Statistically significant at 0.025 (one-sided) for non-inferiority and 0.05 (two-sided) for superiority.
Note: Per Protocol, safety and ITT refer to per protocol, safety, and ITT excluding Czech site.

Compliance and Time in therapeutic range (TTR)(23;26;28)

Mean compliance, based on the proportion of days study drug was taken for rivaroxaban and rivaroxaban placebo was [redacted]% for both groups. The compliance of warfarin was not possible to measure directly due to the individual patient variation in dosing, hence the intake of rivaroxaban placebo and INR levels / anticoagulation control were taken as surrogates for indirect measure of treatment compliance.

In the warfarin group, Time in Therapeutic Range (TTR), for the INR range of 2.0 to 3.0 was 55% (mean) and 58% (median)(safety analysis set)(23). [redacted]

Some variability was observed in TTR by region: North America had the highest overall INR control by followed by Western Europe, Latin America, Asia Pacific, and Eastern Europe (Table 21).

Table 21. Percentage (Median) of INR Values in therapeutic range for warfarin by region (safety population)

Therapeutic range INR	North America (n=1,327)	Western Europe (n=1,033)	Latin America (n = 924)	Eastern Europe (n=2,705)	Asia Pacific (n=1,036)
2–3	64.13	60.62	55.19	49.73	52.38

Enrollment per region was as follows (ITT population): North America (18.8%), Latin America (13.17%), West Europe (14.69%), East Europe (38.56%) and Asia Pacific (14.78%).

Table 22[redacted] Heart failure, diabetes, and prior stroke, all components of the $CHADS_2$ classification system, have been shown in other studies to be moderate predictors of lower TTR.(41) Those with a $CHADS_2$ score of 2 had a mean TTR of 59.26% while those with $CHADS_2$ of 3 and 4 had a mean TTR of 55.04% and 54.26%, respectively. Those with a $CHADS_2$ score of 5 and 6 had a mean TTR of 53.62% and 53.49%, respectively (Table 22).

As would be expected, the TTR for patients without congestive heart failure [redacted] was higher than for those with congestive heart failure [redacted] Given the high representation of heart failure in the study (approximately 62%), this population contributed substantially to the overall TTR for the study.

Table 22: Percentage of INR Values in range of 2-3 for Warfarin (Imputed) by Baseline $CHADS_2$ Score (Safety Analysis Set)

ıseline $CHADS_2$	Warfarin							
	N	Mean	SD	Min	Q1	Median	Q3	Max
1	2	33.33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	921	59.26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	3118	55.04	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	1973	54.26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	856	53.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	155	53.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The percentage is calculated within each subject firstly and descriptive statistics are summarized for the percentages over all subjects.

Frequency of INR monitoring

[redacted]

Investigators adjusted study medication (whether active warfarin or placebo warfarin) accordingly to maintain an INR target of 2.5 (range 2.0 to 3.0, inclusive). During investigator meetings, INR monitoring was reviewed and treating physicians were encouraged to achieve and maintain an INR target of 2.5 (range 2.0 to 3.0) for all subjects.

Impact of INR control on efficacy outcome

Assessing the impact of the level of INR control in the warfarin group on the comparative treatment effect of rivaroxaban is challenging, since there is no established method to match rivaroxaban patients with corresponding warfarin patients according to level of INR control. In order to meet this challenge, an analysis was performed to take into account site-related factors (and provide a randomised comparator group) by grouping centres according to level of INR control in the warfarin group and then comparing the rivaroxaban patients to the warfarin patients within each centre. The results of this analysis are shown in Table 23 and suggest that the rivaroxaban treatment effect is independent of the level of INR control in the warfarin group. The comparison of the treatment effect by quartiles of centre-level TTR demonstrated consistently lower primary endpoint rates with rivaroxaban versus warfarin.

Table 23. Treatment effects by quartiles of centre Time in Therapeutic Range (safety on treatment population)*† (28)

Centre TTR‡	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin
	Total, n (%)	Event rate (100 Pt-yr)	Total, n (%)	Event rate (100 Pt-yr)	Hazard Ratio (95% CI)
0.00–50.6%	45/1735 (2.59)	1.77	62/1689 (3.67)	2.53	0.70 (0.48, 1.03)
50.7–58.5%	53/1746 (3.04)	1.94	63/1807 (3.49)	2.18	0.89 (0.62, 1.29)
58.6–65.7%	54/1734 (3.11)	1.90	62/1758 (3.53)	2.14	0.89 (0.62, 1.28)
65.7–100.0%	37/1676 (2.21)	1.33	55/1826 (3.01)	1.80	0.74 (0.49, 1.12)

* p-value for interaction = 0.736.
† Time in therapeutic range = 2–3 inclusive.
‡ Centre TTR is calculated using total number of international normalised ratio (INR) values in target range from all warfarin subjects within a centre divided by total number of INR values from all warfarin subjects within the centre

Safety data on all safety endpoints including bleeding and adverse events are reported in Section 5.9 – Adverse Events.

- **Conclusion**

ROCKET AF is the largest trial of this design completed to date in AF. The study population involved patients at elevated risk of stroke (mean $CHADS_2$ score of 3.5), with many patients having pre-existing hypertension and congestive heart failure. The majority also had a history of prior stroke, TIA or systemic embolism. These characteristics define a population in whom anticoagulation is clearly indicated, and one in which the current standard therapy, warfarin, is highly effective.

The ROCKET AF study, by virtue of its size and double blind design, has performed the most rigorous test to date of a novel anticoagulant in the prevention of stroke and systemic embolism in patients with atrial fibrillation. The double blind, double dummy design limits the introduction of bias into the ascertainment and reporting of clinical events and thus the interpretation of study results. As this study is more than three times larger than the previously largest double blind trial, the robustness of the data is substantial.

At the same time, the double blind design imposed a restriction in managing the transition of patients to open label vitamin K antagonists at the end of study drug administration. This penalty likely resulted in the increase in events in the rivaroxaban group early in the observation period that could be more easily addressed in clinical practice.

The following conclusions can be drawn from the efficacy results of the ROCKET AF trial (see section 5.9 'Adverse Events' for conclusions on safety aspects of the trial):

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

- As pre-specified, if non inferiority was demonstrated there should be an a priori analysis of superiority in the safety on treatment population. This demonstrated a statistically significant reduction in stroke and non-CNS systemic embolism by 21% [event rate per 100 patient year: rivaroxaban (1.7); warfarin (2.2)] (HR 0.79 95% CI 0.65, 0.95; p-value 0.02). This was confirmed by an additional ITT on treatment analysis and supported by a sensitivity analysis in the ITT population up to site notification which showed directional consistency. Sensitivity analyses in other populations and across all major demographic subgroups demonstrated a consistent treatment effect

- Furthermore, rivaroxaban-treated patients also had fewer strokes that led to death or severe disability than warfarin patients. Therefore, rivaroxaban use was not only associated with a favourable trend in reducing the number of strokes, but those that did occur showed a trend to being less severe and less likely to be associated with a fatal outcome.

- Major secondary efficacy endpoints, consisting of a composite of stroke, non-CNS systemic embolism, and vascular death, or a composite of stroke, non-CNS systemic embolism, MI, and vascular death, both showed statistically significant reductions compared to warfarin, confirming rivaroxaban superiority to warfarin for both Major Secondary Efficacy endpoints in the safety on treatment population

Rivaroxaban is a once-daily, proven alternative to warfarin for stroke prevention in patients with AF with superior efficacy 'on-treatment' and providing a similar safety profile in terms of overall bleeding (see section 5.8).

Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable.

If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Data from only one rivaroxaban study (ROCKET AF) are relevant to the submission. Therefore, a meta-analysis is not possible.

If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Data from only one rivaroxaban study (ROCKET AF) are relevant to the submission. Therefore, a meta-analysis is not possible.

Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

The scope for this appraisal specifies that rivaroxaban should be compared against adjusted dose warfarin, dabigatran and antiplatelet agents.

As there are no head-to-head comparative studies comparing rivaroxaban to dabigatran or antiplatelet agents, indirect comparisons are required.

We therefore conducted:

- A systematic search and review to identify available data
- A network meta-analysis comparing all available agents.

<u>Systematic search and review</u>

A literature search was conducted of the following data bases using Ovid SP to identify cost-effectiveness studies relevant to the scope of the decision problem

- MEDLINE and MEDLINE in process (OVID SP) 1950 to Present
- EMBASE (OVID SP) 1988 to Present
- The Cochrane Central Register of Controlled Trials (CENTRAL)

Inclusion criteria were

- Patients with chronic non-valvular AF documented by electrocardiogramm
- Studies comparing long-term treatment (≥12 weeks), with any of the following drugs: VKAs, antiplatelet agents, idraparinux, rivaroxaban, ximelagatran, dabigatran and apixaban.

All the records retrieved from the search strategies were screened and assessed for inclusion according to the eligibility criteria. Two reviewers independently assessed all the potential studies identified.

Details of methods are provided in the review protocol(42).

Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Eighteen trials met the inclusion criteria for the NMA. Details of the included studies are provided in the systematic review report appended(43).

Provide a summary of the trials used to conduct the indirect comparison.

A brief summary of the trials used in the NMA is provided below.

Table 24. Summary of the trials used to conduct the network meta-analysis

Study name / Acronym (ref)	Riva-roxaban	Adjusted-dose warfarin	Dabigatran 50mg bd	Dabigatran 150mg bd	Placebo / no treatment	Aspirin	Other
ROCKET AF(23;26)	✓	✓					
AFASAK I(44;45)		✓			✓	✓ 75mg od	
BAATAF(46)		✓					Control (patients allowed aspirin)
CAFA(31)		✓			✓		
SPINAF(47)		✓			✓		
EAFT(48)					✓	✓ 300mg	Oral coagulant, mostly coumarin derivatives
LASAF(49)						✓ 125mg od; 125mg alternate days	control
JAST(50)						✓	control
SPAF II(51;52)		Coumadin				✓ 325mg od	
AFASAK II(53)		✓				✓ 300mg daily	Fixed-dose warfarin; Warfarin+aspirin
PATAF(54)		Coumarin (standard)				✓ 150mg daily	Coumarin (low)
Vemmos et al (2006)(55)		Coumadin				✓ 100mg daily	Coumadin fixed-dose
WASPO(56)		✓				✓ 300mg daily	
ACTIVE-W(57)							Vitamin K agonist; Clopidogrel +aspirin
BAFTA(58;59)		✓				✓ 75mg daily	
PETRO(60)		✓	✓ + no aspirin / 81mg aspirin / 325 mg aspirin	✓ + no aspirin / 81mg aspirin / 325 mg aspirin			Dabigatran 300mg bd + no aspirin / 81mg aspirin / 325 mg aspirin
RE-LY(32)		✓		✓			Dabigatran 110mg bd
ACTIVE-A(61;62)						✓ + placebo	CLOPIDOGREL + ASPIRIN

od = once daily; bd= twice daily

For the selected trials, provide a summary of the data used in the analysis.

Data were prepared for the following endpoints:

- composite
- total stroke
- ischaemic stroke
- haemorrhagic stroke / ICH
- systemic embolism
- MI
- cardiovascular death
- mortality
- major haemorrhage
- minor bleed
- gastrointestinal bleed
- dyspepsia
- transient ischaemic attack

The composite endpoint was that in the ROCKET trial of ischaemic stroke and systemic embolism. Ischaemic stroke included strokes of uncertain type. Major and minor haemorrhage were defined as extracranial and clinically relevant non-major bleeding respectively. Major extracranial haemorrhage is not uniformly reported and data were entered in the NMA in some cases based on subtracting intracranial bleed from overall major haemorrhages. The term clinically relevant non major bleeding is adopted in the more recent trials whereas older studies more typically refer to minor bleeding. Where trials reported 'clinically relevant non-major' bleeding and 'minor' bleeding separately, only the former was included.

The data included are tabulated in the relevant report(43).

Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

A Bayesian network meta-analysis (NMA) was undertaken. NMA was carried out for the following outcomes: composite, total stroke, ischaemic stroke, haemorrhagic stroke / ICH, systemic embolism, MI, cardiovascular death, mortality, major haemorrhage, minor bleed, gastrointestinal bleed, dyspepsia, transient ischaemic attack.

The NMA used the odds ratio as the measure of relative treatment effect and assumed that treatment effects on the odds-ratio scale were multiplicative and exchangeable between trials. The implementation of the statistical model is further described in the study report(63).

Each model was run with two chains. A burn-in period of 10,000 iterations was used to limit the influence of the initial values on the simulated posterior distribution and estimation was based on a further 10,000 simulations.

The parameters for Bayesian network-meta-analysis models were estimated using WinBUGS 1.4.3 , and the results for the frequentist meta-analyses were estimated using R 2.10.1.

An additional description of the methodology used can be found in the report on the NMA(63).

Please present the results of the analysis.

A summary of results for rivaroxaban compared to adjusted dose warfarin, aspirin and dabigatran 110mg and 150mg from the NMA is presented in Table 25

Comparisons between rivaroxaban and each of the comparators in Table 25 were possible for all endpoints with the exception of transient ischaemic attack (TIA). Comparison was not possible with any of these comparators except adjusted dose warfarin for TIA.

The appended NMA report(63) show median odds ratios, 95% credible intervals, plots of odds ratios on a logarithmic scale, and network diagrams for each outcome.

Table 25. Summary of odds ratios for rivaroxaban compared to selected comparators

	adj dose warfarin	ASA	dabigatran 110mg	dabigatran 150mg	placebo
Analysis 1					
Composite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
total stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
haemorrhagic stroke / ICH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
major haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
minor bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
gastrointestinal bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
transient ischaemic attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Frequentist meta-analyses were run with both fixed effects and random effects. The NMA was run using random effects and thus makes allowance for heterogeneity between studies.

Plots are provided that address heterogeneity for the key endpoints of total stroke and major extracranial haemorrhage. For the analysis of total stroke the NMA gave a central estimate for the comparison between rivaroxaban against warfarin which was similar to that derived from head to head data. For the analysis of extracranial haemorrhage the NMA gave a central estimate for the comparison between rivaroxaban against warfarin which was different from but within the 95% CI around the estimates derived from head to head data.

Confidence intervals in the NMA were wider than in the underlying studies for both comparisons.

Both analyses also suggested differences between the NMA and fixed and pairwise analyses for comparisons between placebo, ASA and warfarin.

Meta-regression was not performed.

Figure 13. [redacted]

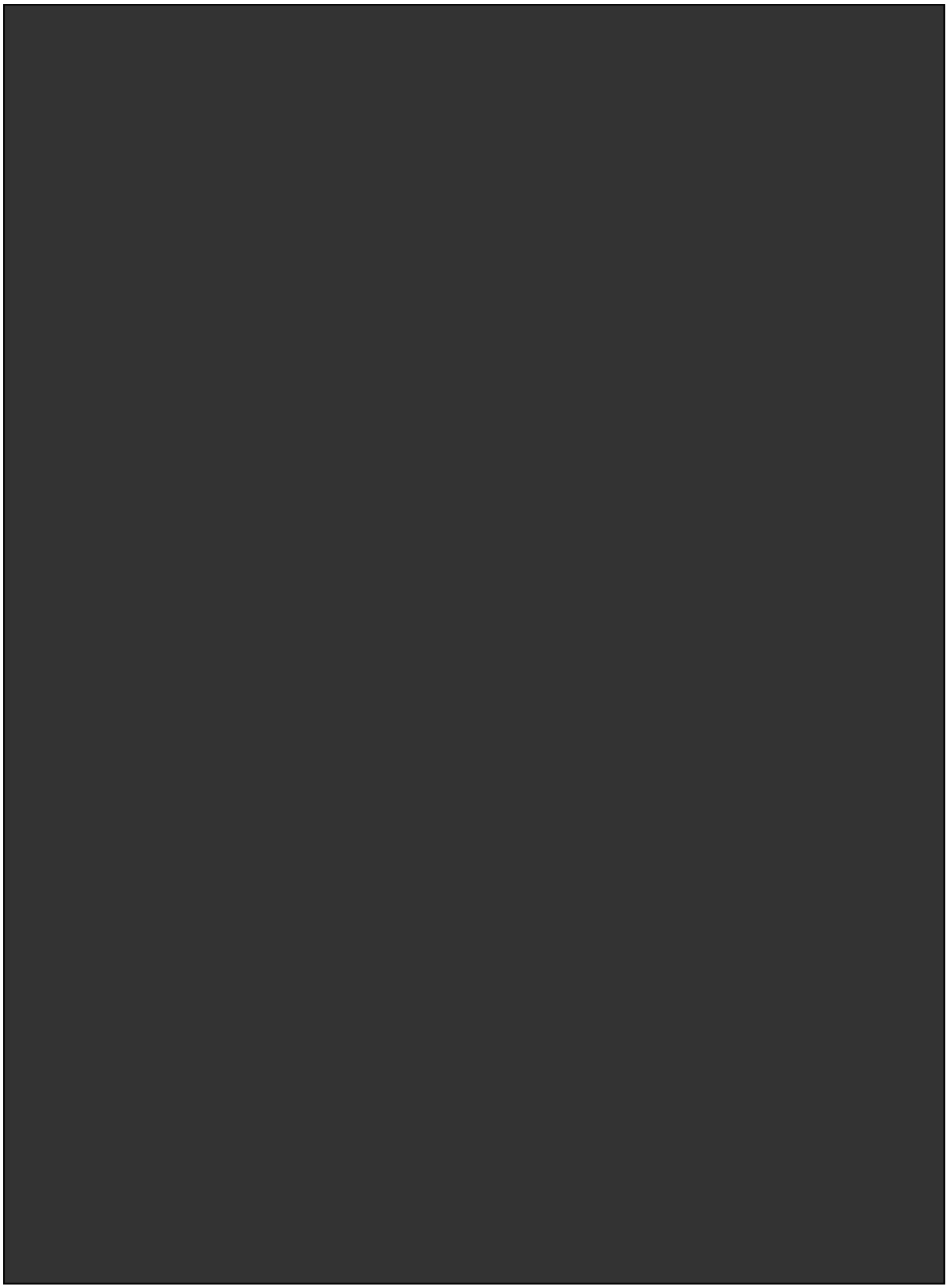
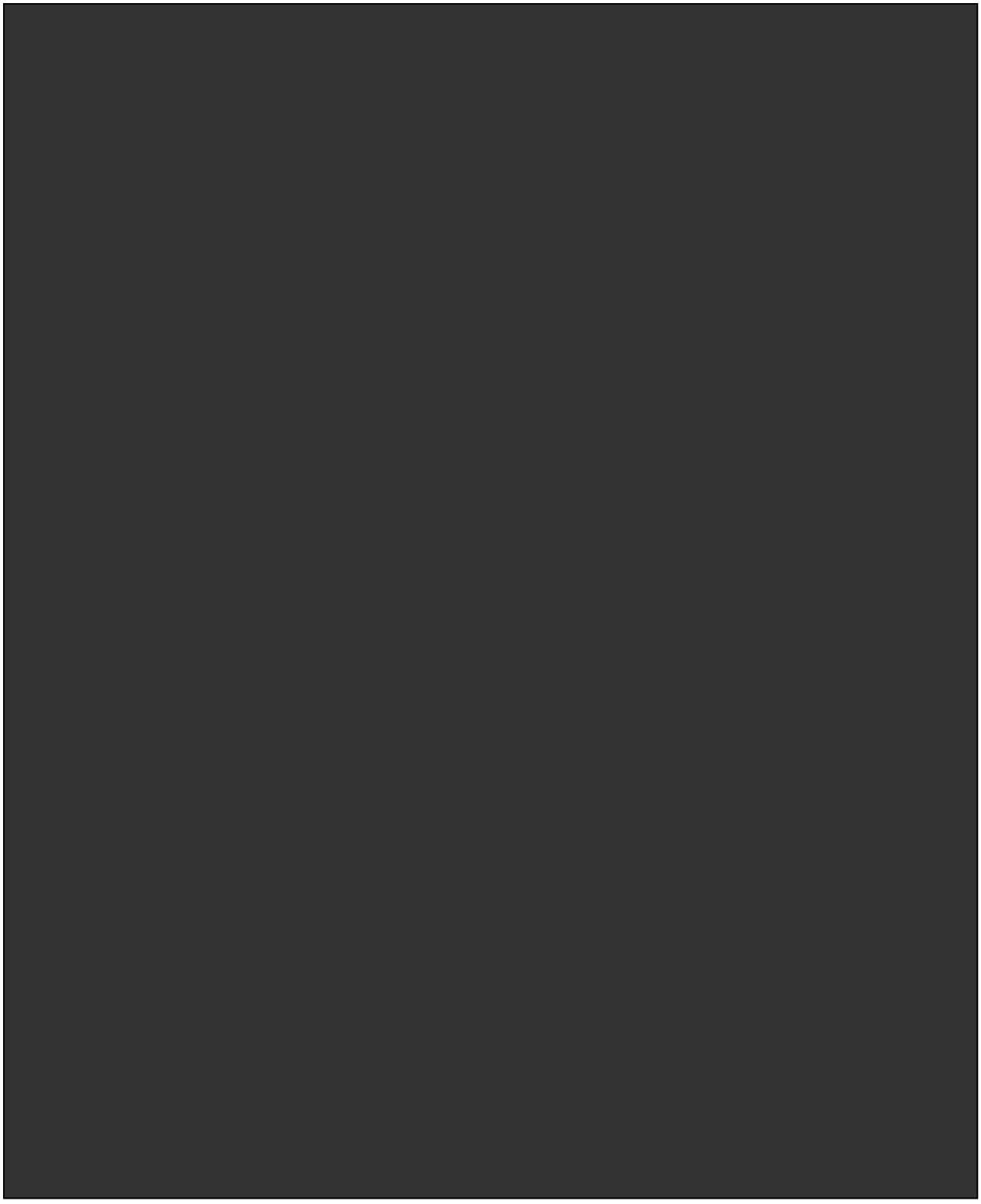


Figure 14. [redacted]



If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Three sensitivity analyses were conducted.

1) Restricted Comparators, Rocket ITT population

2) All Comparators, Rocket Safety Set On-treatment population

3) Restricted Comparators, Rocket ITT population, Blinded Studies Only

The base case analysis was restricted to the following comparators:

- PL
- ASA
- CLO-ASA
- DAB 110
- DAB 150
- APX
- Rivaroxaban
- Adj dose WAR

In the all comparators sensitivity analysis an expanded list of comparators were included:

- Adj dose WAR
- CLO-ASA
- ASA
- PL
- Fix dose WAR-ASA
- Fix dose WAR
- IDPX
- Adj dose WAR-ASA
- Low dose WAR
- TFS
- Low dose WAR-TFS
- DAB 150
- DAB 150-ASA
- DAB 50
- DAB 50-ASA
- DAB 110
- IBF
- Low dose WAR-ASA
- XMG

- Rivaroxaban
- APX

In the sensitivity analysis of blinded studies, the following studies were included:

- ACTIVE-A
- CAFA
- FFAACS
- PATAF eligible"
- SPINAF
- SPORTIF V
- AVERROES
- ROCKET SA (ITT Population)

In general the results of the sensitivity analyses are consistent with the base case. One exception is the MI endpoint: for this endpoint there were relatively few events in the blinded studies leading to uncertainty regarding the treatment effect relative to placebo.

Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

For the comparisons between rivaroxaban and adjusted dose warfarin, the findings of the NMA are similar to the direct study data from ROCKET AF.

For the comparison between rivaroxaban and dabigatran the NMA did not detect significant differences in any endpoint reported at either dose of dabigatran studied. No direct data exist.

For the comparison between rivaroxaban and aspirin, the NMA detected a significant difference in the composite endpoint and in total stroke but was not able to detect a difference in major extracranial bleeding. Direct head to head studied comparing aspiring and VKA therapy have found consistent and clinically significantly lower levels of stroke with VKA therapy compared to aspirin.

(See also section 9.4, appendix 4 and section 9.5 appendix 5.)

Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

There are no relevant non-RCTs included in this submission.

Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a

complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

Evidence of the safety of rivaroxaban when compared with warfarin, in the prevention of stroke and thromboembolic events in non-valvular AF, is provided by safety analyses and adverse event reporting from an international, multicentre, randomised, double-blind, double-dummy, event-driven phase III study (ROCKET AF)(23;26-28). The design, methodology, all clinical and safety endpoints and efficacy results from ROCKET AF are detailed in sections 5.3 to 5.5.

The primary safety objective of ROCKET AF was assessed by the composite of major and non-major clinically relevant bleeding events(23;26-28). Bleeding was defined as major if it was clinically overt and associated with a fall in the haemoglobin concentration of $\geq$2g/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 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 interruption of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life. Minimal bleeds were any other bleed that did not meet the other bleeding criteria. The CEC adjudicated all major and non-major clinically relevant bleeding events.

The total number of patients valid for the safety analysis from the ROCKET AF study was 14,236 (n=7,111 rivaroxaban; n=7,125 warfarin – i.e. including the patients from the Czech Republic site, which were excluded from the efficacy analysis). For the primary safety endpoint, results indicated a comparable safety profile of rivaroxaban to warfarin, with no statistically significant difference between the two treatments (hazard ratio of 1.03 [95% CI 0.96 to 1.11, P= 0.44]) (Table 26). This suggests that the improved efficacy of rivaroxaban over warfarin for primary and major secondary efficacy endpoints outlined in Section 3 is not at the expense of an increased risk of bleeding. This is a key requirement for any new anticoagulant.

The rate of major bleeding was similar between rivaroxaban and warfarin groups (Table 26). Intracranial haemorrhage rates were significantly lower with rivaroxaban than with warfarin (0.5 vs 0.7% per year; HR 0.67; 95% CI, 0.47, 0.93; P=0.02) and

bleeding leading to death was lower in the rivaroxaban arm of the study, while transfusion and haemoglobin-drop favoured warfarin-treated patients. Overall, less than 1% of all patients experienced a fatal bleeding event using the broad or narrow definition.

[redacted]

Clinically relevant non-major bleeding was also similar between treatment groups.

Table 26. Results of Primary Safety Endpoint (23;26) based on safety on treatment population

Parameter	Rivaroxaban		Warfarin		Rivaroxaban vs Warfarin	
	N=7111 n (%)	Event Rate (100 Pt-yr)	N=7125 n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Principal Safety Endpoint Composite of all major and non-major clinically relevant bleeding events	**1475 (20.7)**	**14.9**	**1449 (20.3)**	**14.5**	**1.03 (0.96. 1.11)**	**0.44**
Major	**395 (5.6)**	**3.6**	**386 (5.4)**	**3.4**	**1.04 (0.90, 1.20)**	**0.58**
Haemoglobin Haematocrit drop	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03, 1.44)	0.02*
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01, 1.55)	0.04*
Critical Organ Bleeding(s)	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53, 0.91)	0.007*
Fatal Bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31, 0.79)	0.003*
Intracranial haemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47, 0.93)	0.02
Non-major Clinically Relevant Bleeding	**1185 (16.7)**	**11.8**	**1151 (16.2)**	**11.4**	**1.04 (0.96, 1.13)**	**0.35**
Minimal	**258 (3.6)**	**2.3**	**226 (3.2)**	**2.0**	**1.16 (0.97, 1.39)**	**0.10**

Note: (a) Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding events

Note: (b) Critical organ bleeding are cases where CEC bleeding site = intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal

Note: Minimal events are not included in the principal safety endpoint

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

Note: p-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio

Note: *Statistically significant at nominal 0.05 (two-sided)

Bleeding sites for the principal safety endpoint differed by treatment group: rivaroxaban was more often associated with bleeding at sites throughout the gastrointestinal tract (224 bleeds [3.15%] vs. 154 bleeds [2.16%]; P<0.001) as well as haematuria, and warfarin was more often associated with critical organ bleeding (e.g. intracranial and other critical organ sites) and bleeding associated with non-cardiac surgery(23;28).

The following table sets out major bleeding events by site.

Table 27. Major bleeding by site*

	Rivaroxaban (N=7111)	**Warfarin (N=7125)**
Major bleeding, no. (%)	395 (5.55)	386 (5.42)
Gastrointestinal (upper, lower, and rectal)†	224 (3.15)	154 (2.16)
Intracranial‡	55 (0.77)	84 (1.18)
Intraparenchymal‡	37 (0.52)	56 (0.79)
Non-traumatic‡	33 (0.46)	54 (1.76)
Traumatic	4 (0.06)	2 (0.03)
Intraventricular	2 (0.03)	4 (0.06)
Subdural hematoma	12 (0.17)	22 (0.31)
Subarachnoid	4 (0.06)	1 (0.01)
Epidural hematoma	0	1 (0.01)
Macroscopic hematuria	26 (0.37)	21 (0.29)
Bleeding associated with non-cardiac surgery	19 (0.27)	26 (0.36)
Intraocular/Retinal	17 (0.24)	24 (0.34)
Intraarticular	16 (0.23)	21 (0.29)
Epistaxis	13 (0.18)	14 (0.20)

*Site based on blinded adjudication.
†Combined gastrointestinal bleed rate P<0.001.
‡P<0.05

Please provide details of all important adverse events for each intervention group.

For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative

risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The overall incidence of treatment-emergent adverse events was similar in both treatment arms (81.44% in the rivaroxaban group and 81.54% in the warfarin group) (see Table 28). 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.

Table 28. Adverse event summary

All Adverse Events	**Rivaroxaban**	**Warfarin**	**Rivaroxaban Minus Warfarin**	
	N=7111 n (%)	**N=7125 n (%)**	**Diff (%)**	**95% CI (%)[a]**
Post Baseline Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-emergent Adverse Events	5791 (81.44)	5810 (81.54)	[redacted]	[redacted]
Adverse Events with Onset > 2 days from Stop of Study Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Serious Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]
Post Baseline Serious Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-emergent Serious Adverse Events	2489 (35.00)	2598 (36.46)	-1.46	(-3.04, 0.11)
Serious Adverse Events with Onset > 2 days from Stop of Study Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Post Baseline Adverse Events Leading to Permanent Study Drug Discontinuation	[redacted]	[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

[redacted]

Investigator-reported treatment-emergent serious adverse events (non bleeding and bleeding) based on the rivaroxaban group were reported in 2489 (35.00%) rivaroxaban patients and 2598 (36.46%) warfarin patients.

A summary of the 15 most frequent investigator-reported treatment-emergent adverse events based on the rivaroxaban group by preferred term is provided in Table 29. Overall, the incidence and types of adverse events were similar between the treatment groups although more patients in the rivaroxaban group had epistaxis compared with warfarin (10.14% versus 8.55%, respectively). The most frequent adverse events for rivaroxaban were epistaxis (10.14%), peripheral oedema (6.12%), and dizziness (6.09%) and for warfarin were epistaxis (8.55%), nasopharyngitis (6.39%), and dizziness (6.30%) based on the rivaroxaban group. These adverse events are common in atrial fibrillation patients with multiple risk factors.

Table 29. Incidence of the 15 most frequent treatment-emergent adverse events based on the rivaroxaban treatment group by preferred term(28)

Preferred Term	**Rivaroxaban**	**Warfarin**
	N=7111 n (%)	**N=7125 n (%)**
Total number of subjects with treatment-emergent adverse events	5791 (81.44)	5810 (81.54)
Epistaxis‡	721 (10.14)	609 (8.55)
Peripheral Oedema	435 (6.12)	444 (6.23)
Dizziness	433 (6.09)	449 (6.30)
Nasopharyngitis	421 (5.92)	455 (6.39)
Cardiac failure	397 (5.58)	420 (5.89)
Bronchitis	396 (5.57)	417 (5.85)
Dyspnoea	380 (5.34)	394 (5.53)
Diarrhoea	379 (5.33)	397 (5.57)
Cough	343 (4.82)	353 (4.95)
Back pain	338 (4.75)	347 (4.87)
Upper respiratory tract infection	336 (4.73)	325 (4.56)
Headache	324 (4.56)	363 (5.09)
Arthralgia	301 (4.23)	331 (4.65)
Haematuria‡	296 (4.16)	242 (3.40)
Urinary tract infection	293 (4.12)	321 (4.51)

‡P<0.05

In light of the liver function abnormalities produced by ximelagatran, an oral thrombin inhibitor now withdrawn from research, hepatotoxicity risk was also closely monitored in the ROCKET AF study, involving an external panel of hepatic experts. The overall liver safety profile of rivaroxaban (a direct factor Xa inhibitor) was shown to be comparable to warfarin, with no evidence of imbalance in laboratory parameters or hepatic adverse events. ALT elevations were balanced between the rivaroxaban and warfarin groups at all thresholds.

Table 30. Incidence of Prespecified ALT Laboratory Abnormalities with Hazard Ratios (Based on Central Laboratory) – Safety analysis set(26)

Lab Test	Time Interval	Criteria	Rivaroxaban (N=7111) n/J(%)	Warfarin (N=7125)n/J(%)	HR Rivaroxaban to warfarin (95% CI)
ALT (SGPT)	BASELINE	> 3 X ULN	[redacted]	[redacted]	[redacted]
		> 5 X ULN	[redacted]	[redacted]	[redacted]
		> 8 X ULN	[redacted]	[redacted]	[redacted]
		> 10 X ULN	[redacted]	[redacted]	[redacted]
		> 20 X ULN	[redacted]	[redacted]	[redacted]
	POST BASELINE	> 3 X ULN	[redacted]	[redacted]	[redacted]
		> 5 X ULN	[redacted]	[redacted]	[redacted]
		> 8 X ULN	[redacted]	[redacted]	[redacted]
		> 10 X ULN	[redacted]	[redacted]	[redacted]
		> 20 X ULN	[redacted]	[redacted]	[redacted]
	TREATMENT EMERGENT	> 3 X ULN	[redacted]	[redacted]	[redacted]
		> 5 X ULN	[redacted]	[redacted]	[redacted]
		> 8 X ULN	[redacted]	[redacted]	[redacted]
		> 10 X ULN	[redacted]	[redacted]	[redacted]
		> 20 X ULN	[redacted]	[redacted]	

Note: ULN = Upper Limit of Normal Range
Note: BASELINE: Uses the lab value prior and including the first study dose date.
Note: POST BASELINE: Uses the lab value after the first study dose date.
Note: TREATMENT EMERGENT: events that start on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Note: n = Number of subjects with events.
Note: J = Number of subjects with non-missing baseline lab values (for BASELINE), with non-missing post baseline lab values
(for POST BASELINE), with non-missing post baseline and normal baseline lab values (which are not meeting the corresponding criterion of that line) (for TREATMENT EMERGENT).
Note: Hazard Ratio (95% CI): time to event analysis using a Cox model with the treatment as the covariate.
Hazard ratio will be provided when a total number of events is greater than 10 for two treatment groups and at least 1 event in both groups.

[redacted]

[redacted]

Give a brief overview of the safety of the technology in relation to the decision problem.

In summary,

- Rivaroxaban is well tolerated with adverse events similar to warfarin
- The primary safety endpoint of major and non-major clinical relevant bleeding was not statistically different between rivaroxaban and warfarin
- Treatment with rivaroxaban resulted in more transfusions and 2 gm/dl decreases in haemoglobin than warfarin, however there were fewer intracranial haemorrhages, critical organ bleeds and fatal bleeding for rivaroxaban patients compared to warfarin
- Gastrointestinal bleeding may be modestly increased with rivaroxaban
- The overall liver safety profile of rivaroxaban was comparable to warfarin with no evidence of imbalance in laboratory parameters or [redacted]

- The lower dose of 15 mg of rivaroxaban was well tolerated in patients with decreased renal function

Interpretation of clinical evidence

Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The ROCKET AF study met the primary efficacy endpoint of non-inferiority to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. Rivaroxaban was subsequently found to be superior to warfarin for the primary efficacy endpoint using the safety population during the on-treatment period, according to the pre-specified hierarchy of statistical testing.

When conducting the ITT analysis to the point of site notification, rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint, but did not reach superiority due to dilution of treatment effect in the "off treatment" period, when patients were transitioned to open-label therapy.

Treatment effects with regard to the primary efficacy endpoint were consistent across all pre-specified sub-groups. Importantly, fewer strokes in the rivaroxaban treated patients led to death and severe disability.

For the primary safety endpoint (composite of all major and non-major clinically relevant bleeding events), results indicated comparable safety between rivaroxaban and warfarin, with no statistically significant difference between the two treatments. The specific bleeding profile did however differ, with fewer critical organ bleeds (including intracranial haemorrhage) and fatal bleeds with rivaroxaban.

Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

ROCKET AF was a large, prospective, randomised, double-blind, double-dummy, active-controlled, multicentre, event-driven study. This kind of rigorous study design is generally considered the 'gold standard'.

The patients recruited were those eligible for oral anticoagulation and with significant co-morbidity. This is a strength of the study as the positive results were achieved in

a group of patients with significant co-morbidity and elevated risk of stroke and thus can be considered a rigorous test of rivaroxaban

Employing a double blind, double dummy design and using sham INR testing in the rivaroxaban arm, did not allow any of the practical advantages over warfarin to be tested e.g. removing the need for regular clinic appointments for INR testing and dose adjustment. The trial may therefore underestimate such benefits that may be seen in clinical practice.

In addition, the double-blind design led to difficulties in transferring patients from rivaroxaban to warfarin, in order to maintain the study blind. It took approximately 4 times longer to achieve a therapeutic INR with open label warfarin after the end of double-blind therapy in those randomised to rivaroxaban (13 days) compared to those randomised to warfarin (3 days). This was a limitation of the study which potentially disadvantaged rivaroxaban.

Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Population

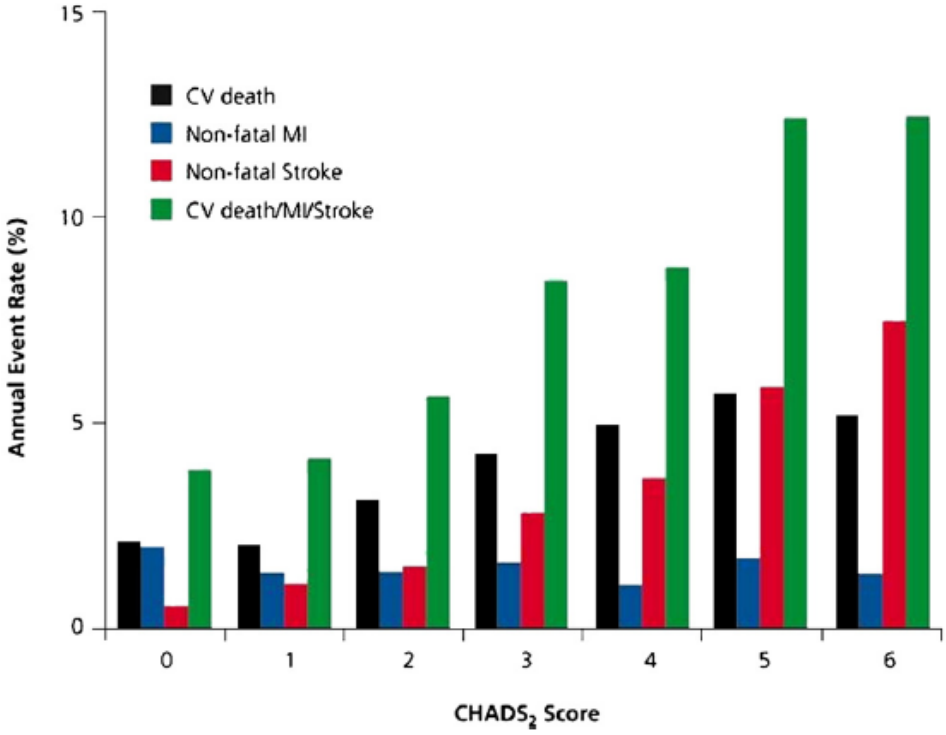
The underlying risk of stroke in patients with AF is dependent on the presence or absence of a number of different risk factors. The ROCKET AF study included patients considered representative of the majority of subjects with non-valvular AF for whom oral anticoagulant therapy is indicated.

Table 31. Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score*(15)

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2 4	4.0	18.2 (10.5-27.4)

*$CHADS_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischaemic attack. CI indicates confidence interval. †The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken

Figure 15. Annual CV event risk in AF patients with various $CHADS_2$ scores(64)



Annual CV event risk in AF patients with various $CHADS_2$ (congestive heart failure [C], history of hypertension [H], age >75 years [A], DM [D], or history of stroke or TIA [S]) scoring (adjusted for age, sex, smoking, diabetes, hypertension, hypercholesterolemia). Annual event rate of CV death, nonfatal stroke, and combined end point of CV death/nonfatal MI/nonfatal stroke are for patients with higher $CHADS_2$ scoring, whereas the rate of nonfatal MI was not influenced by $CHADS_2$ scoring.

Intervention

Rivaroxaban

Comparator(s)

Warfarin is the oral anticoagulant used most commonly in England and Wales and was the comparator in ROCKET AF. Warfarin is however associated with a number of well documented limitations:

- A narrow therapeutic index with a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage. A recent systematic review and meta-analysis reported that the risk of thromboemboli increased significantly at ratios less than 2, and the risk of haemorrhage increased significantly at high international normalised ratios(65).

- The requirement for dose adjustment using frequent, inconvenient and costly INR monitoring. The frequency of monitoring varies depending on individual patient characteristics.
- Response that is significantly influenced by diet, concomitant medications, herbal supplements and intercurrent illness
- The need for individualised patient dosing and adjustment, often requires warfarin to be supplied in a number of different strengths. This may increase the risk of accidental under- or over-dose and requires additional patient education, especially in confused, older people.

In addition, it is reported that switching between generic and branded formulations of warfarin may expose patients to increased risk of thrombotic events and bleeding(66).

These limitations have led to a significant proportion of patients who are eligible for warfarin to receive either aspirin or no treatment at all(4;5;17;67;68). This represents a group with an unmet need as the untreated population remain at elevated risk from stroke (69) and other thromboembolic events. As the study did not include these as comparators, relative treatment effect was calculated via a network meta-analysis.

Outcomes

AF is associated with a prothrombotic state leading to a predisposition to thrombus formation (1). Thromboembolic stroke occurs when stagnant blood in the fibrillating atrium forms a thrombus that then embolises to the cerebral circulation, blocking arterial blood flow and causing ischaemic injury(10).

Additionally, AF is associated with an increased risk of systemic embolism (SE) which may result in major damage to limbs and organs(11).

Therefore, effective prevention of stroke and non-CNS embolism in atrial fibrillation is important to reduce this burden and improve health and socioeconomic outcomes.

By the very nature of these drugs, there is an associated risk of bleeding. Bleeding outcomes therefore need to be incorporated into trials to ensure that the studied drugs can be used safely in clinical practice with a good benefit-risk profile.

Recommended outcome parameters for trials in atrial fibrillation have been published, and include(30):

- All strokes (ischaemic and haemorrhagic) and systemic embolic events
- Major bleeding, usually as a safety outcome parameter

As in other recent phase III trials of the oral anticoagulants in development for stroke prevention in AF(32;70), the primary efficacy endpoint chosen in the ROCKET AF trial is the composite of stroke and non-CNS systemic embolism. The principal safety endpoint is the composite of major bleeding and clinically relevant non-major bleeding.

As highlighted in section 5.10.3, employing a double blind, double dummy design and using sham INR testing in the rivaroxaban arm, did not allow any of the practical advantages over warfarin to be tested e.g. removing the need for regular clinic appointments for INR testing and dose adjustment.

Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Stroke risk

The results of the ROCKET AF trial are directly applicable to the population of AF patients in England and Wales who are eligible for oral anticoagulation.

ROCKET AF enrolled patients for whom guidelines(14) recommended anticoagulation.

ROCKET AF recruited patients with a prior stroke, TIA or non-CNS systemic embolism or those patients with two or more of the following risk factors: age ≥75 years, hypertension, heart failure and/or left ventricular ejection fraction ≤35%, or diabetes mellitus. The number of subjects without a prior stroke, TIA or non-CNS systemic embolism and only 2 risk factors was limited 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. The patients recruited to the study therefore represent a population at elevated risk of thromboembolic events in whom anticoagulation is clearly indicated, according to guidelines.

A systematic review conducted to support this submission (already described in Sections 5.1-5.2 and found in Section 9.2, Appendix 2), found that there does not appear to be an interaction between treatment effect and baseline risk of stroke.

Only four studies reported $CHADS_2$ scores among patients' baseline characteristics: ACTIVE W(57), AMADEUS(71), ACTIVE A(62) and BAFTA(58). Of these, three (ACTIVE A, BAFTA and AMADEUS) reported subgroup analyses based on $CHADS_2$ scores for primary outcomes.

Results from the BAFTA trial showed no significant interaction between $CHADS_2$ scores (subgroups of $CHADS_2$ 1-2 and 3-6) and treatment for the primary outcome (incidence of fatal or non-fatal disabling stroke, intra-cranial haemorrhage or significant arterial embolism) or major haemorrhage.

Analysis of the primary events (stroke or systemic embolism) in the AMADEUS trial showed that there were no significant differences between $CHADS_2$ ≤1, $CHADS_2$ = 2, and $CHADS_2$ ≥3 patients.

In ACTIVE A the authors reported no interaction effect for any outcome by $CHADS_2$ sub-group defined by a higher $CHADS_2$score (e.g. ≥3).

More recently, the RE-LY investigators failed to identify a significant interaction with the treatment effect for dabigatran among any of the subgroups by $CHADS_2$ score(32) or CHA_2DS_2-VASc score(72).

The data from the ROCKET AF trial demonstrate robust efficacy and similar comparative bleeding rates vs warfarin across levels of risk of stroke included in ROCKET AF, and it is notable that the efficacy treatment effect is particularly strong in the patient subgroup without a prior history of stroke, i.e. in primary prevention. It is therefore reasonable to conclude that rivaroxaban would likely provide a favourable benefit-risk profile for patients who are classified as appropriate for anticoagulation according to NICE guidelines(1).

TTR achieved

The mean TTR in the warfarin group (55%) could be considered low compared to what has been seen in recent trials within this area.

However, various methods have been used in clinical trials to calculate the TTR, and the results of all of these methods depend on details such as whether an exact (e.g. 2.0-2.5) or an expanded (e.g. 2.0-3.0) therapeutic range is used, whether warfarin-naive patients are included or only patients already on established therapy, whether INRs obtained during invasive procedures when warfarin therapy might be interrupted are included, and whether different oral anticoagulant preparations are included.

The methodology of TTR determination and of the derived cTTR are different between recently conducted studies, making cross study comparisons challenging. Whereas in the cTTR analysis of ROCKET AF, all INR values were analysed, the published data from the RE-LY study(32) suggest a better INR control, whilst their analysis was based on excluding INRs from the first week and after discontinuation of the study drug. In addition, the RE-LY was an open-label study and the investigators were contacted by the study team with advice for optimal INR control.

Patient clinical history may have impacted on the TTR achieved. ROCKET AF is a unique study because it included patients with many risk factors for stroke and co-morbid conditions. The TTR values observed in ROCKET AF are consistent with those expected in such a group of patients. Heart failure, diabetes, and prior stroke, all components of the $CHADS_2$ classification system, have been shown in other studies to be moderate predictors of lower TTR(41). [redacted] Given the high representation of heart failure in the study (approximately 62%), this population contributed substantially to the overall TTR for the study. Overall, having a patient population who are high risk with multiple co-morbidities would impact on the ability to achieve “good control”. This was evidenced in the study, with lower TTR in those with the highest $CHADS_2$ scores.

Importantly, in ROCKET AF, the centre time in therapeutic range (TTR) achieved for warfarin did not affect the outcomes seen with rivaroxaban i.e. the rivaroxaban treatment effect is independent of the level of INR control in the warfarin group. The

overall benefit-risk assessment favours rivaroxaban even amongst centers with the best warfarin management.(28)

Several UK publications have investigated the TTR achieved in AF patients and the majority of these quote figures between 62 and 68% TTR(58;73-78).. Due to the differences between trials in methods of measuring TTR, the high level of co-morbidity in the ROCKET AF trial compared to a "general" AF population and variation in practice between countries, the TTR achieved is not unexpected and is highly likely to be representative of practice in England and Wales.

Design

As highlighted in the two sections above, employing a double blind, double dummy design and using sham INR testing in the rivaroxaban arm, did not allow any of the practical advantages over warfarin to be tested e.g. removing the need for regular clinic appointments for INR testing and dose adjustment. The trial may therefore underestimate such benefits that may be seen in clinical practice.

Patient selection

Rivaroxaban is expected to gain a licence for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. However, Bayer recognise that the rapid uptake and use of new OACs in all of these AF patients would have substantial service delivery implications and that such changes are most appropriately made in a gradual fashion. Therefore, the economic value and budget impact of rivaroxaban has been evaluated using a range of scenarios including the following cohorts of individuals, with varying levels of unmet need:

- AF population – i.e. all patients eligible for oral anticoagulation
- Patients who are unsuitable for warfarin – e.g. those with allergy, those who have discontinued warfarin (for reasons other than bleeding) and those who may have difficulty with regular INR monitoring
- Patients currently taking warfarin but who are "difficult to manage", with excessive time out of therapeutic range and needing intensive management with associated resource use

What proportion of the evidence base is for the dose(s) given in the SPC?

All of the evidence base is for the doses given in the SPC.

Cost effectiveness

Published cost-effectiveness evaluations

Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A literature search was conducted of the following data bases using Ovid SP to identify cost-effectiveness studies relevant to the scope of the decision problem

- MEDLINE
- EMBASE
- Econlit
- NHS EED

The data bases cover a range of relevant medical and economic literature so that all applicable studies are likely be captured in the searches. A list of search terms, provided in Appendix 10 was constructed to cover important terms for atrial fibrillation, stroke, prophylactic medication and cost-effectiveness analyses. In addition a set of inclusion and exclusion criteria were developed and applied to the search results, after duplicates were removed. Abstracts from conference proceedings were not searched and only English language studies were included. The final included studies were extracted and evaluated.

Inclusion criteria were

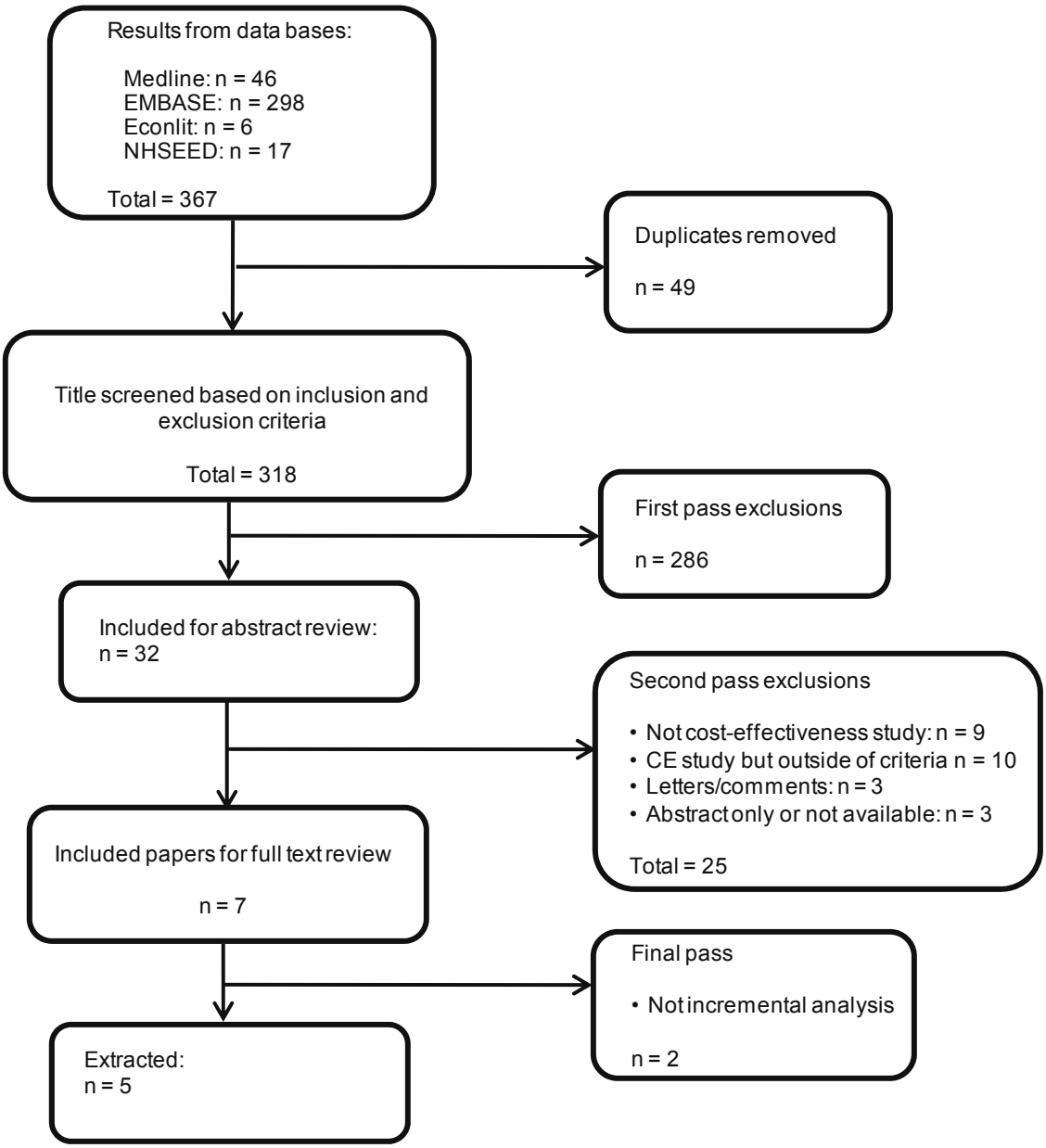
- Cost-effectiveness studies of stroke prevention in atrial fibrillation evaluating antithrombotics

Exclusion criteria were

- Patient populations less than 18 years old
- Treatment based on non-pharmacological management

- Treatment of atrial fibrillation with pharmacotherapy for AF rhythm control
- Valvular atrial fibrillation
- Non -cost effectiveness studies
- Studies which did not compare one antithrombotic with a different antithrombotic or placebo
- Conference papers
- Comparisons focused on method of anticoagulation administration
- Comparators that were mixtures of anticoagulants
- Abstracts
- Reviews
- Letters/comments
- Non-English language

Figure 16. Flow diagram of literature search strategy on cost-effectiveness



Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

After full text review a total of 5 articles were extracted into Table 32 below for inclusion in this submission. All but one of the articles describes a Markov model where patients cycle through defined health states over time. The publication not describing a Markov model is not well described in the text but appears to be a decision tree and is used to extrapolate a patient level study and also a meta-analysis of clinical trials. Most of the studies were set in North America (3 x USA + 1 x Canada) with only one set in Europe (UK).

Warfarin was the most common comparator being analysed in all 5 studies, aspirin and dabigatran were also included in more than one study. The patient population in all of the Markov models were elderly patients of at least 65 years with atrial fibrillation. Different studies may stratify patient populations based on risk factors, for example stroke(79) or on the management of anticoagulation therapy, for example real world versus trial warfarin settings(80). The cost-effectiveness of different treatments is often influenced by the choice of stratification and other variables.

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Table 32. Summary list of other cost-effectiveness evaluations

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Freeman et al.(81)	2011	US	Cohort based Markov model	The model cohort were 65 years old at the start of the simulation	ICH = Intracranial haemorrhage *QALYs reported* Stroke 0.72, $CHADS_2$ 1, ICH 0.74 Wafarin = 10.72 Dabigatran 110mg = 11.2 Dabigatran 150mg = 11.23 Stroke 1.2, $CHADS_2$ 1-2, ICH 0.74 (base case) Wafarin = 10.28 Dabigatran 110mg = 10.7 Dabigatran 150mg = 10.84 Stroke 2.35, $CHADS_2$ 4, ICH 0.74 Wafarin = 9.36 Dabigatran 110mg =	2008 US dollars Stroke 0.72, $CHADS_2$ 1, ICH 0.74 Wafarin = 129,749 Dabigatran 110mg = 148,935 Dabigatran 150mg = 155, 769 Stroke 1.2, $CHADS_2$ 1-2, ICH 0.74 (base case) Wafarin = 143,193 Dabigatran 110mg = 164,576 Dabigatran 150mg = 168,398 Stroke 2.35, $CHADS_2$ 4, ICH 0.74 Wafarin = 161,620 Dabigatran 110mg = 185,822	Stroke 0.72, $CHADS_2$ 1, ICH 0.74 Wafarin = Reference Dabigatran 110mg = 40,355 Dabigatran 150mg = 171,984 Stroke 1.2, $CHADS_2$ 1-2, ICH 0.74 (base case) Wafarin = Reference Dabigatran 110mg = Dominated Dabigatran 150mg = 45,372 Stroke 2.35, $CHADS_2$ 4, ICH 0.74 Wafarin = Reference Dabigatran 110mg = Dominated Dabigatran 150mg = 39,680 Stroke 1.2, $CHADS_2$ 1-2, ICH 0.44 Wafarin = Reference Dabigatran 110mg = Dominated Dabigatran 150mg = 69,574 Stroke 1.2, $CHADS_2$ 1-2, ICH 1.48

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					9.65 Dabigatran 150mg = 10.0 Stroke 1.2, CHADS2 1-2, ICH 0.44 Wafarin = 10.75 Dabigatran 110mg = 11.0 Dabigatran 150mg = 11.21 Stroke 1.2, CHADS2 1-2, ICH 1.48 Wafarin = 9.39 Dabigatran 110mg = 10.05 Dabigatran 150mg = 10.06	Dabigatran 150mg = 186,910 Stroke 1.2, CHADS2 1-2, ICH 0.44 Wafarin = 134,655 Dabigatran 110mg = 163,083 Dabigatran 150mg = 166,652 Stroke 1.2, CHADS2 1-2, ICH 1.48 Wafarin = 158,912 Dabigatran 110mg = 169,482 Dabigatran 150mg = 173,721	Wafarin = Reference Dabigatran 110mg = 16,147 Dabigatran 150mg = 263,543
Gage et al.(79)	1995	US	Markov model, 10 year time horizon	Patients were aged 65 years old at the start of the simulation.	High risk of stroke Warfarin: = 6.51 Aspirin: = 6.27 No therapy: = 6.01 Medium risk of stroke	Costs in 1994 USD High risk of stroke Warfarin: = 12,500 Aspirin: = 13,200 No therapy: = 15,300	Warfarin vs comparator High risk of stroke Aspirin: = Dominated No therapy: = Dominated

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					Warfarin: = 6.60 Aspirin: = 6.46 No therapy: = 6.23 Low risk of stroke Warfarin: = 6.7 Aspirin: = 6.69 No therapy: = 6.51	Medium risk of stroke Warfarin: = 10,900 Aspirin: = 9,700 No therapy: = 11,400 Low risk of stroke Warfarin: = 9000 Aspirin: = 5,400 No therapy: = 6,300	Medium risk of stroke Aspirin: = 8000 No therapy: = Dominated Low risk of stroke Aspirin: = 370,000 No therapy: = 14,000
Lightowlers & McGuire(82)	1998	UK	Not clear, possibly decision tree	Not clear, extrapolation of published studies	Life years gained free from stroke over a 10 year period Base Case 1 = 0.33061 Base Case 2 = 0.5349 Base Case 3 = 0.9349 Base Case 4 = 1.908	Total costs GBP 1997 discounted over 10 years for stroke treatment for each base case No treatment group Base Case 1 = 818,488.39 Base Case 2 = 696,531.87 Base Case 3 = 1,036,393.30	Cost per life year gained (Benefits discounted) Base case 1: = 13,221.29 Base case 2: = 5,497.59 Base case 3: = 1,751.05 Base case 4: = - 400.45

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	
						Base Case 4 = 1,484,875.90 Wafarin group Base Case 1 = 743,974.58 Base Case 2 = 316,422.81 Base Case 3 = 386,456.50 Base Case 4 = 334,527.87		
Shah et al.(83)	2011	US	Cohort based Markov model, 1 month cycle length, 20 year time horizon	The model cohort were 70 years old at the start of the simulation	Absolute QALYs Dabigatran 150 mg twice daily = 8.65 Dabigatran 110 mg twice daily = 8.54 Warfarin = 8.40	USD 2010 Dabigatran 150 mg twice daily = 43,700 Dabigatran 110 mg twice daily = 44,300 Warfarin = 23,000	Versus Aspirin Dabigatran 150 mg twice daily = 50,000 Dabigatran 110 mg twice daily =	Versus Warfarin Dabigatran 150 mg twice daily = 86,000 Dabigatran 110 mg twice daily = 150,000

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	
					Aspirin & clopidogrel = 8.32 Aspirin = 8.17	Aspirin & clopidogrel = 34,000 Aspirin = 20,000	66,000 Warfarin = 12,500 Aspirin & clopidogrel = 99,000	Aspirin & clopidogrel = Dominated
Sorensen et al.(80)	2011	Canada	Cohort based Markov model, 3 month cycles,	The patient population was matched to the RE-LY trial. Patients were stratified based in this trial into <80 years old or ≥80 years old	<u>Base Case</u> "Trial-like" warfarin = 7.08 Dabigatran etexilate = 7.29 <u>Scenario 1</u> "Real-world" prescribing warfarin = 7.01 Dabigatran etexilate = 7.29 <u>Scenario 2</u> "Trial-like" warfarin = 6.68 Dabigatran etexilate 150 mg bid = 6.86	2010 Canadian dollars <u>Base Case</u> "Trial-like" warfarin = 42,946 Dabigatran etexilate = 45,124 <u>Scenario 1</u> "Real-world" prescribing warfarin = 44,020 Dabigatran etexilate = 45,124 <u>Scenario 2</u> "Trial-like" warfarin = 40,169 Dabigatran etexilate 150 mg bid = 41,824	<u>ICER ($/QALY)</u> <u>Base Case</u> Dabigatran etexilate vs "Trial-like" warfarin vs = 10,440 <u>Scenario 1</u> Dabigatran etexilate vs "Real-world" prescribing warfarin = 3,962 <u>Scenario 2</u> Dabigatran etexilate 150 mg bid vs "Trial-like" warfarin = 9,041 <u>Scenario 3</u> Dabigatran etexilate 110 mg bid vs	

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					<u>Scenario 3</u> "Trial-like" warfarin = 6.68 Dabigatran etexilate 110 mg bid = 6.82	<u>Scenario 3</u> "Trial-like" warfarin = 40,169 Dabigatran etexilate 110 mg bid = 44,379	"Trial-like" warfarin = 29,994
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)							

Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

	Study name: Freeman et al. 2011(81)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	No	Only references were provided
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	

17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	N/A	All variables included
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Gage et al. 1995(79)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	No	The aspirin dose was not stated
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	Study mainly reports DRGs
18. Were currency and price data recorded?	Yes	

19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Lightowlers & McGuire 1998(82)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	However it is not clear what life years gained free from stroke means in the context of the analysis
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	

19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	Information was provided but some details are unclear
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Shah et al 2011(83)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	No	Only references were provided
13. Were the details of the subjects from whom valuations were obtained given?	No	This was stated for one study but not for many others
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	

19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Sorenson et al 2011(80)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	The introduction mainly focused on the clinical aspects of the disease area
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	The reference is given but details of the study are not in the text
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	

19. Were details of price adjustments for inflation or currency conversion given?	No	Inflation was referenced but not detailed for reported costs
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	No	Life time horizon is stated but the number of years is not
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

De novo analysis

Patients

What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the

evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The base case analysis considered the population from the ROCKET AF clinical trial. As outlined in Section 0 patients included within the ROCKET AF study were those with non-valvular atrial fibrillation with a $CHADS_2$ score ≥ 2, having either a history of stroke or transient ischaemic attack (TIA) or any two of the following risk factors: congestive heart failure, hypertension, diabetes or age greater than 75 years.

As outlined in section 0, the proposed indication for rivaroxaban includes patients with atrial fibrillation and a $CHADS_2$ score ≥1. Despite the base case modelling the trial population (CHADS2 ≥2), Bayer feel the results are generalisable to the wider proposed licensed population due to the apparent lack of interaction between treatment effect and baseline risk of stroke [See section 5.10.4].

In addition, the following populations are modelled:

Based on the ROCKET AF data

- Patients with atrial fibrillation and $CHADS_2$ score ≥ 2 who are not well controlled on warfarin and have a requirement for frequent INR monitoring.

- Warfarin naive – patients who have not been previously treated with warfarin as consistent with the sub-group identified within the Final Scope for this Single Technology Appraisal.

Based on a network meta-analysis

- Warfarin unsuitable – specifically patients with atrial fibrillation and $CHADS_2$ score ≥ 1 who are not receiving OAC therapy due to discontinuation of previously prescribed OAC, contraindication to warfarin or anticipated inability to manage regular INR monitoring. The evidence base is not derived from the ROCKET AF trial but are taken from a network meta-analysis since these patients are likely to be receiving aspirin or no treatment.

- Patients currently taking dabigatran 110mg bid or 150mg bid as their anti-thrombotic therapy. This population has been included in this as dabigatran was identified in the Final Scope as a potential comparator. The Single

Technology Appraisal for dabigatran etexilate is still ongoing at the time of this submission.

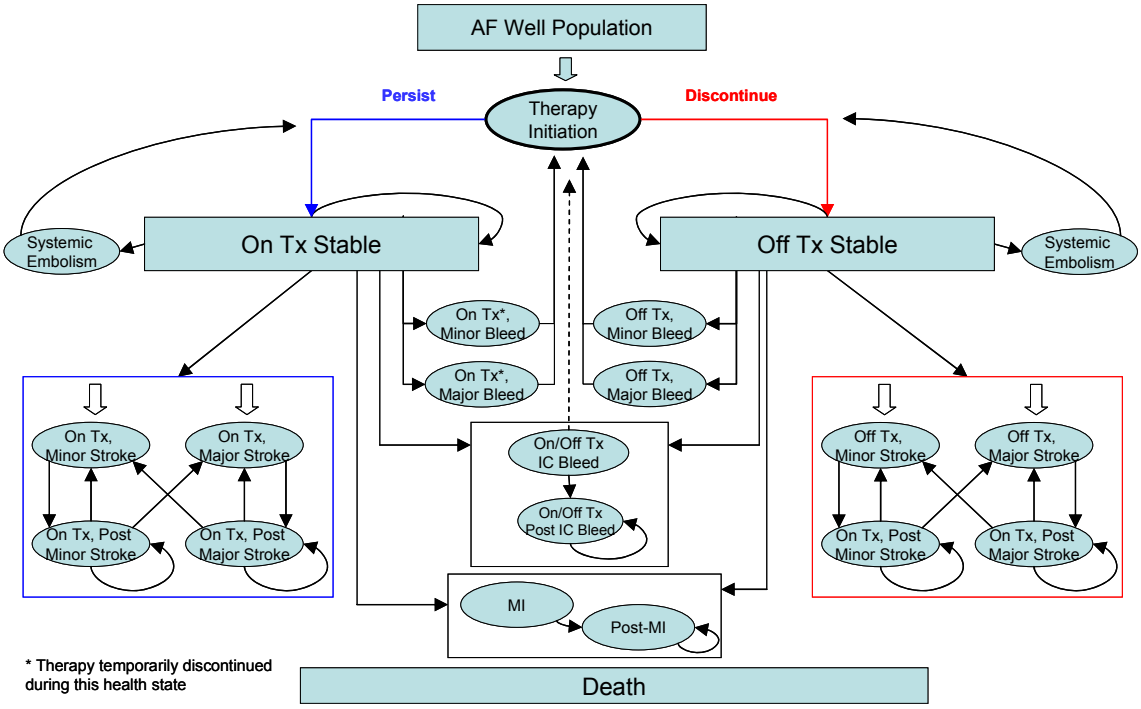
Please provide a diagrammatical representation of the model you have chosen.

The economic model was developed to assess the long-term costs and health outcomes of rivaroxaban for the secondary prevention of stroke in AF vs. the standard of care (warfarin). The model developed is a Markov state-transition cohort model with 22 health states:

1. Therapy initiation
2. On therapy stable
3. Minor stroke (on therapy)
4. Major stroke (on therapy)
5. Post minor stroke (on therapy)
6. Post major stroke (on therapy)
7. Minor bleed (on therapy)
8. Major bleed (on therapy)
9. Intracranial bleed (on therapy)
10. Post intracranial bleed (on therapy)
11. Systemic embolism (on therapy)
12. Stable atrial fibrillation (off therapy)
13. Minor stroke (off therapy)
14. Major stroke (off therapy)
15. Minor bleed (off therapy)
16. Major bleed (off therapy)
17. Intracranial bleed (off therapy)
18. Post intracranial bleed (off therapy)
19. Systemic embolism (off therapy)
20. MI (on or off therapy)
21. Post MI (on or off therapy)
22. Death

Patients enter the model with stable uncomplicated atrial fibrillation and receive prophylactic medication (Figure 17).

Figure 17. Model diagram



Tx = Therapy; IC = Intracranial; MI = Myocardial Infarction

In the model schematic, strokes, IC bleeds, MI and deat are considered permanent while other events are considered transient. Following an IC bleed, patients with CHADS2 ≥ 2 will follow the dotted line and re-initiate therapy, while patients with CHADS2 ≤ 1 will stay off anti-coagulation in the post IC bleed state.

Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

To perform an economic evaluation of the long-term cost-utility of rivaroxaban for stroke prevention in patients with atrial fibrillation, a health state transition model was designed. The model simulates the long-term clinical outcomes for a cohort of patients with atrial fibrillation receiving competing interventions for secondary prevention of stroke. The use of Markov models is common in the economic modelling of chronic diseases (such as AF) which have recurring events over a prolonged period of time, with these events being characterised by recurrent costs and health outcomes. The findings of the literature review presented in section 0 are consistent with this.

Clinical outcomes captured in the model included cardiovascular events, treatment-related adverse events, patient-specific management practices and mortality (event related and background all-cause mortality). Direct medical costs and health-related

quality of life values for specific health states were also captured in the model to facilitate cost-utility estimates. Future costs and clinical outcomes were discounted to present values.

The following sections outline in further detail the rationale for each of the key health states in the model.

Stroke health states

Ischaemic stroke and intracranial bleed were captured in separate health states.

Ischaemic stroke shows wide variability in terms of acute severity and of clinical consequence, with outcomes ranging from minor aphasia to long-term institutional care. The model separately considered minor and major strokes in order to more accurately describe clinical and economic sequelae.

Strokes were classified into major (modified Rankin score 3-5) or minor strokes (modified Rankin score 1-2) (Table 33).

To calculate minor or major stroke events, the model calculated what proportion of all reported ischaemic strokes in ROCKET AF were minor versus major. This was done by taking the number of events in each category over the total number of events reported overall. To keep it treatment-independent events from both warfarin and rivaroxaban arms were summed.

Table 33. Stroke severity used in the model and the equivalent severities the modified Rankin scale

Model state	Modified Rankin scale score	Modified Rankin scale definition
No stroke	0	No symptom
Mild stroke	1	No significant disability despite symptoms, able to carry out all usual activities and duties;
Mild stroke	2	Slight disability, unable to carry out all previous activities, but able to look after own affairs
Major stroke	3	Moderate disability, requires some help but able to walk without assistance
Major stroke	4	Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance
Major stroke	5	Severe disability, bedridden, incontinent and requiring constant nursing care and attention
Death due to stroke	6	Dead

Bleeding health states

Bleeding events were the primary safety endpoint of the ROCKET AF study and may have a major impact on patient mortality, morbidity or cost.

After review of available literature, bleeding events in the model are reported as minor extracranial bleed, major extracranial bleed or intracranial bleed, where intracranial bleeds include haemorrhagic strokes. Intracranial bleeds are associated with major risks of residual disability stemming from their impact on the central nervous system, therefore a post-intracranial bleed state was included in the model.

No health state representing post-extracranial bleed was included in the model, based on clinician advice that the need for specific follow up care is rare.

Depending on the type of bleeding event and level of stroke risk, patients may discontinue treatment following a bleed event, switch treatment following a bleed event, or continue with their existing treatment. Management strategies based on clinical opinion are listed in Table 34. Note that during acute bleed states, patients are assumed to temporarily discontinue prophylactic treatment.

It was conservatively assumed that those patients initially on no treatment are not contraindicated to aspirin, and would receive this following an ischaemic stroke.

Table 34. Second-line treatment strategies after patient experiences an event

From		Stroke	Extracranial Bleed	Intracranial Bleed ($CHADS_2 < 3$)*	Intracranial Bleed ($CHADS_2 \geq 3$)*
Rivaroxaban	**To**	No Change	No Change	Aspirin	No Change
Warfarin	**To**	No Change	No Change	Aspirin	No Change
Aspirin	**To**	Aspirin	No Change	No Treatment	No Change
No Treatment	**To**	Aspirin	No Change	No Change	No Change

*The trial based analysis does not distinguish patients by risk score. Therefore this feature only applies to network meta-analysis comparisons

Systemic Embolism health states

A systemic embolism (SE) is a blood clot that travels through the circulation system and becomes lodged in an artery, restricting blood flow. SE was included in the primary endpoint of the ROCKET trial and is an important potential clinical outcome for patients with non-valvular AF.

Myocardial Infarction

Myocardial infarction (MI) was included as a state in the model as different interventions for stroke prevention in atrial fibrillation may also have an impact on the risk of MI. For example, aspirin has shown clinical benefits versus placebo in the primary prevention of MI(84). As MI may have lasting sequelae the model also included a post-MI health state.

Please define what the health states in the model are meant to capture.

Further to the rationale presented for the key health states above, the section below summarises the purpose of each of the 22 health states in the model. All states other than anticoagulation initiation, stable atrial fibrillation (on and off therapy) and death were associated with event related costs and impaired health related quality of life

reflective of their severity. Furthermore, on therapy states incur the costs and consequences associated with patients' original treatment allocation. Off therapy states incur the costs and consequences of the pre-defined second line treatment option.

1. Anticoagulant initiation. This health state was designed to assign patients to the interventions analyzed in the cost-effectiveness study at baseline, or to re-assign patients to an intervention following a bleeding, stroke or embolism event.

2. Stable atrial fibrillation (on therapy). This health state represented a patient with stable (without haemodynamic instability), non-valvular atrial fibrillation on assigned therapy, who did not experience any clinical events in the current cycle of the model.

3. Minor stroke (on therapy). This health state represented patients on assigned therapy who experienced a stroke with a Rankin score ≤ 2, representing a stroke without major long-term effects, or a stroke resulting in minimum residual sequelae, where patients were assumed capable of returning to independent living.

4. Major stroke (on therapy). This health state represented patients on assigned therapy who experienced a stroke with a Rankin score 3-5. Such strokes were associated with excess mortality and considered to require inpatient rehabilitation after stabilisation and with residual sequelae that prevented patients from returning to independent living. Fatal strokes (Rankin score of 6) were also included in this health state.

5. Post minor stroke (on therapy). This health state represented patients on assigned therapy who had experienced a minor stroke prior to the current model cycle. These patients are considered not to require long-term medical care, but are exposed to a higher risk of stroke compared to patients who had never experienced a minor stroke.

6. Post major stroke (on therapy). This health state represented patients on assigned therapy who had experienced a major stroke prior to the current model cycle. These patients required long-term medical care and were at higher risk of stroke and mortality compared to patients who had never experienced a major stroke.

7. Minor bleed (on therapy). This health state represented patients on assigned therapy who were experiencing a minor bleeding event. Therapy was temporarily withheld during the cycle in which the bleeding event took place. An example of this would be spontaneous bleeding from gums which requires acute medical intervention.

8. Major bleed (on therapy). This health state represented patients on assigned therapy who were experiencing a major bleeding event (e.g. gastrointestinal bleeds). Therapy was temporarily withheld during the cycle in which the bleeding event took place.

9. Intracranial bleed (on therapy). This health state represented patients on assigned therapy who were experiencing an intracranial bleeding event. Therapy was temporarily withheld during the cycle in which the intracranial bleeding event took place. Intracranial bleeding events were associated with excess mortality.

10. Post intracranial bleed (on therapy). This health state represented patients on assigned therapy who had previously experienced an intracranial bleeding event. Intracranial bleeds are associated with major risks of residual disability and mortality stemming from their impact on the central nervous system.

11. Systemic embolism (on therapy). This health state represented patients on assigned therapy who were experiencing a systemic embolism, a blood clot that travels through the circulation system and becomes lodged in an artery, restricting blood flow.

12. Stable atrial fibrillation (off therapy). This health state represented a patient with stable (without haemodynamic instability), non-valvular atrial fibrillation not receiving therapy, who did not experience any clinical events in the current cycle of the model.

13. Minor stroke (off therapy). This health state represented patients not receiving therapy who experienced a stroke with a Rankin score ≤ 2, representing a stroke without major long-term effects, or a stroke resulting in minimum residual sequelae, where patients were assumed capable of returning to independent living.

14. Major stroke (off therapy). This health state represented patients not receiving therapy who experienced a stroke with a Rankin score 3-5. Such strokes were associated with excess mortality and considered to require inpatient rehabilitation after stabilisation and with residual sequelae that prevented patients from returning to independent living. Fatal strokes (Rankin score of 6) were also included in this health state.

15. Minor bleed (off therapy). This health state represented patients not receiving therapy who were experiencing a minor bleeding event. An example of this would be spontaneous bleeding from gums which requires acute medical intervention.

16. Major bleed (off therapy). This health state represented patients not receiving therapy who were experiencing a major bleeding event (e.g. gastrointestinal bleeds).

17. Intracranial bleed (off therapy). This health state represented patients not receiving therapy who were experiencing an intracranial bleeding event. Intracranial bleeding events were associated with excess mortality.

18. Post intracranial bleed (off therapy). This health state represented patients who were not on their originally assigned therapy and who had previously experienced an intracranial bleeding event. Intracranial bleeds are associated with major risks of residual disability and mortality stemming from their impact on the central nervous system.

19. Systemic embolism (off therapy). This health state represented patients not receiving their originally assigned therapy who were experiencing a systemic embolism.

20. MI (on or off therapy). MI was included as a complication in the modelling analysis, as interventions for stroke prevention in atrial fibrillation may have a differential impact on the risk of MI. Patients were at risk of MI both on or off treatment and with or without a history of stroke and bleeding events.

21. Post MI (on or off therapy). As a history of MI results in increased costs and elevated mortality, a health state specific for patients with a history of MI was defined in the model.

22. Death. Terminal state. Patients could die either due to events captured in the model such as major stroke, MI or intracranial bleed, and could also die due to all-cause mortality.

How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Anticoagulation in the management of atrial fibrillation is associated with both a reduction in ischaemic events as well as an increased risk of bleeding. By including health states relevant to each of these potential events the model was able to capture both the risks and benefits of treatment.

Disease progression was not modeled as atrial fibrillation is, for the majority of patients, a chronic condition that is not categorized by severity. For bleeding events and also MI the underlying risk of events is independent of time. However, age is an important risk factor for ischaemic stroke and systemic embolism. Since the cohort ages over the course of the Markov process the underlying risk of events was adjusted in line with the cohort age (see Section 6.3.2 for details).

Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 35. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime analysis	To capture the lifetime clinical and cost outcomes of patients with AF who are 73 years of age at entry into the model based on the ROCKET AF trial (Section 5)	NICE(85)
Cycle length	3 months	To enable the capture of short-term events (e.g. treatment related adverse events) and their acute impact on costs and clinical outcomes	
Half-cycle correction	Not applied	Unnecessary when using a short cycle length	
Were health effects measured in QALYs; if not, what was used?	Yes		NICE(85)
Discount of 3.5% for utilities and costs	Yes		NICE(85)
Perspective (NHS/PSS)	NHS Perspective		
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The model includes the treatments outlined below for the prevention of stroke in atrial fibrillation as well as an option to undertake analyses against no treatment. Although the licensed indications for warfarin and aspirin do not exactly match that expected for rivaroxaban these interventions have been widely investigated in clinical trials for atrial fibrillation. Furthermore, they are commonly used in clinical practice for both primary and secondary stroke prevention (4;67).

Rivaroxaban 20mg once daily (currently awaiting marketing authorisation) – dose based on ROCKET AF trial.

Adjusted dose warfarin at 4.5mg once daily, target INR 2.5, range 2.0 to 3.0 inclusive (licensed for prophylaxis of systemic embolism in patients with atrial fibrillation) - dose based on NICE CG36, Atrial Fibrillation: the management of atrial fibrillation(17).

Aspirin 150mg once daily (licensed for the secondary prevention of thrombotic cerebrovascular events) – dose based on recommended guidelines of 75mg-300mg; median value based on two 75mg tablets were assumed.

Dabigatran 110-150mg twice daily (see below for details of marketing authorisation) – dose based on RE-LY trial(32)

No treatment (placebo)

Dabigatran is now licensed for the prevention of stroke in atrial fibrillation(86):

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

Previous stroke, transient ischaemic attack, or systemic embolism (SEE)

Left ventricular ejection fraction < 40 %

Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2

Age ≥ 75 years

Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

The recommended daily dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

Patients aged 80 years or above should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily due to the increased risk of bleeding in this population.

Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be

presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).

The robustness and plausibility of the endpoint on which the rule is based.

Whether the 'response' criteria defined in the rule can be reasonably achieved.

The appropriateness and robustness of the time at which response is measured.

Whether the rule can be incorporated into routine clinical practice.

Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.

Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No treatment continuation rule has been assumed.

Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

Please demonstrate how the clinical data were implemented into the model.

Base case analysis

Key event rates were annual rates of (stroke, systemic embolism, myocardial infarction, bleeding events) drawn from the warfarin arm of ROCKET AF. Relative risks of events from ROCKET AF for rivaroxaban were applied to the event rates observed with warfarin.

In the base case the model included differential treatment effects only for outcomes where a statistically significant difference was observed in the trial. The safety-on-treatment population was the population in which superiority analysis was conducted

as part of the pre-specified sequential hierarchical hypothesis testing between rivaroxaban and warfarin and was therefore used in the base case. For outcomes where there was no significant difference the relative risk for rivaroxaban vs. warfarin was set to 1. This was tested in sensitivity analysis with a scenario conducted that included all treatment effects observed in ROCKET AF, irrespective of statistical significance.

A further scenario analysis was conducted using effectiveness and safety data from the ITT analysis to site notification.

Additional analyses based on the ROCKET AF data

Patients poorly controlled on warfarin

This group describes patients with atrial fibrillation and $CHADS_2$ score ≥ 2 who are not well controlled on warfarin having > 50% of time outside of the target INR range (2.0-3.0) and have a requirement for frequent INR monitoring.

Conservatively, the analysis was undertaken using the same event rate data as the base case analysis and did not adjust for efficacy and safety.

People who have not been previously treated with warfarin

Due to intra-patient variability in response, the initiation of warfarin in those not previously treated with warfarin, requires more intensive monitoring of INR. Consistent with the Scope for this Single Technology Appraisal, data for this subgroup has been included in the model.

Efficacy and safety data were sourced from the relevant subgroup of patients (i.e. warfarin naïve) within ROCKET AF using the safety on treatment data with non-significant differences removed. There was no significant interaction for treatment effect in the warfarin experienced and naïve patients in ROCKET AF.

Additional analyses based on the network meta analysis

Warfarin unsuitable - Patients with atrial fibrillation and CHADS2 score ≥ 1 who are not receiving OAC therapy

Despite having a CHADS2 score of ≥1, some patients do not receive oral anticoagulation. These patients are prescribed either aspirin or no therapy.

To estimate risk in these patients a network meta-analysis (NMA) was conducted (see section 5.7) using no treatment (placebo) as the reference comparator.

Baseline event rates for analyses undertaken using the NMA are taken from relevant studies identified during the literature review undertaken for the NMA. The distribution of patients across $CHADS_2$ risk scores was from a UK observational study(13). Relative risks from the NMA were applied to this baseline to estimate event rates with aspirin.

Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Ischaemic Stroke

The baseline risk of ischaemic stroke from the ROCKET AF trial data used in the base case is an annual rate for ischaemic stroke of 1.42% in the warfarin arm. This rate was converted into a quarterly rate by the following formula (Briggs et al. 2006)(87):

Quarterly rate = 1- (1-annual rate)^(1/4)

The quarterly risk of ischaemic stroke for patients receiving warfarin was therefore 0.36%.

In the systematic review carried out for the NMA, a number of studies were identified reporting the event rate of ischaemic stroke in patients with placebo or no treatment. The Atrial Fibrillation Investigators(88) study provided the best source for this as it is a pooled analysis of 5 studies. The placebo arm represented a total of 1236 patients followed for 1802 patient years. During that time 81 ischaemic strokes were recorded, resulting in an annual rate of 4.5%, or a quarterly rate of 1.14% as applied in the model.

Ischaemic stroke events were divided into minor or major events to ensure a more accurate view of the cost consequences of stroke events, given the wide variation in the severity of stroke. The probability that a stroke would be minor or major was based on ROCKET AF. The definition of minor and major stroke used in the model

was based on the modified Rankin score. A minor stroke was defined as a stroke resulting in minimum residual sequelae, able to return to independent living; these were Rankin scores of 0-2. A major stroke was a severe stroke requiring inpatient rehabilitation after stabilisation and with residual sequelae that prevented patients from returning to independent living. The distribution of minor/major was obtained by pooling all ischaemic stroke events across treatment arms by modified Rankin score. In this way, we distinguished between patients requiring long-term follow-up care costs and those who would have acute treatment costs only. Based on ROCKET AF, the proportion of all ischaemic strokes that were major are shown in Table 36.

Table 36. Proportion of all ischaemic strokes considered major

Source of data	Point estimate	CI
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CI = 95% confidence interval; ITT = intention to treat

The baseline risk of ischaemic stroke was adjusted by patient age in the model. The adjustment was based on material from the risk score calculator derived from the Framingham Heart Study(89). The relative risk of stroke has been calibrated with a patient age of 70-74 as the reference group (Table 37).

Table 37. Relative risk of stroke by age

	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+
1 Risk factor	0.571	0.714	0.857	1.000	1.143	1.286	1.429	1.786
2 Risk factors	0.667	0.750	0.833	1.000	1.167	1.250	1.500	1.750
≥3 Risk factors	0.667	0.762	0.857	1.000	1.143	1.286	1.476	1.714

Relative treatment effects describing the efficacy of rivaroxaban versus warfarin in patients with $CHADS_2$ score ≥ 2 were available from the ROCKET AF trial. Relative treatment effects for the other comparators and rivaroxaban for all $CHADS_2$ scores ≥ 1 were derived from the NMA. The NMA reported the odds ratios for each treatment (including warfarin) versus placebo. Reported odds ratios were converted into relative risks for use in the modelling analysis using the following formula:

Relative risk = Odds ratio/((1-baseline probability)+(baseline probability*Odds ratio))

The relative risk values used for ischaemic stroke for each treatment in the modelling analysis are presented in Table 38. For the base case analysis based on trial data only significant differences between rivaroxaban and warfarin were included. Where non-significant differences were observed a RR of 1 was assumed for rivaroxaban. PSA was undertaken on point estimates and associated 95% confidence intervals.

Table 38. Relative risk rates for ischaemic stroke

Intervention	Source of data	Risk relative to	CI	RR	RR used in model
Rivaroxaban (base case)	ROCKET AF trial (SOT)	Warfarin	0.75 – 1.17	0.94	1
Rivaroxaban	ROCKET AF trial (ITT)	Warfarin	[redacted]	[redacted]	1
Rivaroxaban	NMA	Placebo	[redacted]	[redacted]	[redacted]
Aspirin	NMA	Placebo	[redacted]	[redacted]	[redacted]
Warfarin	NMA	Placebo	[redacted]	[redacted]	[redacted]

CI = 95% confidence interval; ITT = intention to treat; NMA = Network meta-analysis; RR = relative risk; SOT = Safety on treatment

Systemic embolism

The baseline risk of SE was obtained from the warfarin arm of the ROCKET AF trial. The annual rate for systemic embolism was 0.19%, which was converted to a quarterly rate of 0.05% for use in the modelling analysis. When deriving the risk of SE for the NMA, the baseline risk was obtained from a pooled analysis of placebo reported by the Atrial Fibrillation Investigators(88), identified during the systematic literature review for the NMA. The AFI study gave an annual rate of SE of 0.5%. A quarterly rate of 0.125% was therefore used in the model to represent the baseline risk of SE when the placebo (no treatment) arm was applied in the analyses.

Relative risks of SE for each treatment, either relative to warfarin when the analysis was based on the ROCKET AF trial or relative to placebo when based on the NMA, were based on efficacy data from the ROCKET AF trial or the NMA (Table 39). The baseline risk of SE was also adjusted by age based on the risk adjustments from the Framingham Heart Study that were applied in the stroke section of the model (Table 37)(89). For the base case analysis based on trial data only significant differences between rivaroxaban and warfarin were included. Where non-significant differences were observed a RR of 1 was assumed for rivaroxaban. PSA was undertaken on point estimates and associated 95% confidence intervals.

Table 39. Relative risk rates for systemic embolism

Intervention	Source of data	Risk relative to	CI	RR	RR used in model
Rivaroxaban	ROCKET AF trial (SOT)	Warfarin	0.09 – 0.61	0.23	0.23
Rivaroxaban	ROCKET AF trial (ITT)	Warfarin	[redacted]	[redacted]	[redacted]
Rivaroxaban	NMA	Placebo	[redacted]	[redacted]	[redacted]
Aspirin	NMA	Placebo	[redacted]	[redacted]	[redacted]
Warfarin	NMA	Placebo	[redacted]	[redacted]	[redacted]

CI = 95% confidence interval; ITT = intention to treat; NMA = Network meta-analysis; RR = relative risk; SOT = Safety on treatment

Bleeding events

The baseline risks of bleeding events were obtained from the warfarin arm of the ROCKET AF trial. Annual rates for minor extracranial, major extracranial and intracranial bleeds were [redacted] respectively. These were converted to quarterly risks of [redacted] respectively.

The baseline rate of bleeding events for an untreated population was derived from a secondary prevention trial of 1,007 atrial fibrillation patients that compared aspirin to placebo, reporting that placebo-controlled patients were at risk of non-fatal bleeding events(48). Bleeding for an untreated population is difficult to locate; from the studies identified during the literature review for the NMA, only 5 studies reported event rates for all three types of bleed endpoints used in the model. Out of these 5, the EAFT study was the only European study and also the only study to report non-zero event rates in all three bleed endpoints. During 869.4 patient years of follow-up in the EAFT study, 21 minor extracranial bleed events were reported (annual rate 2.42%), 3 major extracranial bleeds were reported (annual rate 0.46%), and one intracranial bleed was reported (annual rate 0.12%). The quarterly rates of minor extracranial, major extracranial and any intracranial bleeds were 0.61%, 0.12% and 0.03%, respectively.

Relative risks for bleeding events for rivaroxaban versus warfarin treatment were obtained from the ROCKET AF trial. Relative risks for other therapies and rivaroxaban in patients with a CHADS2 score ≥ 1 were derived from the NMA. Note that the intracranial bleeds includes haemorrhagic stroke. The relative risks of bleeding events are shown in (Table 40, Table 41, Table 42). For the base case analysis based on trial data, only significant differences between rivaroxaban and warfarin were included. Where non-significant differences were observed a RR of 1 was assumed for rivaroxaban. PSA was undertaken on point estimates and associated 95% confidence intervals.

Table 40. Relative risks for intracranial haemorrhage

Intervention	Source of data	Risk relative to	CI	RR	RR used in model
Rivaroxaban	ROCKET AF trial	Warfarin	0.47 – 0.93	0.67	0.67
Rivaroxaban	NMA	Placebo	[redacted]	[redacted]	[redacted]
Aspirin	NMA	Placebo	[redacted]	[redacted]	[redacted]
Warfarin	NMA	Placebo	[redacted]	[redacted]	[redacted]

CI = 95% confidence interval; NMA = Network meta-analysis; RR = relative risk

Table 41. Relative risks for major extracranial haemorrhage

Intervention	Source of data	Risk relative to	CI	RR	RR used in model
Rivaroxaban	ROCKET AF trial	Warfarin	[redacted]	[redacted]	1
Rivaroxaban	NMA	Placebo	[redacted]	[redacted]	[redacted]
Aspirin	NMA	Placebo	[redacted]	[redacted]	[redacted]
Warfarin	NMA	Placebo	[redacted]	[redacted]	[redacted]

CI = 95% confidence interval; NMA = Network meta-analysis; RR = relative risk

Table 42. Relative risks for minor extracranial haemorrhage

Intervention	Source of data	Risk relative to	CI	RR	RR used in model
Rivaroxaban	ROCKET AF trial	Warfarin	[redacted]	[redacted]	1
Rivaroxaban	NMA	Placebo	[redacted]	[redacted]	[redacted]
Aspirin	NMA	Placebo	[redacted]	[redacted]	[redacted]
Warfarin	NMA	Placebo	[redacted]	[redacted]	[redacted]

CI = 95% confidence interval; NMA = Network meta-analysis; RR = relative risk

Myocardial infarction

The baseline risk of MI for the warfarin arm was derived from analysis of the ROCKET AF trial. The annual rate of MI was 1.12%, and a quarterly rate of 0.28% was applied in the model.

When treatments from the NMA were applied, the baseline risk of MI was derived from the SAFT study(90), which reported 18 myocardial infarctions during 918.5

patient years of follow up. An annual rate of 1.96% was calculated, and a quarterly rate of 0.49% was applied in the model. The SAFT study was the largest European study identified during the systematic review for the NMA.

The relative risk of myocardial infarction associated with rivaroxaban when compared with warfarin was obtained from the ROCKET AF trial. For other scenarios the relative risks were derived from the NMA. For the base case analysis based on trial data only significant differences between rivaroxaban and warfarin were included. Where non-significant differences were observed a RR of 1 was assumed for rivaroxaban. PSA was undertaken on point estimates and associated 95% confidence intervals.

Table 43. Relative risk for myocardial infarction

Intervention	Source of data	Risk relative to	CI	RR	RR used in model
Rivaroxaban	ROCKET AF trial	Warfarin	0.63 – 1.06	0.81	1
Rivaroxaban	NMA	Placebo	[redacted]	[redacted]	[redacted]
Aspirin	NMA	Placebo	[redacted]	[redacted]	[redacted]
Warfarin	NMA	Placebo	[redacted]	[redacted]	[redacted]

CI = 95% confidence interval; NMA = Network meta-analysis; RR = relative risk

Discontinuation rates

Treatment discontinuation rates for rivaroxaban and warfarin were derived from the ROCKET AF trial. Discontinuation probabilities were calculated based on the proportion of patients persisting on therapy at 3 months (x) and 12 months (y) in the ROCKET AF trial based on the formulae:

Discontinuation at 3months = 1- x

Subsequent discontinuation = 1- (1- (y-x)^1/3)

Based on data from the ROCKET AF trial, the quarterly probability of treatment discontinuation was [redacted] in the initial cycle for rivaroxaban, [redacted] in the initial cycle for warfarin, [redacted] in the subsequent cycles for rivaroxaban and [redacted] in the subsequent cycles for warfarin. Aspirin discontinuation was assumed equivalent to rivaroxaban discontinuation as they are both once-daily oral pills with no monitoring requirement. This assumption was tested in one-way sensitivity analysis. ROCKET AF showed that there was no significant difference in discontinuation between

interventions; the model preserves that assumption among other interventions since there is no evidence of differential discontinuation at this stage.

Mortality rates

Background mortality and mortality specific to the clinical events captured in the model were included. Patients could transition to the death health state from all other health states. All-cause mortality was based on UK life tables(91); this describes mortality possible from any health state.

The 30-day case-fatality of major stroke applied in the model was 12.6%, and was independent of treatment or history of prior stroke. This was derived by taking the number of fatal events over the number of total events. In the post stroke state independent of therapy the rates were derived from an Italian study(92). Based on 8 years of follow-up, the annual mortality rate from year 4 was selected as the median value and represents a conservative estimate. This value of 10.1% was converted to a quarterly rate of 2.6% for application in the model in cycles following the acute event. The paper by Marini and colleagues was one of only two papers returned via the systematic literature review on mortality rates associated with model events that also analysed AF patients as a specific subgroup; the other paper only reported stroke case-fatality and not long-term mortality; the Marini study was therefore the only source for long-term mortality.

Case-fatality following major extracranial bleeding events was [redacted] based on the number of events that were fatal in both treatment arms of the ROCKET AF trial. This case-fatality rate was assumed to be independent of treatment. No long-term mortality from major extracranial bleeding events was modelled (i.e. patients could only die from major extracranial bleeding events in the cycle of the event).

Case-fatality for intracranial bleeds was [redacted] based on the pooled rate from both treatment arms in the ROCKET AF trial. As no literature could be identified describing long-term mortality in patients who experienced intracranial bleeds that was attributable to the bleed, long-term mortality was assumed to be equal to that for major stroke(92). Mortality from intracranial bleed was therefore independent of treatment.

Case-fatality from MI was [redacted] and was based on the ROCKET AF trial (for both treatment arms). Following MI, the long-term mortality rate was 10.3% per annum(93), and a quarterly rate of 2.68% was applied in the model independently of

treatment. The paper by Hoit and colleagues was used because it reported both case-fatality and long-term mortality; other publications retrieved via a systematic literature review reported either case-fatality or long-term mortality, but not both.

Case-fatality rates were not analysed by age in the ROCKET AF analysis. However, given the overall number of events, stratification by age is likely to have significantly decreased the overall sample size of events available for analysis in each age group.

Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is no evidence that transition probabilities for events captured in the model should vary as a function of time spent with atrial fibrillation. Stroke risk equations that include atrial fibrillation as a regression coefficient have not included a term for the duration of atrial fibrillation(94). The assumption that risk of events was not dependent on duration of atrial fibrillation was in line with the assumption that atrial fibrillation was not graded in the model, i.e. atrial fibrillation is not classified by paroxysmal, persistent or permanent, and did not worsen over the time horizon of the simulation. The estimation of long-term events (stroke, MI, systemic embolism, bleeding events) was based on event rates observed in clinical trials and were applied beyond the follow-up period of the trials from which they were derived. For ischaemic stroke and systemic embolism, risk varied by age as described earlier. Other-cause mortality (i.e. causes of death not due to stroke, MI or cerebral haemorrhage) varied as a function of patient age, based on life table data for the UK.

Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No intermediate outcomes were linked to final outcomes. The endpoints of the clinical trials used to inform the effectiveness parameters for each intervention in the model were hard endpoints and were not surrogate markers of disease progression or control.

If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

the criteria for selecting the experts

the number of experts approached

the number of experts who participated

declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought

the background information provided and its consistency with the totality of the evidence provided in the submission

the method used to collect the opinions

the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)

the questions asked

whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical parameters were from the trial or a systematic literature review and therefore expert opinion was not sought for these values.

Summary of selected values

Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-

references to other parts of the submission. Please present in a table, as suggested below.

Table 44. Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Stroke related variables (except mortality)			
Probability of stroke at baseline for patients on warfarin	0.36%	[redacted]	Section 6.3.2
Annual rate of stroke on warfarin (NMA analysis)	[redacted]	[redacted]	Section 5.7
Likelihood that stroke is minor stroke	47.55%	Linked to likelihood that stroke is major stroke	Section 6.3.2
Likelihood that stroke is major stroke	52.45%	47.60% - 57.27%	Section 6.3.2
Relative risk of stroke compared to reference age group 70-74			
Patients aged 55-59 with one risk factor	0.571	N/A	Section 6.3.2
Patients aged 55-59 with two risk factors	0.667	N/A	Section 6.3.2
Patients aged 55-59 with three or more risk factors	0.667	N/A	Section 6.3.2
Patients aged 60-64 with one risk factor	0.714	N/A	Section 6.3.2
Patients aged 60-64 with two risk factors	0.750	N/A	Section 6.3.2
Patients aged 60-64 with three or more risk factors	0.762	N/A	Section 6.3.2
Patients aged 65-69 with one or more risk factors	0.857	N/A	Section 6.3.2
Patients aged 65-69with two risk factors	0.833	N/A	Section 6.3.2
Patients aged 65-69with three or more risk factors	0.857	N/A	Section 6.3.2
Patients aged 75-79 with one risk factor	1.143	N/A	Section 6.3.2
Patients aged 75-79 with two risk factors	1.167	N/A	Section 6.3.2
Patients aged 75-79 with three or more risk factors	1.143	N/A	Section 6.3.2
Patients aged 80-84 with one risk factor	1.286	N/A	Section 6.3.2
Patients aged 80-84 with two risk factors	1.250	N/A	Section 6.3.2

Variable	Value	CI (distribution)	Reference to section in submission
Patients aged 80-84 with three or more risk factors	1.286	N/A	Section 6.3.2
Patients aged 85-89 with one risk factor	1.429	N/A	Section 6.3.2
Patients aged 85-89 with two risk factors	1.500	N/A	Section 6.3.2
Patients aged 85-89 with three or more risk factors	1.476	N/A	Section 6.3.2
Patients aged 90 and above with one risk factor	1.786	N/A	Section 6.3.2
Patients aged 90 and above with two risk factors	1.750	N/A	Section 6.3.2
Patients aged 90 and above with three or more risk factors	1.714	N/A	Section 6.3.2
Treatment related relative risks for ischaemic stroke			
Rivaroxaban versus warfarin	1	0.75 - 1.17	Section 5.5.3, Table 18
Rivaroxaban versus placebo	[redacted]	[redacted]	NMA – Section 5.7
Warfarin versus placebo	[redacted]	[redacted]	NMA – Section 5.7
Aspirin versus placebo	[redacted]	[redacted]	NMA – Section 5.7
Systemic embolism related variables			
Probability of systemic embolism at baseline for patients on warfarin	0.05%	[redacted]	Section 5.5.3 & ROCKET Health Economic analysis
Annual rate of systemic embolism on warfarin (NMA analysis)	[redacted]	[redacted]	Section 5.7
Treatment related relative risks for systemic embolism			
Rivaroxaban versus warfarin	0.23	0.09 - 0.61	Section 5.5.3, Table 18
Rivaroxaban versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Warfarin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Aspirin versus placebo	[redacted]	[redacted]	NMA -Section 5.7
Bleeding event related variables (except mortality)			
Minor extracranial bleed			
Probability of minor extracranial bleeding event at baseline for patients on warfarin	[redacted]	[redacted]	ROCKET Health Economic analysis
Annual rate of minor extracranial bleeding event on warfarin (NMA analysis)	[redacted]	[redacted]	NMA - Section 5.7
Treatment related relative risks for minor extracranial bleed			

Variable	Value	CI (distribution)	Reference to section in submission
Rivaroxaban versus warfarin	1.00	0.96 - 1.13	Section 5.9.1 Table 26
Rivaroxaban versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Warfarin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Aspirin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Major extracranial bleed			
Probability of major extracranial bleeding event at baseline for patients on warfarin	[redacted]	[redacted]	ROCKET Health Economic analysis
Annual rate of major extracranial bleeding event on warfarin (NMA analysis)	[redacted]	[redacted]	Section 5.7
Treatment related relative risks for major extracranial bleed			
Rivaroxaban versus warfarin	1.00	0.98 - 1.33	Section 5.9.1 Table 26
Rivaroxaban versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Warfarin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Aspirin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Intracranial bleed			
Probability of intracranial bleeding event at baseline for patients on warfarin	[redacted]	[redacted]	ROCKET Health Economic analysis
Annual rate of intracranial bleeding event on warfarin (NMA analysis)	[redacted]	[redacted]	Section 5.7
Treatment related relative risks for intracranial bleed			
Rivaroxaban versus warfarin	0.67	0.47 – 0.93	Section 5.9.1
Rivaroxaban versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Warfarin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Aspirin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Myocardial infarction related variables (except mortality)			
Probability of myocardial infarction event at baseline for patients on warfarin	[redacted]	[redacted]	ROCKET Health Economic analysis
Annual rate of myocardial infarction event on warfarin (NMA analysis)	[redacted]	[redacted]	NMA - Section 5.7
Treatment related relative risks for myocardial infarction			
Rivaroxaban versus warfarin	1.00	0.63 – 1.06	Section 5.5.3, Table 18
Rivaroxaban versus placebo	[redacted]	[redacted]	NMA - Section 5.7

Variable	Value	CI (distribution)	Reference to section in submission
Warfarin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Aspirin versus placebo	[redacted]	[redacted]	NMA - Section 5.7
Treatment discontinuation related variables			
Rivaroxaban discontinuation in first three-month cycle	[redacted]	[redacted]	Section 6.3.2
Rivaroxaban discontinuation in subsequent cycles	[redacted]	[redacted]	Section 6.3.2
Warfarin discontinuation in first three-month cycle	[redacted]	[redacted]	Section 6.3.2
Warfarin discontinuation in subsequent cycles	[redacted]	[redacted]	Section 6.3.2
Aspirin discontinuation in first three-month cycle	[redacted]	[redacted]	Section 6.3.2
Aspirin discontinuation in subsequent cycles	[redacted]	[redacted]	Section 6.3.2
Mortality related variables			
Stroke case-fatality	12.6%	9.4% - 15.7%	Section 6.3.2
Annual mortality of stroke long-term (per quarter)	2.63%	0.91% - 13.50%	Section 6.3.2
Major extracranial bleed event case-fatality	1.55%	1.16% - 1.94%	Section 6.3.2
Intracranial bleed case-fatality	38.8%	29.1% - 48.6%	Section 6.3.2
Myocardial infarction case-fatality	9.69%	7.27% - 12.11%	Section 6.3.2
Annual mortality of myocardial infarction long-term (per quarter)	2.68%	0.00% - 6.75%	Section 6.3.2
CI, confidence interval			

Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

A state transition model was used to extrapolate from events occurring during the trial period to costs and outcomes that occur beyond the trial period. SPAF is a chronic condition.

Event rates for both rivaroxaban and warfarin observed during the ROCKET AF trial were assumed to continue but to be modified as patients age. Risk of ischaemic stroke and systemic embolism were extrapolated using the Framingham risk equation. Other risks were constant.

Relative risks due to therapy were constant.

Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

A list of assumptions made in the model and their justification is in Table 45.

Table 45. Model assumptions and justifications

Assumption	Justification
Case-fatality and long-term event mortality are equal for each treatment and for placebo	The current evidence base can support a difference in event rates between the two treatments, but there is not enough evidence to support a reduction in severity of consequences. Using such a difference confers an indirect mortality benefit to a treatment that cannot be justified by the evidence in hand.
Event rates observed during the ROCKET AF trial are applicable to periods beyond the follow-up.	SPAF is a chronic condition. Event rates observed during the ROCKET AF trial were assumed to continue but to be modified as patients age. Risk of ischaemic stroke and systemic embolism were extrapolated using the Framingham risk equation.
Treatment effects measured in the ROCKET AF trial and the NMA are applicable beyond the follow-up periods of the studies	While long term evidence is not available, anti-thrombotic therapy is required for the lifetime to treat AF which is a chronic condition. Treatment effect was assumed to be constant as long as a patient remains on therapy, as the anti-coagulant properties of therapy should continue to prevent formation of emboli.
When using the ROCKET AF trial data, the cohort is assumed to have the same risk levels as the trial population on average and does not distinguish between different levels of stroke risk.	The ROCKET-based analysis uses the event rate from the warfarin arm and a RRR reported for rivaroxaban. The event rate reflects the risk of the cohort which is a mixture of $CHADS_2$ risk 2-6 patients and is their average value. There is therefore no further adjustment made to patients' risk after experiencing a stroke or systemic embolism.
In the NMA-based analyses, patients who	Clinical experts advised that this is a

experience an intracranial bleed will discontinue therapy except for those at higher risks of stroke ($CHADS_2$>3)	case-by-case decision, but as a simplification for the model this would be an acceptable rule to implement.
Only one type of event can occur per three-month cycle of the model	Markov models require some degree of simplification in comparison to the real-world. A 3-month cycle was considered appropriate to capture the events for AF, as although it is not impossible for a patient to experience two events within the space of three months, this is relatively rare.
Patients who have experienced a stroke or intracranial bleed will maintain a lower HRQoL utility value for the remainder of their life associated with the post-event state.	Utility values from primary studies are available to describe the HRQoL of stroke and other cardiovascular event survivors(95-97), supporting the assumption that the long-term sequelae will have a lasting impact on patient HRQoL.
Ischaemic stroke is described by two severity levels based on the modified Rankin score.	While some studies have divided the severity of stroke into three different levels, there is little evidence available to quantify the economic and HRQoL consequences with such granularity. A scenario using three severity levels of stroke was considered but discarded as there was not much impact on the results and required assumptions to be made for the resource use and costs.
All patients experiencing an ischaemic stroke will re-initiate the anti-thrombotic therapy they used to be on regardless of their treatment status before the event.	AF patients who experience an embolic event and come under the care of a physician will be placed back on to anti-thrombotic therapy. In the model, the patient will always re-initiate on the therapy they started on to allow for comparison of treatment effects. In cases where a patients starts on anti-platelet therapy and experiences an embolic event, the patient will still re-initiate on an anti-platelet as the target patient is considered unsuitable for VKA therapy (i.e. their risk status makes them eligible for anti-coagulation therapy, but other characteristics make VKA therapy unsuitable).
All patients die upon reaching age 100.	The interim life tables provided by ONS do not provide all-cause mortality rates beyond age 100.
All patients experiencing a minor or major bleed will temporarily discontinue anti-thrombotic therapy for a short term, but will re-initiate therapy.	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.

Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

Please outline the aspects of the condition that most affect patients' quality of life.

Atrial fibrillation is a sustained heart rhythm abnormality where the atria (upper chambers of the heart) do not function properly, leading to incomplete and irregular squeezing of the lower chambers (left and right ventricles) of the heart, sub-optimal blood flow (fractional shortening) and an erratic heart rate. The prolonged pooling of blood in sections of the heart may lead to the formation of blood clots, which may subsequently travel to other parts of the circulatory system resulting in ischaemia.

Atrial fibrillation may be either silent or symptomatic, and if present the symptoms typically worsen over time. Paroxysmal atrial fibrillation typically develops into a sustained abnormality during long-term follow-up studies(98). Patients with atrial fibrillation experience a range of symptoms, including palpitations at rest and/or exertion, dyspnea, chest pain, dizziness and syncope. A survey of patients with atrial fibrillation in Spain revealed that dyspnea (shortness of breath) was the most common symptom reported in patients with permantent atrial fibrillations, followed by palpitations(99).

The worst aspect of the condition in terms of quality of life is ischaemic stroke, where atrial fibrillation is a major risk factor due to the potential for migration of blood clots from the heart to critical locations in the cerebral vasculature. The current Single Technology Appraisal focuses on rivaroxaban for the prevention of stroke in patients with atrial fibrillation. Stroke has a devastating effect on the lives of patients and their families, and results in a high health care burden. Patients with stroke may face high

short-term mortality risk, or may survive to long-term but with major neurological deficits and physical disabilities that impact most domains of health-related quality of life. Patients with history of major stroke may experience emotional and mental disturbances, may experience sensory disturbances, may lose speech, may require long-term institutional care, or may be confined to a wheelchair with major physical disabilities but intact cognitive faculties.

Please describe how a patient's HRQL is likely to change over the course of the condition.

A patient with atrial fibrillation is likely to experience poor health-related quality of life if a major cerebrovascular infarction occurs. The absolute risk of stroke increases in people with and without atrial fibrillation, due to both modifiable risk factors (e.g. systolic blood pressure, lipid profile and glycemia), and non-modifiable risk factors (e.g. age).

Deleterious effects over time on health-related quality of life in patients with atrial fibrillation may not be detected by standard, non-disease-specific utility elicitation techniques until a catastrophic cerebrovascular event occurs. Utility values derived using a standard gamble approach in patients with atrial fibrillation revealed that the suggested impact of stroke on health-related quality of life was a multiple of other events captured in the elicitation, including warfarin monitoring and bleeding events (100). The utility value for severe stroke was 0.189 compared to 0.841 for major bleed and 0.948 for GP-managed warfarin, when anchored to the health state of atrial fibrillation but without warfarin monitoring and with limited alcohol consumption. Once a patient with atrial fibrillation experiences a stroke, factors that may influence health-related quality of life over the long term include depression, cognitive impairment and incontinence(95).

If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

Method of elicitation.

Method of valuation.

Point when measurements were made.

Consistency with reference case.

Appropriateness for cost-effectiveness analysis.

Results with confidence intervals.

No data suitable for HRQL analysis was collected as part of the ROCKET AF study.

Mapping

If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.

Details of the methodology used.

Details of validation of the mapping technique.

No mapping techniques were performed for the derivation of health-state utility values applied in the cost-utility model described in this Single Technology Appraisal.

HRQL studies

Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A systematic search was performed to identify health state utility values in atrial fibrillation, stroke, post-stroke, embolism, myocardial infarction and bleeding events occurring in a non-valvular atrial fibrillation population.

The search incorporated a number of strategies, combining free text and medical subject heading search terms.

Searches were carried out using the following databases on the OVID SP platform:

- EMBASE (for the period 1988 to May 2011)
- MEDLINE, including Medline® In-Process (for the period 1950 to May 2011)
- Econ Lit (for the period 1969 to May 2011)

- The Cochrane Library (including: the Cochrane database of systematic reviews [CDSR], Database of abstracts of reviews of effects [DARE], the Cochrane central register of controlled trials, the Health Technology Assessment [HTA] database, and the NHS Economic Evaluation Database [NHS EED] accessed via Wiley Interscience (for the period 1999 to May 2011)

In addition, a manual search was conducted and relevant papers were retrieved from bibliographies of papers found in the systematic review.

Details of the search strategy and search terms are provided in appendix 12. All references were exported to Reference Manager bibliographic database and Microsoft Excel.

The exclusion and inclusion criteria used to identify health state utility values and treatment-related utility values in atrial fibrillation are shown in Table 46. Studies were included irrespective of the country of origin, provided that they were published in English.

Table 46. Inclusion criteria for utility-related papers in literature search

HRQOL	*Exclusion*	*Inclusion*
Population	Children **OR** Mixed patient populations for which the results of AF patients are not separable	Non-valvular Atrial Fibrillation
Intervention	Drug therapies	
Comparator	N/A	N/A
Outcomes	Reporting utility's instruments without conversion to utility measure **OR** Diagnostic, surgical, interventional procedures compared to other diagnostic, surgical, interventional procedures (i.e. ablations, pacing, etc.)	utility weights associated w/ warfarin **OR** utility weights associated w/ phenprocoumon **OR** utility weights associated w/ acenocoumarol **OR** utility weights associated w/ clopidogrel **OR** utility weights associated w/ aspirin **OR** utility weights associated w/ warfarin **OR**

		utility weights associated w/ clopidogrel plus aspirin **OR** utility weights associated w/ rivaroxaban **OR** utility weights associated w/ dabigatran **OR** utility weights associated w/ apixaban **OR** utilities value for atrial fibrillation **OR** utilities value for stroke **OR** utilities value for post-stroke **OR** utilities value for embolism **OR** utilities value for bleeds **OR** utilities value for myocardial infarction
Study design	Letters **OR** comments	All others **including** economic evaluations

AF = Atrial fibrillation

The initial search strategy identified 1276 article for papers that reported utility values associated with the event and 393 for papers that reported utility values associated with treatment of atrial fibrillation. These were assessed for inclusion using the information reported in title and abstract.

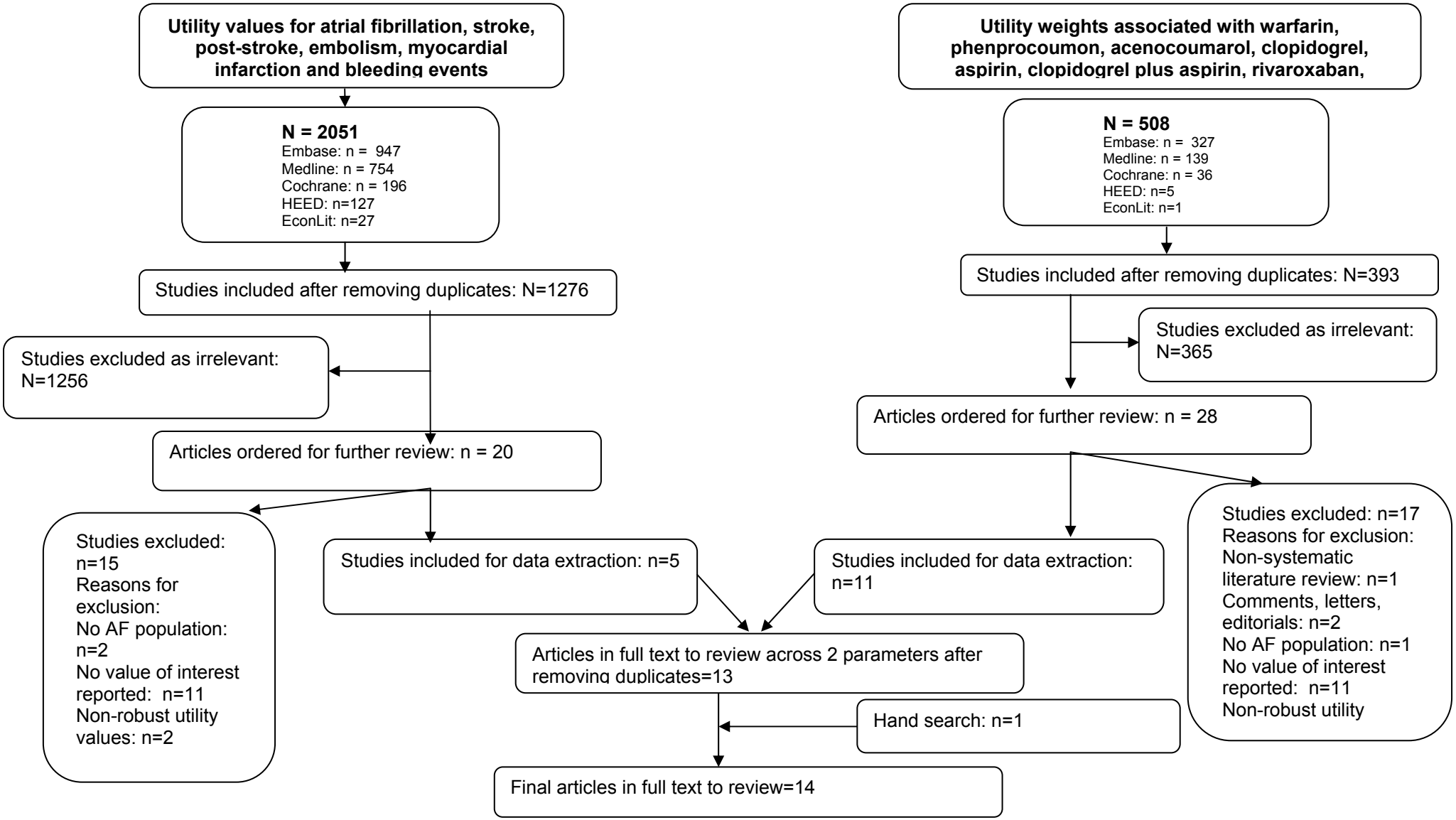
A large proportion of the papers identified (1256 articles in the search for papers reporting utility values associated with the event and 365 articles in the search for papers reporting utility values associated with treatment of atrial fibrillation) did not satisfy initial inclusion criteria. The remaining 20 studies found in the search for papers reporting utility values associated with the event and 28 found in the search for papers reporting utility values associated with treatment were assessed in full for inclusion. Overall, 44 full-text papers were reviewed (excluding duplicates) across both parameters and assessed for inclusion.

Overall, we identified 5 studies in the search for utility values associated with the event and 11 studies in the search for utility values associated with treatment for inclusion in this systematic review. When further assessed, a proportion of articles overlapped across the 2 parameters, therefore duplicates were eliminated and each paper was assessed only once, extracting values of interest for both parameters.

In addition, a hand search was conducted to identify potentially relevant publications; in total, 1 paper was identified for inclusion during this process. In total, 14 papers were identified and included in the data extraction stage.

The two flow diagrams below represent the searches conducted for utility values associated with the event and utility values associated with treatment of atrial fibrillation.

Figure 18 Flow diagram for search for health state utility values in atrial fibrillation


Utility values for atrial fibrillation, stroke, post-stroke, embolism, myocardial infarction and bleeding events
N = 2051
Embase: n = 947
Medline: n = 754
Cochrane: n = 196
HEED: n=127
EconLit: n=27
Studies included after removing duplicates: N=1276
Studies excluded as irrelevant: N=1256
Articles ordered for further review: n = 20
Studies excluded: n=15
Reasons for exclusion:
No AF population: n=2
No value of interest reported: n=11
Non-robust utility values: n=2
Studies included for data extraction: n=5
Utility weights associated with warfarin, phenprocoumon, acenocoumarol, clopidogrel, aspirin, clopidogrel plus aspirin, rivaroxaban,
N = 508
Embase: n = 327
Medline: n = 139
Cochrane: n = 36
HEED: n=5
EconLit: n=1
Studies included after removing duplicates: N=393
Studies excluded as irrelevant: N=365
Articles ordered for further review: n = 28
Studies excluded: n=17
Reasons for exclusion:
Non-systematic literature review: n=1
Comments, letters, editorials: n=2
No AF population: n=1
No value of interest reported: n=11
Non-robust utility
Studies included for data extraction: n=11
Articles in full text to review across 2 parameters after removing duplicates=13
Hand search: n=1
Final articles in full text to review=14

The systematic literature review was updated in May 2011 to include any articles published between May 2010 and May 2011. This systematic search identified 241 further studies which were included for abstract review, of which 236 were excluded after abstract review. Five papers were identified as relevant and included for full-text review. Full data extraction was completed for two papers in total. The review identified only health-state related utility values, no therapy related utility values were found in this update of the systematic review.

A summary of the five papers identified and reasons for exclusion are outlined in Table 47 below.

Table 47. Papers reviewed in full text for utility values for atrial fibrillation, stroke, post-stroke, embolism, myocardial infarction and bleeding events (i.e., for all events in the model); and utility weights associated with warfarin, phenprocoumon, acenocoumarol, clopidogrel, aspirin, clopidogrel plus aspirin, rivaroxaban, dabigatran and apixaban in update review

#	Author/s	Reference	Excluded (Yes/No)	Reason for exclusion
1	Berg et al, 2010	(101)	No	
2	Guedon-Moreau et al, 2010	(102)	Yes	No utility values reported
3	Kamel et al, 2010	(103)	Yes	Utility values reported from other sources prior to 2010
4	Freeman et al, 2011	(81)	Yes	Utility values reported from other sources prior to 2010
5	Radholm et al, 2011	(104)	No	

Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

Population in which health effects were measured.

Information on recruitment.

Interventions and comparators.

Sample size.

Response rates.

Description of health states.

Adverse events.

Appropriateness of health states given condition and treatment pathway.

Method of elicitation.

Method of valuation.

Mapping.

Uncertainty around values.

Consistency with reference case.

Appropriateness for cost-effectiveness analysis.

Results with confidence intervals.

Appropriateness of the study for cost-effectiveness analysis.

A summary table containing information derived from the data extraction of papers relating to health state utility values in atrial fibrillation is shown in Table 48. Please refer to Appendix 12 for further details. The appropriateness of references for cost-effectiveness analysis is discussed in section 6.4.9

.

Table 48. Details of the studies from which health state utility values were derived

Author	Pub. Year	Country	Population	Information on recruitment	Sample size	Health states	Method of elicitation	Method of valuation	Results (CI/SD)
Identified via Systematic Literature Review									
Berg et al.(101)	2010	35 European countries	AF patients	Patients enrolled at outpatient cardiology clinics and specialised hospital departments	At baseline n = 5,050. At follow-up: n = 3,045	Atrial fibrillation	Directly measured by authors	EuroQOL Index and Health Utility Index (UK)	Baseline: 0.751 (SD 0.269); follow up: 0.779 (SD 0.253)
Gage et al(79)	1995	USA	AF Patients	Patients at two major institutions	69 completed interviews	Mild, moderate-to-severe, recurrent neurologic event	Computer-based utility assessment tool	Standard gamble and time trade-off	Mild = 0.75 Moderate = 0.39 Recurrent Stroke = 0.12
Gage et al(105)	1996	USA	AF Patients	Patients referred from primary care, general medical wards and cardiology clinics to a single institution.	83 out of 140 total referred patients participated; 70 completed interviews	Mild, moderate and major stroke	Computer-based utility assessment tool	Standard gamble and time trade-off	Mild stroke = .94 Moderate stroke = 0.07 Major stroke = 0
Gage et al(106)	1998	USA	AF Patients	Patients referred from primary care, general medical wards and cardiology clinics to a single institution.	69 volunteers	Mild, moderate-to-severe, and second stroke	Computer-based utility assessment tool	Standard gamble and time trade-off	Mild = 0.85 Moderate = 0.51 Recurrent Stroke = 0.15
Robinson et al.(100)	2001	UK	A sample of patients with atrial fibrillation from three family practices in the North-East UK	Identified from computer records and invited to take part by post	69 people agree to participate out of 180 postal invitations issued	1. GP-managed warfarin treatment 2. Hospital-managed warfarin treatment 3. Major bleed 4. Mild stroke 5. Severe stroke.	Interviews with health state descriptions printed on cards	Standard gamble	Utility mean values (SD): GP-managed warfarin = 0.948(0.089) Hospital-managed warfarin = 0.941(0.101) Major bleed = 0.841(0.172) Mild stroke = 0.641(0.275) Severe stroke = 0.189(0.276)
Thomson et al(107)	2000	UK	Same study as Robinson et al above						

Radholm et al.(104)	2011	Sweden	85 year old subjects with atrial fibrillation or in sinus rhythm/ pacemaker	Population-based survey where all residents of a locality in Sweden aged 85 at the time of the study (n=650) were invited by letter to join the study	n = 53 AF patients n = 283 sinus rhythm/ pacemaker	Atrial fibrillation Sinus rhythm/ pacemaker fitted	Questionnaire	EuroQOL Index and Health Utility Index	Point estimate: 0.73 (Interquartile Range): 0.62–0.81
Selected after systematic review failed to identify appropriate studies									
Hallan et al.(96)	1999	Norway	Healthy subjects and stroke survivors	The healthy people were recruited from an old people's centre, from the neighbourhood of the authors, from the hospital staff and from a brass band. Non-stroke patients were consecutive patients from the hospital's medical outpatient clinic and they all suffered from one or more symptomatic, serious chronic diseases. All stroke survivors during a 1-year period identified by the hospital database who still had functional deficits but no major cognitive deficits and no aphasia were contacted.	Healthy people, n=66 Non-stroke patients, n=51 Stroke survivors, n=41	Minor stroke (Rankin scale, level 2-3): Unilateral weakness Walk with limp Write with left arm Some help with dressing and feeding Major stroke (Rankin scale, level 4-5): Paralysis Slow speech Wheelchair Feeding, dressing and transport help Bathing help Possible nursing home admission	Interview with health state descriptions given, visual analogue scale monitor, time-trade-off and standard gamble illustrations presented	Standard gamble and time trade-off	Median minor stroke utilities for all 3 groups: Standard gamble – 0.91 Time trade-off – 0.88 Direct scaling – 0.71 Median major stroke utilities for all 3 groups: Standard gamble – 0.61 Time trade-off – 0.51 Direct scaling – 0.31

Sullivan et al*(108)	2006	US	Large, nationally representative sample of individuals in the Medical Expenditure Panel Survey	None	Not known	Not known	Not known	EQ-5D	Utilities for: Atrial fibrillation 0.81 (0.67819 – 0.91373) Warfarin – first month 0.98 (0.957 – 0.995) Warfarin – ongoing after month 1 0.987 (0.967 – 0.998) Minor bleeds (2 days only) 0.8 (0.68-0.92) Decrements for: Age -0.00029 (0.00025-0.00034) Hemorhaggic stroke - 0.13850 (0.118122 – 0.16022) Ischaemic stroke – 0.13850 (0.11842 – 0.15998) Myocardial infarction – 0.12470 (0.10645 – 0.14356) Other major bleeds – 0.18140 (0.15476 – 0.20899) System embolic event – 0.11990 (0.10224 – 0.13880) Subdural hematoma – 0.1814 (0.15500 – 0.20885) Transient ischaemic attack - -0.10322 (0.08812 – 0.11894)
Lenert et al(109)	1997	US	30 healthy women from general population, and 30 physicians, all in and around Stanford University	Flyers in shopping malls	N=60	1. Mild post-thrombotic syndrome 2. Severe post-thrombotic syndrome 3. Central nervous system bleeding	Descriptions and pictures of health states, trade-off slider and visual analog scale all via a computer program	Standard gamble	Utilities for each health state for all patients (Mean and 95% CI): Mild post-thrombotic syndrome – 1.00 (0.91 – 1.00) Severe post-thrombotic syndrome – 0.95 (0.79 – 1.00)= Central nervous system bleeding – 0.60

Haacke et al(95)	2006	Germany	77 patients admitted to the department of neurology after experiencing stroke (ischaemic or haemorrhagic) or TIA (mean age 72 years)	The study included all patients who were admitted to the Department of Neurology, Philipps-University Marburg, between January 1 and March 31, 1999, after experiencing an ischaemic stroke, a transient ischaemic attack (TIA), or a haemorrhagic stroke	N=77	None – no standard gamble or time trade-off methods, which require the description of a health state, were included	Questionnaire	EuroQOL Index and Health Utility Index (German)	Mean EQ 5D – 0.74 Mean HUI2 – 0.67

*Sullivan et al (2006)(108) was not extracted in the systematic review since it was not the primary publication for the utility values. The utility values were determined by Sullivan et al (2005)(110) as part of a wider utility elicitation exercise. Sullivan et al (2006)(108) is cited here as this publication explicitly reports the utility values of interest.

Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No mapping techniques were performed for the derivation of health-state utility values applied in the cost-utility model described in this Single Technology Appraisal.

Adverse events

Please describe how adverse events have an impact on HRQL.

Three types of bleeding related adverse events were included in the model; minor extracranial bleeds, major extracranial and intracranial bleeds. The HRQL impact of bleeds depends on their location and duration of impact. For further discussion of the long term consequences of bleeding please refer to section 6.2.3 and 6.2.4.

Quality-of-life data used in cost-effectiveness analysis

Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 49. Summary of quality-of-life values for cost-effectiveness analysis

Health state	Utility	Source	Justification
Stable AF – not on treatment	0.779	Berg et al 2010(101)	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 2010(101)	As above – no disutility applied for warfarin monitoring (conservative)
Stable AF – maintained on other therapy	0.779	Berg et al 2010(101)	As above - not on treatment (conservative)
Stable AF – initiating warfarin treatment	0.779	Berg et al 2010(101)	As above – no disutility applied for warfarin monitoring (conservative)
Minor Stroke	0.6410	Robinson et al. 2001(100)	Patient reported utility valuations in the UK, using standard gamble; only study from systematic literature review to provide values for model definitions.
Major Stroke	0.1890	Robinson et al. 2001(100)	As above.
Post Minor Stroke	0.7189	Hallan et al. 1999(96)	Not available from systematic literature review; used a patient and general population reported utility valuations study in Norway as proxy. Adjusted for an AF population for model use.
Post Major Stroke	0.4819	Hallan et al. 1999(96)	As above
Systemic Embolism	0.6601	Sullivan et al. 2006(108)	Not available from systematic literature review. EQ-5D scores adjusted for age and gender in the US as part of a national project. Adjusted for AF population for model use.
Minor Bleed	0.7767	Sullivan et al. 2006(108)	As above
Major Bleed	0.5990	Sullivan et al. 2006(108)	As above
Intracranial Bleed	0.6000	Lenert et al. 1997(109)	Not available from systematic literature review. General population and physician estimates in US used as proxy.
Post IC Bleed	0.7400	Haacke et al. 2006(95)	Not available from systematic literature review. Patient reported outcomes in Germany
Myocardial Infarction*	0.683	Lacey et al 2003(111)	UK based primary study using EQ-5D in line with NICE reference case
Post Myocardial	0.6848	Sanders et al 2001(97)	Primary study focusing on MI

Infarction*			survivors allowing for capture of the post-MI health state.

* No utilities for MI in AF patients found in the systematic review, so an additional search was conducted for MI utility values (see section 6.4.9.13)

Table 49 displays the health state utility values applied in the reference case analysis. Health state utility values were not assumed to differ by treatment under intervention, and no treatment specific values were applied. Of note, no disutility was applied for warfarin monitoring, which is a conservative approach given evidence from a range of publications (see Table 48).

Stable AF – not on treatment

This health state represents the baseline untreated state of an AF patient who is 73 years old. In the systematic review conducted, two studies were identified reporting three different values. Berg et al (2010)(101) reported a utility value at baseline and at 1-year follow-up, which were 0.751 and 0.779. Radholm et al (2011)(104)reported a value of 0.73. The level of evidence rating between these two studies showed that Berg et al had a higher ranking. Since the model covers a life-time and the utility value is applied for that duration to anyone who remains in stable AF, the value at the 1-year follow-up of 0.779 was considered appropriate; Berg et al also uses the EQ-5D which is in line with the NICE Reference case. This is also in line with the UK population norm utility value of 0.78 for a 73-year old (age category 65-74) as reported by Kind (1999)(112).

Stable AF – maintained on warfarin treatment

This health state is designed to capture the utility associated with ongoing warfarin therapy. Several studies(100;105;105;105;107;107;113;113;114) have implied that there is a disutility associated with warfarin therapy. However, the application of a general utility decrement for warfarin use 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. Health-related disutilities associated with warfarin use should be captured in the model through the disutilities applied for the bleed events resulting from warfarin use. Therefore the model considers stable AF patients on warfarin to have the same baseline utility as stable AF patients treated with the other drugs.

Stable AF – maintained on other therapy

This health state is intended to capture the utility associated with any other anti-thrombotic treatment administered orally. Aspirin, rivaroxaban and dabigatran or any other new anti-coagulant would fall into this state. While no studies for disutilities associated with the new anti-coagulants exist, disutility associated with aspirin therapy has been valued at 0, that is, there is no difference in utility for a patient on treatment with aspirin to someone who is untreated, by Gage (1996)(105).

The model currently assumes that there is no disutility associated with aspirin, rivaroxaban or dabigatran therapy and uses the same utility as the baseline state of 0.779. This is conservative in the case of dabigatran as it requires twice daily administration.

Stable AF – initiating warfarin treatment

Sullivan 2006(108) and O'Brien 2005(115) indicate a greater disutility associated with warfarin initiation than warfarin maintenance. However, no disutiltity has been applied in this model.

Minor and Major Stroke

These two health states describe the acute episode of a minor and major stroke and the immediate follow-on period up to 3 months after the onset of the index event. The actual duration of an acute stroke episode is extremely short, and therefore utility valuation studies must usually rely on a longer period of time, which includes the stroke episode.

While level of evidence ratings were graded for each of the studies identified, the ratings may not be appropriate indicators of the robustness of the utility elicitation, as they may only be components within a larger study. Thomson (2000)(107) had an evidence rating of 1a, but is an economic evaluation that uses the same study described in Robinson et al (2001)(100), which has an evidence rating of 2b.

Among the studies reporting utility values for stroke, the ones that were most appropriate to the model definitions were selected. The available studies were Gage (1996)(105), Gage (1998)(106), Thomson (2000)(107) and Robinson (2001)(100). The focus was on primary utility studies rather than economic evaluations that report utility values as part of their study. This left Gage (1996)(105) and Robinson (2001)(100).

Given the wide range of symptoms and variation in lasting disability that is described within each of the studies, the resulting utility values are also far-ranging. Robinson et al. 2001(100) reports a utility value of 0.641 for mild stroke, and a utility value of 0.189 for a severe stroke. Gage's 1996 study(105) valued stroke at three different severities rather than at two, and found that minor strokes have a utility weight of 0.94, moderate strokes 0.07, while a major strokes have a utility weight of 0, equivalent to death. These severe states described by Gage imply a stroke with lasting debilitating effects and the general inability to look after oneself – this would be the reason for the extremely low utility weights given. The extremely wide gap between the value for a minor stroke and a moderate stroke in the Gage study implies that the definitions used to elicit the values may have been more extreme than what has been used in the Robinson study. Since the major stroke survivors in the model would be a mixture of those requiring little to considerable aid, the values from the Robinson study were deemed to be more appropriate.

In conclusion, the utility values for major (0.189) and minor (0.641) strokes used for the model are those derived from the study by Robinson.

Post Minor and Major Stroke

This health state is intended to capture the utility of an AF patient who is experiencing the long-term sequelae of a minor or major stroke. This model uses the modified Rankin scale to provide a functional definition of a minor stroke or major stroke. The systematic review did not identify any relevant studies within the AF population. Hallan et al. 1999(96) however reported utility values for patients in Norway, some of whom had experienced a cerebrovascular stroke. The value reported for the post-minor stroke state is 0.91 and the post-major stroke state is 0.61. These authors used SG, TTO and direct scaling to provide utilities for health states describing a stroke (modified Rankin scale 2-3). The combination of the prospective study methodology on a European sample using validated techniques (data from the SG is used here), means that these provide a robust data source. However, these utility values are not elicited from a population of patients who also all have AF, and in this respect, the utility value of 0.91 and 0.61 have been adjusted by the baseline utility of having AF, which has been set as 0.779 based on the value from Berg et al 2010.(101) The resulting utility value used in the model for post-minor stroke is 0.72 and for post-major stroke is 0.48.

Systemic Embolism

This health state is intended to represent the utility associated with experiencing a systemic embolism, and the impact that associated acute care and impact on day to day life that this event has for the first three months after the event. The value chosen for this health state was 0.6591 which was calculated using the decrement associated with a systemic embolic (-0.11990) event presented by Sullivan et al. 2006(108), and applied to the baseline health state of 0.779. Although the data were from an economic evaluation analysing a patient population from the US, this report used the EQ-5D with the Medical Expenditure Survey Panel to generate the utility decrements. In light of the fact that there is very little data available on the utility associated with systemic embolism and none were returned within the systematic literature review that fit the inclusion/exclusion criteria, this datum provides a reasonably robust estimate of the impact of a systemic embolism on HRQoL for use in this model.

Minor Bleed

This health state is intended to model the impact on HRQoL that a minor bleed has on a patient with AF. No study fitting the inclusion/exclusion criteria of the systematic literature review reported a value for minor bleed. An economic analysis identified before the screening criteria was applied was therefore selected as giving the most appropriate utility weight. The economic analysis presented by Sullivan et al. 2006(108) used a utility value of 0.8 applied for two days only, after which the utility returned to the baseline health state. We used the multiplicative approach and assumed that with a minor bleed, the resulting utility would be a weighted average of 0.779*0.81 = 0.63099 for two days and of no disutility 0.779 for the remaining days out of the cycle. The result is a utility weight of 0.7757 for the minor bleed state.

Major Bleed

This health state is intended to model the impact on HRQoL that a major bleed has on a patient with AF. While Robinson et al. 2001(100) identified in the systematic review reported a utility value for a major bleed, the value was 0.841 and therefore higher than the baseline utility value. Since the study was based on a population of AF patients, there was no way to adjust with the baseline value. As a proxy, therefore the Sullivan et al. 2006(108) study was used which reported a decrement of 0.181,

which gives a value of 0.599 when applied to the baseline utility of 0.779 This also has the advantage of using the same source for the two extracranial bleed states.

Intracranial Bleed

A general utility value for intracranial bleeds was scarce in the literature, and since the majority of reported intracranial bleeds are haemorrhagic strokes (or intracerebral bleeds), the utility literature around haemorrhagic strokes was utilised here. Even searching for a utility value for haemorrhagic stroke, no study was identified in the systematic literature within an AF population specifically. Lenert & Soetikno 1997(109) was the best fit proxy data identified, as it provided a direct measurement valuation of a central nervous system bleed from the general public. The value selected is 0.6(109).

Post IC Bleed

Several other published cost-effectiveness analyses found in the literature review, but later excluded, used the utility observed in patients surviving an ischaemic stroke (Catherwood et al 2001(116)) to describe the long-term utility in intracranial bleed survivors. No specific study was found describing the utility value of an intracranial bleed in an AF population. This model therefore uses a paper excluded at the last screening stage that uses a haemorrhagic-stroke specific utility value from a German study by Haacke et al. 2006(95). The Haacke et al. study assessed utility during 4-years follow-up of patients surviving a haemorrhagic stroke, and provides a value of 0.74 for the post IC bleed state using the EQ-5D index.

Myocardial Infarction

The systematic literature review did not identify any values for myocardial infarction within an AF population. A subsequent search was therefore undertaken in the Tufts University CEA Registry to search for utility values specific to MI. Most studies identified in the registry were CEA studies citing utility values from other studies. Hand-searching these references, a primary study taking place in the UK using EQ-5D was identified. This reported a value of 0.683(111).

Post Myocardial Infarction

The systematic literature review did not identify any values for myocardial infarction within an AF population. A subsequent search was therefore undertaken in the Tufts University CEA Registry to search for utility values specific to MI. Sanders et al

2001(97) was selected as the population studied were patients who had previously had a myocardial infarction, and therefore fit the definition of a post-MI state. For this Sanders et al reports a utility value of 0.88 but this was elicited in patients specifically without AF (or any other heart arrhythmia) and was therefore adjusted by the baseline utility to 0.69.

If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

the criteria for selecting the experts
the number of experts approached
the number of experts who participated
declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
the background information provided and its consistency with the totality of the evidence provided in the submission
the method used to collect the opinions
the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
the questions asked
whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical experts were engaged to estimate health related quality of life values for this Single Technology Appraisal.

Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

With the exception of minor bleeds HRQL is assumed to remain constant with respect to time within health states. For minor bleeds patients were assumed to experience a short (2 day) disutility, following which their HRQL returned to baseline. The three-month cycle length was assumed sufficient to capture the short-term impact of other events on health related quality of life.

Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Yes, disutility associated with warfarin, which has been discussed in the literature, was omitted from the base case (please refer to 0 and 0.

If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The health state utility value in the stable atrial fibrillation health states (both on and off therapy) was 0.779. Patients were assumed to experience this value while they remained in the stable atrial fibrillation health states (both on and off therapy)

The impact of adverse events and cardiovascular events on health related quality of life was captured by applying a health state utility value derived from studies that focused on events captured in the model. For utility values that were derived from non-AF patients, the reported utility was adjusted by the baseline AF utility. This included post- minor and major stroke, as well as systemic embolism and minor bleed.

Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Health related quality of life was assumed to be constant over time. There were no adjustments made for cohort aging, although the baseline utility value from UK general population estimates was derived from patients in a relevant age group. Health related quality of life in the modelling analysis could only change as a function of clinical events experienced by the patient. Furthermore, the health state utility values applied for each event in the modelling analysis did not vary as a function of time since the event or patient age.

Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Please refer to section 6.4.9 for further details.

Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Since AF is a risk factor for thromboembolism, in particular stroke, current UK guidelines recommend that all patients with paroxysmal, persistent, or permanent AF be assessed for risk of stroke or thromboembolism(1). Stroke risk prophylaxis involves anticoagulation with warfarin or prescribing of the antiplatelet, aspirin. Choice is based on individual factors, importantly, stroke risk and risk of bleeding.

Complications of anticoagulation include an increased risk of bleeding (intracranial or extracranial); the most devastating complication associated with warfarin prophylaxis is the risk of intracranial haemorrhage. Poor anticoagulation control is considered another risk factor for bleeding, with increased bleeding risk demonstrated when INRs are greater than 3.0(117).

Costs of long-term anticoagulation and stroke prevention in atrial fibrillation are incurred in the primary and secondary care NHS settings. Unit costs used in the model reflect the UK NHS perspective and are taken wherever possible from the NHS National Schedule of Reference Costs 09-10 (NHS Reference Costs)(18), the Personal Social Services Research Unit 2010 (PSSRU)(19) and the British National Formulary 61 (BNF, March 2011)(118). Costs are mainly focussed around:

- The provision of anticoagulants
    - Drug acquisition (BNF)
    - Drug administration and resource e.g. Initial assessment, subsequent monitoring and, for warfarin, management of INR levels

- Event treatment costs
    - Costs of stroke, acute management and follow-up including rehabilitation
    - Costs of bleeding, extracranial and intracranial
    - Costs of dealing with any other adverse events e.g. myocardial infarction

The event treatment costs in the model were built up from a mix of staffing costs (PSSRU) and hospital episode costs (with HRG codes) sourced from NHS Reference costs. Tests and procedures relating to ongoing care of stroke patients or dealing with the complications of bleeding or MI usually take place in the secondary care setting and are costed under HRG codes (NHS Reference costs).

A summary of the unit costs (and the related codes) derived from published NHS reference costs is presented below. Where costs and information on resource use could not be sourced from NHS reference costs, a systematic review of the literature was undertaken. Details of the systematic review are outlined in section 6.5.3 along with a summary of the remaining costs and resource use data required for the model.

Drug acquisition unit costs in the UK were obtained from the BNF (March 2011) and are shown in Table 50.

Table 50. Drug Acquisition Costs

Drug	Strength	Cost per pack	Cost per tab	Source	Dose	Source	Cost per Day
Rivaroxaban	20 mg		[redacted]	Bayer HealthCare **(provisional price)**	20mg/ day	Bayer HealthCare	[redacted]
Warfarin	0.5mg 1.0 mg 3.0 mg 5.0 mg	£1.49 per 28 tab £0.93 per 28 tab £0.95 per 28 tab £1.03 per 28 tab	£0.053 £0.033 £0.034 £0.037	BNF61 BNF61 BNF61 BNF61	4.5mg/ day	NICE Clinical Guideline 36: Atrial fibrillation(17;118)	£0.12
Aspirin	75mg	£1.03 per 56 tab	£0.018	BNF61	150mg/ day		£0.037
Dabigatran	110mg 150mg				110mg bd 150mg bd	Personal communication	£2.52 £2.52

BNF= British National Formulary; NICE= National Institute for Health and Clinical Excellence

Drug Administration / Monitoring Costs

When monitoring was assumed to take place in a specialised anti-coagulation clinic in secondary care, costs were derived from the NHS Reference Costs for NHS Trusts only for Anticoagulant Service (Code 324) for first or subsequent visits. Recently more anticoagulation clinics have been set up in primary care. For the costs of primary care anticoagulation monitoring it was assumed that 50% of visits would be conducted by a GP and 50% by a nurse using PSSRU 2011 and the cost of an INR test (based on the NICE Commissioning guide for Oral Anticoagulation (OAC) services(119)). Table 51 outlines the unit costs applied in the model. Relevant reference costs are presented in Table 52 and the approach taken to derive weight mean costs for secondary care is described in Table 53.

Table 51. Drug monitoring visits – costs

Cost element	Unit cost (£)	Cost source	Reference description
Warfarin Monitoring – First Visit (secondary care model)	47.19 per visit	National Schedule of Reference Costs 2009/10 for NHS Trusts	324: Anticoagulant Service. Consultant and Non-Consultant, First Attendance Non-Admitted Face to Face.
Warfarin Monitoring Visit (subsequent) (secondary care model)	24.69 per visit	National Schedule of Reference Costs 2009/10 for NHS Trusts	324: Anticoagulant Service. Consultant and Non-Consultant, Follow Up Attendance Non-Admitted Face to Face.
GP-based warfarin monitoring	24.00 + 3.00 per visit	PSSRU 2010 NICE commissioning guide for OAC services	50% GP cost per surgery consultation lasting 11.7 minutes; 50% nurse consultation; INR test
Initiation of long term treatment with oral anticoagulants/ antiplatelets	36.00 per visit	PSSRU 2010	GP cost per surgery consultation lasting 11.7 minutes

Table 52. National Schedule of Reference Costs Year: '2009/10' – NHS Trusts (Appendix NSRC01) Anticoagulant services

Code	Anticoagulant Service	Activity	National Average Unit Cost (£)	Lower Quartile Unit Cost (£)	Upper Quartile Unit Cost (£)
324	Consultant Led: First Attendance Non-Admitted Face to Face	71,646	47.30	9.46	44.85
324	Consultant Led: Follow up Attendance Non-Admitted Face to Face	1,201,276	29.35	14.99	31.41
324	Non-Consultant Led: First Attendance Non-Admitted Face to Face	24,700	46.87	21.49	68.46
324	Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face	790,414	17.61	10.87	18.63

Table 53. Weighted average costs for first attendance and follow-up (subsequent) visits

	Secondary care only	% Consultant	% Non-consultant	Weighted (£) Consultant	Weighted (£) Non-Consultant	TOTAL COST
Table 52	First Attendance Non-Admitted Face to Face	74.36%	25.64%	35.17 (47.30*74.36%)	12.02 (46.87*25.64%)	47.19
Table 52	Follow up Attendance Non-Admitted Face to Face	60.31%	39.69%	17.70 (29.35*60.31%)	6.99 (17.61*39.69%)	24.69

The resource use according to primary or secondary care and frequency of monitoring visits / INR tests were obtained via systematic review of the literature and are detailed in section 6.5.3. Calculations of annualised overall costs for anticoagulation (i.e. warfarin) monitoring are then built up using the NHS reference costs presented here and the data sourced from the systematic review (see Section 6.5.3.).

A small proportion of patients who attend anticoagulation monitoring clinics make use of the NHS-sponsored patient transport service (PTS) for their transportation. The cost of using patient transport services to attend the warfarin monitoring clinics was therefore incorporated in the modelling analysis. Based on a survey conducted by pH Associates describing patient pathways associated with different approaches to oral anticoagulation care(20) 8.55% of patients were estimated to use PTS. This cost was only applied to patients receiving anticoagulation care in Secondary Care since primary care services were assumed to be delivered in close proximity to patients (Table 54).

Table 54: Cost of Patient Transport Services

Cost element	Unit cost/cost per visit (£)	Cost source	Reference description
Patient Transport Services	30.96	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	Outpatient PTS

Event Treatment Costs

Costs for the treatment of ischaemic stroke, bleeding events, systemic embolism and myocardial infarction were identified and applied in the modeling analyses. The events included acute treatment of strokes of varying severity (e.g. minor or major stroke), extracranial bleed severities (major or minor), the acute treatment of intracranial bleeds, the acute treatment of systemic embolism and the acute treatment of myocardial infarction. It should be noted that costs derived from stroke events in the general population are likely to be on the conservative side when used in economic models for an atrial fibrillation population. This is due to AF patients who develop stroke having a greater level of mortality, morbidity (e.g. more severe strokes), disability, longer hospital stays and a lower rate of discharge to their own homes when compared with other non-AF patients(94;120-122).

The modelling analysis captured the costs associated with treatment using a single cost for acute treatment in the cases of mild events or those events which were not assumed to have long lasting clinical consequences. More severe events, specifically major strokes, intracranial bleeds and MIs, were modelled using multiple components in the cost calculation. Not only was there the cost of acute treatment, but the duration of the treatment was extended based on excess days of treatment. Additionally, the model captured the costs associated with the impact of the event on the patient's functionality by including a cost for rehabilitation. The rehabilitation costs were assumed to run to the end of the first three month cycle in which a major stroke, an IC or an MI occurs.

Ischaemic stroke Events

The cost of a minor stroke was based on the acute treatment costs from the NHS Reference Costs for Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy (code AA22Z). It was assumed that there were no additional costs of rehabilitation associated with a mild stroke or with excess days of stay. The NHS reference costs for the acute treatment of a stroke is £2,829.66 over a 9.72 day period (NHS Reference Costs 09-10 AA22Z).

The cost of treatment for a major stroke was modelled by using the 9.72-day cost associated acute stroke treatment and combining this with a further 24.68 excess days of acute treatment(123), identified in the systematic review) costing £210.53 per day (NHS Reference Costs 09-10 AA22Z). In addition to this longer period of acute treatment, the rest of the three month cycle in which the major stroke occurs also has a cost of rehabilitation associated with it (14 days from clinical expert) costed at £308.94 per day (NHS Reference Costs 06-07 VC04Z). The total 3 month cost for a major stroke was therefore £8,334.57.

The costs of stroke applied in the model are reported in Table 55. Resource use is reported in Table 56. Life-time follow on care costs (after the first 3 months) were sourced via the literature (see section 6.5.3.).

Table 55. Ischaemic stroke treatment - costs

Cost element	Unit cost/cost per visit (£)	Cost source	Reference description
Stroke – acute treatment	2,829.66	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined - Non-Elective Inpatient	AA22Z: Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy
Stroke – acute treatment. Excess bed days (cost per day)	210.53	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined - Non-Elective Inpatient	AA22Z: Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy
Rehabilitation cost per day	308.94	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	VC04Z: Rehabilitation for stroke (weighted average)

Table 56. Ischaemic stroke treatment - resource use

Resource use element	Resource use/ Units	Source	Reference description
Average length of stay for a stroke patient	34.4 days	Saka et al (2009)(123) identified from the systematic review, see section 0	South London Stroke Register
Average length of stay for a stroke patient - NHS reference costs 09-10	9.72 days	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	AA22Z: Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy
Rehabilitation days – minor stroke	0 days	Clinical opinion	
Rehabilitation days – major stroke	14 days	Clinical opinion	

ALOS = Average Length of Stay;

a. Extracranial Bleeding Events

Based upon the approach adopted by NICE in Clinical Guideline 92 (Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism)(124) in patients admitted to hospital, 2010), gastrointestinal bleeding was used as a proxy for major bleeding. Costs associated with major extracranial bleeds (£866.00) were modelled by using the non-elective NHS reference cost data from gastrointestinal bleeds with intermediate or major complications (Table 57); the codes were selected by focusing on any HRG that referred to disorders of the GI tract. These costs were weighted by the frequency of reporting of the different codes included (Table 58); the weighting was done by activity (number of finished consultant episodes) reported for each code over the total number of episodes. It was assumed that there were no further costs associated with this event after three months.

Table 57. Major extracranial bleeding – resource use

FZ16Z	Very Major Procedures for Gastrointestinal Bleed
FZ25A	Therapeutic Endoscopic or Intermediate Stomach or Duodenum Procedures 19 years and over
FZ29Z	Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed
FZ30Z	Diagnostic Endoscopic or Intermediate Procedures for Gastrointestinal Bleed
FZ38D	Gastrointestinal Bleed with length of stay 2 days or more with Major CC
FZ38E	Gastrointestinal Bleed with length of stay 2 days or more without Major CC
FZ43A	Non-Malignant Stomach or Duodenum Disorders with length of stay 2 days or more with Major CC
FZ43B	Non-Malignant Stomach or Duodenum Disorders with length of stay 2 days or more without Major CC
FZ43C	Non-Malignant Stomach or Duodenum Disorders with length of stay 1 day or less

Table 58. Major extracranial bleeding – Reference cost components

Code		Activity	National Average Unit Cost
FZ16Z	Non-Elective Inpatient (Long Stay) HRG Data	415	£4,932.41
FZ16Z	Non-Elective Inpatient (Short Stay) HRG Data	115	£2,035.13
FZ16Z	Day Cases HRG Data	30	£915.42

Code		Activity	National Average Unit Cost
FZ25A	Non-Elective Inpatient (Long Stay) HRG Data	1,119	£1,319.86
FZ25A	Non-Elective Inpatient (Short Stay) HRG Data	5,828	£571.48
FZ25A	Day Cases HRG Data	13,865	£503.25
FZ29Z	Non-Elective Inpatient (Long Stay) HRG Data	8,318	£1,682.19
FZ29Z	Non-Elective Inpatient (Short Stay) HRG Data	7,181	£504.13
FZ29Z	Day Cases HRG Data	6,276	£493.30
FZ30Z	Non-Elective Inpatient (Long Stay) HRG Data	592	£1,862.63
FZ30Z	Non-Elective Inpatient (Short Stay) HRG Data	433	£463.65
FZ30Z	Day Cases HRG Data	7,594	£452.14
FZ38D	Non-Elective Inpatient (Long Stay) HRG Data	9,975	£1,943.51
FZ38D	Non-Elective Inpatient (Short Stay) HRG Data	42	£290.72
FZ38D	Day Cases HRG Data	1	£442.23
FZ38E	Non-Elective Inpatient (Long Stay) HRG Data	13,093	£1,260.81
FZ38E	Non-Elective Inpatient (Short Stay) HRG Data	71	£301.08
FZ38F	Non-Elective Inpatient (Long Stay) HRG Data	4,731	£649.08
FZ38F	Non-Elective Inpatient (Short Stay) HRG Data	34,705	£403.29
FZ38F	Day Cases HRG Data	235	£443.92
FZ43A	Non-Elective Inpatient (Long Stay) HRG Data	11,633	£2,153.22
FZ43A	Non-Elective Inpatient (Short Stay) HRG Data	73	£338.57
FZ43A	Day Cases HRG Data	1	£567.82
FZ43B	Non-Elective Inpatient (Long Stay) HRG Data	19,218	£1,493.45
FZ43B	Non-Elective Inpatient (Short Stay) HRG Data	120	£302.85
FZ43B	Day Cases HRG Data	7	£577.88

Code		Activity	National Average Unit Cost
FZ43C	Non-Elective Inpatient (Long Stay) HRG Data	3,901	£661.74
FZ43C	Non-Elective Inpatient (Short Stay) HRG Data	39,315	£388.18
FZ43C	Day Cases HRG Data	1,517	£391.39

Costs associated with minor extracranial bleeds were modelled using the costs for "Accident and Emergency Services: Minor Injury Service: Not Leading to Admitted" from the NHS reference costs (£126.34) (NHS Reference Costs 09-10 VB07Z). It was assumed that the only costs associated with a minor bleed are those for acute treatment and full recovery was within three months. The costs of bleeding events are shown in Table 59.

Table 59. Extracranial bleeding events - costs

Cost element	Unit cost/cost per visit (£)	Cost source	Reference description
Minor bleeding – acute treatment	126.34	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	VB07Z: Accident and Emergency Services. Category 2 investigation with category 2 treatment (weighted average)
Major bleeding – acute treatment	866.00	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	Cost of a gastro-intestinal bleeding treatment episode. Weighted average codes FZ16Z, FZ25A, FZ29Z, FZ30Z, FZ38D, FZ38E, FZ38F, FZ43A, FZ43B, FZ43C

b. Intracranial Bleeding Events

Costs associated with intracranial bleeding events were modelled using the costs for acute care of stroke (£2,072.72) (NHS Reference Costs 09-10 AA23Z) followed by 14 days of rehabilitation. The duration of rehabilitation was modelled on the rehabilitation costs for a major stroke, an assumption that was derived from expert clinical opinion. The cost of rehabilitation was taken from the NHS reference cost of £308.94 per day (NHS Reference Costs 09-10 VC04Z). This resulted in a total cost for the treatment of intracranial bleeds in the UK of £6,397.87. Follow on care was assumed to be identical to the follow-on care for a major ischaemic stroke the costing

of which was sourced from the literature (see section 6.5.3). Unit costs for intracranial bleeds are displayed in Table 60.

Table 60. Intracranial bleeding events - costs

Cost element	Unit cost/cost per visit (£)	Cost source	Reference description
Intracranial bleeding	2072.72	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	AA23Z: Haemorrhagic Cerebrovascular Disorders (weighted average)
Rehabilitation cost per day	308.94	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	VC04Z: Rehabilitation for stroke (weighted average)

NHS = National Health Service; PCT = Primary Care Trust

c. Systemic embolism

The NHS reference costs used to provide a cost estimate for the treatment of systemic embolism (£536.83) were based on the cost of non-surgical peripheral vascular disease (see Table 61). The cost of each tarrif was weighted by the amount of activity of each code. The cost of systemic embolism is shown in Table 61.

Table 61.Systemic embolism - costs

Cost element	Unit cost/cost per visit (£)	Cost source	Reference description
Systemic embolism - acute treatment costs	1658.12	National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	Cost of Non-Surgical Peripheral Vascular Disease. Weighted average codes QZ17A, QZ17B, QZ17C

The specific codes and corresponding tarrifs for each are shown in the table below.

Table 62. Systemic Embolism – codes used for weighting

Code		Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
QZ17A	Non-Surgical Peripheral Vascular Disease with Major CC (Long stay)	1,091	£4,562.25	£2,820.01	5,674
QZ17B	Non-Surgical Peripheral Vascular Disease with Intermediate CC (Long stay)	11,478	£2,524.03	£1,855.73	2,974
QZ17C	Non-Surgical Peripheral Vascular Disease without CC (Long stay)	3,216	£1,682.69	£1,116.32	2,041
QZ17A	Non-Surgical Peripheral Vascular Disease with Major CC (Short stay)	286	£785.45	£292.44	883
QZ17B	Non-Surgical Peripheral Vascular Disease with Intermediate CC (Short stay)	6,539	£575.87	£314.94	585
QZ17C	Non-Surgical Peripheral Vascular Disease without CC (Short stay)	4,935	£470.70	£284.92	520

d. Myocardial Infarction

Acute treatment and follow-on care (i.e. after the first three months) costs of myocardial infarction were sourced from the literature (see section 6.5.3). In addition to this, the rest of the three month cycle in which the myocardial infarction occurs also was associated with a cost of rehabilitation, costed at £264.77 (NHS Reference Costs 09-10 VC38Z).

Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

This model used NHS reference costs, as they provide relevant costs and volume that enable the estimation of a weighed average that reflects the pattern of care delivered in the NHS. Furthermore, Reference Costs represent the cost burden to the NHS rather than a reflection of internal reimbursement between NHS organisations. Also, when compared to Tariff values, the Reference costs allow for a greater level of granularity to be assessed.

Resource identification, measurement and valuation studies

Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

country of study

date of study

applicability to UK clinical practice

cost valuations used in study

costs for use in economic analysis

technology costs.

A systematic search of the literature was performed to identify all resource and cost data associated with prevention of stroke in Atrial Fibrillation / Stroke / Anticoagulation services. The searches were conducted across Medline, Medline-in-process, EMBASE, EconLIT, and Cochrane Library 2011 Issue 1 (including NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (HTA) database and Cochrane Groups). Additionally, searches were performed in the websites of National Institute for Health & Clinical Excellence (NICE), NHS Improvement, the Department of Health and The National Institute for Health Research (NIHR) Health Technology Assessment programme.

Studies that were based on UK practice and costs were the focus of the systematic review, although the literature searches in the databases were kept intentionally broad (i.e. included non-UK publications) in case there was a need to consult international or non-UK studies later on in the process.

The searches were conducted on 17th and 18th February 2011 and resulted in a total of 3,613 titles being reviewed for relevance. A total of 3,497 studies were excluded and 116 reviewed based on the complete publication. One hundred and three of these references were subsequently rejected for not meeting the study inclusion criteria and 13 were left that described some or all resource use and costs involved in stroke prophylaxis in atrial fibrillation or stroke or anticoagulation in a more general population. Full details of the literature search strategy including search terms

employed and the flow diagram for the search of resource use data in the UK are provided in section 9.13 (Appendix 13).

Of the 13 studies selected, three studies contained data derived completely from an atrial fibrillation population (Abdelhafiz & Wheeldon 2003, Freeman et al 2011 & Jowett et al. 208) (81;125;126) and another study Kerr (2008)(127) reported data on stroke patients, separating them into AF and non-AF populations (See Appendix 13). Data from atrial fibrillation populations are identified in this section, and throughout Appendix 13 by a pink background colour to the table cells.

The remaining studies contained data derived from mixed indications including atrial fibrillation patients (CG36 National Institute for Health and Clinical Excellence 2006;Connock et al. 2007; McCahon et al. 2007; Parry et al. 2001)(17;128-130) or from general populations who had either experienced a stroke (CG68 National Institute for Health and Clinical Excellence 2008; National Audit Office 2010;Saka et al. 2009)(123;131;132) or were in hospital requiring thromboprophylaxis (CG92 National Clinical Guideline Centre 2010)(124). The Commissioning and benchmarking tool (119) included costs and resource associated with the setting up and the running of an anticoagulation clinic service.

Resource and cost data were fully extracted from these 13 studies / reports.

The systematic review provided a broad understanding of the required inputs for any economic model to be developed on the use of anticoagulation in the prevention of stroke in patients with atrial fibrillation. As the model for this submission was to be developed from an NHS perspective (see section 6.5.2), values for model input were taken from current PSSRU / NHS Reference costs wherever possible as this was the most up-to-date reference source. These have been described in section 6.5.1.

Where gaps in data were identified, model input values were drawn from the results of the systematic review. Therefore, of all the data identified in the systematic review, only data used for input into the model are described within this section. This report includes data extraction tables and tabulation of all identified costs and resources for Anticoagulation, Bleeding complications and Stroke.

Upon review of section 6.5.1, the following value inputs were still required for the model:

- Anticoagulation management in the UK - how these services are now provided (primary or secondary care)

- Frequency of visits / INR tests
- Follow-on care for major stroke and intracranial bleeding
- Acute treatment of myocardial infarction
- Follow-on care of myocardial infarction

Anticoagulation management in the UK

Warfarin requires dose-titration and regular international normalised ratio (INR) monitoring visits for the duration of therapy; this has been captured in the model. The per-visit cost of a monitoring visit in the UK differs according to the setting of care. Traditionally, patients taking warfarin both in the short and long term were managed solely in secondary care. However, as services have evolved over time to more closely match the needs of the local population, follow-up patient care has diversified away from purely secondary care.

The systematic review did not identify any information on the ratios of primary care and secondary care provision of anticoagulation services in the UK, however, a survey of anticoagulation management by pH associates was commissioned for the UK NHS in 2011(20). One-to-one semi-structured interviews of either healthcare professionals leading anticoagulation care, or a PCT/health board recommended knowledgeable person, were used to gather data on current anticoagulation management. Data were collected from a total of 78 PCTs in England, 3 local health boards in Wales and 1 PCT from a health board in Scotland. The data was found to cluster into 6 groups each representing a different approach to anticoagulation care in the UK. Results suggested that instead of the traditional secondary care consultant led services, primary care is now the most common setting for the provision of these services. Additionally, many PCTs and acute Trusts operate a hybrid approach incorporating a number of different care delivery structures within their service. The survey suggested 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]

The reported data suggests that of the [redacted] of patients managed in hybrid clinics, 50% of patients would be treated in Primary Care anticoagulation clinics and the remaining 50% would be treated in Secondary Care. Self monitoring was not

included as it only represented a small percentage of the population. Furthermore, patient self-management has previously been found to be more expensive than current routine care and does not appear to be a cost-effective approach(128).

Overall, the cost-effectiveness model assumes that 66.45% of warfarin patients are managed in Primary Care, while the remaining 33.55% are managed in Secondary Care.

Monitoring - Frequency of visits / INR tests

The systematic review identified the following resource / costs associated with the frequency of INR monitoring:

Resource	Resource use	Source / cost year
INR test	Every 31 days (mean)(16-87 days) (4.2 to 23 visits)	McCahon 2007(129); NHS Ref costs / PSSRU 2003
	20 appointments per year	NICE CG36 (2006)(17); NHS ref costs 2004/2005
	14 tests per year (plus an extra 8 tests allowed for patients initiating therapy)	Freeman (2011)(81); Cost year 2008
	20 clinic visits per year Each visit lasts 15 minutes	NICE Anticoagulation Service Commissioning and benchmarking tool (2010)(119) NHS costs 2009/2010

NR=not reported

In clinical practice when patients are initiated on warfarin, either for the first time, or after a period of therapy interruption, it is recommended that they see a physician more regularly in order to adjust the dose of warfarin until the patient achieves stabilisation of the INR, which for AF has a target therapeutic range of between 2.0 to 3.0.

McCahon (2007)(129) reports INR testing from 40 patients used as controls in a patient self-testing study. These patients were already established on long-term warfarin and may not be representative of the patient population in the model.

The NICE Commissioning and benchmarking tool for Anticoagulation Therapy Services (119) use the assumption of 20 clinic visits per year. Freeman (2011)(81) reports 14 tests per year plus an additional 8 tests during the warfarin initiation phase, based on practice in the US.

In the NHS Clinical Knowledge summary for management of Oral Anticoagulation ((133)), people with atrial fibrillation are recommended to initiate warfarin therapy using a slow loading regimen, achieving therapeutic coagulation in the majority of people within 3-4 weeks. The summary recommends that during initiation of therapy the INR should be measured daily or on alternate days until warfarin is within therapeutic range on two consecutive occasions, then twice weekly for 1-2 weeks, followed by weekly measurements until the INR is stable within therapeutic range. These recommendations are based on *Guidelines on oral anticoagulation (warfarin): third edition — 2005 update*, published by the British Committee for Standards in Haematology(134), and are consistent with American evidence-based guidelines(135;136), guidance published by the National Institute of Health and Clinical Excellence(1), and the British National Formulary (March 2011)(118). In the model, based on the above recommendations, the number of INR monitoring visits during the initiation phase of warfarin therapy is approximated to 9 (assuming warfarin is initiated on a Monday - first visit, day 3 visit, day 5 visit, day 8 visit, day 11 visit, week 3 visit, week 4 visit, week 5 visit, week 9 visit).

Once the INR has stabilised, the number of physician visits may decrease, but due to the intrapatient variability of warfarin kinetics/dynamics and the influence of concomitant drugs and dietary factors on the INR, long-term INR monitoring and subsequent dose adjustment remains a necessity.

The number of visits in the subsequent cycles (i.e. after initiation) was assumed to be 5 visits, based on Anticoagulation Commissioning benchmarking tool(119) (most recent UK reference source from systematic review and validated for use within the NHS), which assumes 20 clinic appointments per patient per year.

In the model, when patients were re-initiated on therapy, it was assumed that the experience of the previous dose titration would expedite stabilisation of warfarin dose and INR, requiring fewer visits compared to initiation in warfarin-naïve patients, therefore 7 visits were assumed.

Resource use for warfarin monitoring is displayed in Table 63.

Table 63. Warfarin monitoring visits – resource use

Resource use element	Resource use/ Units (per cycle)	Source	Reference description
Therapy initiation phase (first three months for warfarin naïve)	9 visits	Based on recommendations for frequency of monitoring (see above for breakdown of visit timings)	NHS Clinical Knowledge Summary for Management of Oral Anticoagulation(133)
Course of anticoagulation therapy (subsequent visits, per three months cycles)	5 visits	NICE	NICE Anticoagulation Therapy Commissioning and Benchmarking Tool (NICE 2010) (119)
Course of anticoagulation therapy re-initiation	7 visits	Based on expedited stabilisation compared to warfarin naive patients	NHS Clinical Knowledge Summary for Management of Oral Anticoagulation(133)

GP = General practitioner, NICE = National Institute for Health and Clinical Excellence

Although rivaroxaban, dabigatran and aspirin are fixed-dose oral therapies that do not require any additional blood monitoring, it was assumed in the modelling analysis that patients incur the additional cost of one GP visit during therapy initiation only. The rationale for this was that patients were considered likely to receive regular clinical attention from their physicians, comparable to that of patients on warfarin (independent of INR monitoring) (Table 64).

Table 64. Oral anticoagulants/ aspirin monitoring visits – resource use

Resource use element	Resource use/ Units	Source	Reference description
Rivaroxaban	1 visit	Clinical opinion	Assume 1 GP visit – for therapy initiation
Aspirin	1 visit	Clinical opinion	Assume 1 GP visit – for therapy initiation
Dabigatran	1 visit	Clinical opinion	Assume 1 GP visit – for therapy initiation

GP = General practitioner

Annual Costs of Warfarin monitoring

Table 65 and Table 66 illustrate the annual cost of warfarin monitoring derived from the sources described above and in section 6.5.1. Monitoring costs during the first

year for warfarin naïve patients were higher due to the more intensive monitoring required when patients are first initiated on warfarin.

Table 65. Annual cost warfarin monitoring (first year, warfarin naïve patients)

Setting	Distribution of patients	Cost per visit (£)	Number of visits per year	Cost per year (£)
Primary care	66.45%	24.00 + 3.00 (1st visit) 24.00 + 3.00 (subsequent)	1 8 + 5*3 = 24	£448.54
Secondary care	33.55%	47.19 (1st visit) 24.69 (subsequent)	1 8 + 5*3 = 24	£214.64
TOTAL	£663.18			

Table 66. Annual cost warfarin monitoring (subsequent years)

Setting	Distribution of patients	Cost per visit (£)	Number of visits per year	Cost per year (£)
Primary care	66.45%	24.00 + 3.00	5*4 = 20	£358.83
Secondary care	33.55%	24.69	5*4 = 20	£165.67
TOTAL	£524.50			

Follow-on care for major stroke or intracranial bleeding

Subsequent to the first three months, a major stroke also incurred a cost associated with follow-on care for the rest of the patient's life at £1,206.50 per quarter. This was based on NICE Clinical Guideline CG92(124), which reported the yearly cost of stroke care in subsequent years following the index event (£4,826.00). This costing was selected from the systematic review as it presented a clear annualised costing which took into account the mix of patient dependency resulting after major stroke (38% dependent stroke and 62% independent stroke).

Follow-on care in patients who have experienced intracranial bleeding was assumed to be identical to the follow-on care for a major ischaemic stroke costing £1,206.50 per quarter for the rest of the patient's life, as the long-term neurological sequelae was considered to be similar between the two types of stroke.

Acute treatment and Follow-on care of myocardial infarction

The cost of a myocardial infarction was modelled using the acute treatment cost as reported in the NICE Clinical Guidance 48 (Cooper et al. 2007)(137), sourced from

the systematic review. This was the only MI treatment cost found during the systematic review.

Subsequent to the first three months, a myocardial infarction also incurred a cost associated with follow-on care for the rest of the patient's life at £140.88 per quarter. This was based on NICE Clinical Guideline 48 (Cooper et al. 2007)(137), which reported the yearly cost of MI care in subsequent years following the index event (£500.00). The costs of MI are reported in Table 67.

Table 67. Myocardial Infarction - costs

Cost element	Unit cost/cost per visit (£)	Cost source	Reference description
MI – acute treatment	5277.77*	National Institute for Health and Clinical Excellence & National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined	NICE CG48(137), Annual unit cost per patient £4,448 (inflated) + VC38Z Rehabilitation for acute myocardial infarction and other cardiac disorders
Follow-on care (per quarter	140.88*	National Institute for Health and Clinical Excellence	NICE CG48(137), Annual unit cost subsequent care per patient £500 (inflated)

* Inflated to 2010 prices

All model inputs concerning resource and unit costs were able to be populated using current PSSRU / NHS Reference costs (section 6.5.1) or data identified during the systematic review (this section) or from expert clinical opinion. Model inputs are further summarised in section 6.5.5 (Intervention and comparators costs) and section 6.5.6 (Health states).

If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

the criteria for selecting the experts
the number of experts approached
the number of experts who participated
declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
the background information provided and its consistency with the totality of the evidence provided in the submission

the method used to collect the opinions

the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)

the questions asked

whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two clinical experts were approached to provide validation on the model structure and values. The first was Dr. Gregory Lip from Birmingham University and the second was the in-house (Bayer) medical advisor (John Paolini). The first was selected as a leading clinical KOL who is widely published in atrial fibrillation in the UK. The second clinical expert was selected as being able to provide any insight that may be required specifically for rivaroxaban. No declaration of interest was sought from either participants.

With Dr Lip, the trial outputs were not yet available but the purpose of the economic model, the design of the economic model and the preliminary suggested input values were all presented via a webex. The clinical background was not presented as he was already familiar with the field and compound. With the Bayer in-house medical advisor, the structure and value of inputs suggested were presented at a face-to-face meeting.

In both cases, the suggested input values (number of rehabilitation days following major stroke and IC bleed) were presented and the experts were asked to agree or disagree and provide rationales for both. No iterations were performed, however, a second webex meeting did take place with Dr. Lip.

Intervention and comparators' costs

Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

The costs of the therapies included in the cost effectiveness analysis are presented in Table 68. These costs are presented as cost per 90-day cycle, and do not account for therapy discontinuation in any of the treatment arms.

Table 68. Unit costs associated with the technology in the economic model

Items	Rivaroxaban	Warfarin	Aspirin	Dabigatran (110mg/150mg)	Reference in Submission
Technology Cost	[redacted]	£0.12	£0.037	£2.52	6.5.1. – Table 50
Monitoring Cost	£36 on initiation	Primary: £24 for monitoring vist + £3 for INR testing Secondary: £47.19 for first visit, £24.69 for each subsequent visit	£36 on initiation	£36 on initiation	6.5.1. – Table 51
Total for initiation cycles	[redacted]	£254.44	£39.33	£262.80	
Total for maintenance cycles	[redacted]	£141.99	£3.33	£226.80	

Health-state costs

Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Table 69. Unit costs associated with the technology in the economic model (per cycle)

Health State	Health State	Cost (£)	
1	Anticoagulant initiation	Dependent on therapy	Table 68
2	Stable atrial fibrillation (on therapy)	Warfarin monitoring only	Table 68
3	Minor stroke (on therapy)	2,829.66	Section 6.5.1, Table 55
4	Major stroke (on therapy)	8,334.57	Section 6.5.1, Table 55
5	Post major stroke (on therapy)	1,206.50	Section 6.5.3
6	Minor bleed (on therapy)	126.34	Section 6.5.1, Table 59
7	Major bleed (on therapy)	866.00	Section 6.5.1, Table 59

Health State	Health State	Cost (£)	
8	Intracranial bleed (on therapy)	6397.87	Section 6.5.1, Table 60
9	Post intracranial bleed (on therapy)	1,206.50	Section 6.5.3
10	Systemic embolism (on therapy)	536.83	Section 6.5.1, Table 61
11	Stable atrial fibrillation (off therapy)		Section 6.5.1
12	Minor stroke (off therapy)	2,829.66	Section 6.5.1, Table 55
13	Major stroke (off therapy)	8,334.57	Section 6.5.1, Table 55
14	Minor bleed (off therapy)	126.34	Section 6.5.1, Table 59
15	Major bleed (off therapy)	866.00	Section 6.5.1, Table 59
16	Intracranial bleed (off therapy)	6397.87	Section 6.5.1, Table 60
17	Post intracranial bleed (off therapy)	1,206.50	Section 6.5.1, Table 60
18	Systemic embolism (off therapy)	536.83	Section 6.5.1, Table 61
19	MI (on or off therapy)	5277.77	Section 6.5.1, 6.5.3, Table 67
20	Post MI (on or off therapy)	140.88	Section 6.5.3, Table 67
21	Death (on or off therapy)	0.00	Section 6.5.1

Adverse-event costs

Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

It is assumed that all adverse events associated with the therapies examined are captured via the bleeding-related health states. Further details on the costs associated with these states are provided in Section 6.5.1 and 6.5.6.

Miscellaneous costs

Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

There are no additional costs in the model

Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The uncertainty around model structural assumptions were discussed with clinical and health economic experts when finalizing the model structure. Professor Martin Buxton from Brunel University reviewed the model assumptions at an early stage and provided comments on the overall methodology; at the same time the NICE Scientific Advice Consultancy Service reviewed the planned model and provided comments. At a later stage of development, Professor Bengt Jonsson reviewed the model structure, assumptions and techniques and provided his comments; These comments were taken into account for the finalisation of the model structure.

Alternative structures for capturing the consequences of stroke were considered, including a combined endpoint of ischaemic and haemorrhagic stroke, and systemic

embolism. Using weighted pay-offs for the combined endpoint yielded similar results, but found that there was not as much transparency in the description of endpoints.

Other structural assumptions such as time horizon and discount rates are tested in the one-way sensitivity analyses.

Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A range of one way sensitivity analyses were performed for the modelling analyses for this Single Technology Appraisal to consider the variation in the incremental cost, incremental benefit and incremental cost-effectiveness ratios (ICERs) outcomes when viable ranges of parameter values were independently considered. The parameters and ranges included within the one-way sensitivity analyses can be found in Table 70 for analyses where treatment effects were derived from the ROCKET AF trial. The rationale for the ranges tested are as follows:

- **Discounting**: A range of 0-6% was tested, in accordance with NICE guidance.
- **Efficacy parameters** (RR and baseline probabilities of events): Base case RR were adjusted based on 95% confidence intervals from the analysis of the ROCKET AF trial or the Network Meta Analysis (NMA) when available. Alternatively, point estimates were varied by ±25%, which was considered sufficient variation to capture relevant uncertainty.

  The relative risk of stroke by age group was not tested individually in the one-way sensitivity analysis, as these are relative to the reference (starting) age group of 70-74, which is included in the one-way sensitivity analysis.

- **Utility data**: Utility values were varied by ±25% when alternative estimates were not available from the literature. Variations in utility values were bounded between 0 and 1.
- **Drug costs**: Variations in drugs costs were derived from alternative pack sizes as reported by the BNF(118).
- **Other costs**: The interquartile ranges reported in the National Schedule of Reference costs were used where possible. If costs were from alternative sources they were varied by ±25%.

Table 70. Parameters tested in the one-way sensitivity analysis (trial based)

	Sensitivity Analysis	Base case values	Low estimate	High estimate	Source
1	Discount Rates - Benefits	3.50%	0.00%	6.00%	NICE guidelines(85)
2	Discount Rates - Costs	3.50%	0.00%	6.00%	NICE guidelines(85)
3	Discount Rates - Both	3.50%	0.00%	6.00%	NICE guidelines(85)
4	Baseline rate of stroke	[redacted]	[redacted]	[redacted]	Section 6.3.2
5	Stroke RR for Riva	[redacted]	[redacted]	[redacted]	Table 19, section 5.5.3
6	Stroke RR for Aspirin	1.61	1.22	2.08	Based on Hart 2007(138)
7	Minor Bleed Rate	[redacted]	[redacted]	[redacted]	ROCKET Health Economic analysis
8	Major Bleed Rate	[redacted]	[redacted]	[redacted]	ROCKET Health Economic analysis
9	IC Bleed Rate	[redacted]	[redacted]	[redacted]	ROCKET Health Economic analysis
10	Bleed RR for Riva	1	[redacted]	[redacted]	ROCKET Health Economic analysis
11	Bleed RR for Warfarin (fixed to 1 for trial based analysis)	1	1	1	
12	Bleed RR for ASA	0.59	0.30	1.16	Hart 2007(138)
13	IC Bleed RR for Riva	0.67	0.47	0.93	Section 5.9.1
14	IC Bleed RR for Warfarin	1	1	1	
15	IC Bleed RR for ASA	0.44	0.20	0.96	Hart 2007(138)
16	SE rate (warfarin)	0.05%	[redacted]	[redacted]	Section 5.5.3 & ROCKET Health Economic analysis
17	Probability of major stroke	0.59	0.42	0.63	Hylek 2003(139)
18	Case-fatality of major stroke	[redacted]	[redacted]	[redacted]	Section 6.3.2

	Sensitivity Analysis	Base case values	Low estimate	High estimate	Source
19	Case-fatality of major bleed	[redacted]	[redacted]	[redacted]	Section 6.3.2
20	Case-fatality of IC bleed	[redacted]	[redacted]	[redacted]	Section 6.3.2
21	Post-stroke mortality	2.6%	0.9%	13.5%	Section 6.3.2
22	Discontinuation Rate Riva	[redacted]	[redacted]	[redacted]	Section 6.3.2
23	Discontinuation Rate Warfarin	[redacted]	[redacted]	[redacted]	Section 6.3.2
24	Discontinuation Rate ASA	[redacted]	[redacted]	[redacted]	Section 6.3.2
25	Discontinuation Rate Dabigatran	[redacted]	[redacted]	[redacted]	Section 6.3.2
26	Subsequent Discontinuation Rate Riva	[redacted]	[redacted]	[redacted]	Section 6.3.2
27	Subsequent Discontinuation Rate Warfarin	[redacted]	[redacted]	[redacted]	Section 6.3.2
28	Subsequent Discontinuation Rate ASA	[redacted]	[redacted]	[redacted]	Section 6.3.2
29	Subsequent Discontinuation Rate Dabigatran	[redacted]	[redacted]	[redacted]	Section 6.3.2
30	Rivaroxaban Price	[redacted]	[redacted]	[redacted]	Bayer
31	Warfarin Price	£0.12	£0.06	£0.24	Mean value ± 50% variation
32	ASA Price	£0.016	£0.010	£0.03	BNF 61(118)
33	Warfarin Monitoring Cost - first	£47.19	£12.54	£50.90	NHS Reference Costs
34	Warfarin Monitoring Cost – follow up Secondary Care	£23.86	£13.39	£25.88	NHS Reference Costs
35	Stroke Acute Tx minor cost	£2,830	£2,133	£3,224	NHS Reference Costs
36	Stroke Acute Tx major cost	£2,830	£2,133	£3,224	NHS Reference Costs
37	Stroke Acute XS days cost	£211	£171	£251	NHS Reference Costs

	Sensitivity Analysis	Base case values	Low estimate	High estimate	Source
38	Stroke treatment cost - post	£1,207	£905	£1,508	NHS Reference Costs
39	XS days for stroke	25	0	18	Saka 2009(123)
40	Minor Bleed Tx cost	£126	£106	£144	NHS Reference Costs
41	Major Bleed Tx cost	£866	£628	£989	NHS Reference Costs
42	IC Bleed Tx Cost	£2,073	£1,520	£2,434	NHS Reference Costs
43	IC Bleed Tx Cost - post	£1,207	£905	£1,508	NHS Reference Costs
44	SE treatment Cost	£537	£302	£565	NHS Reference Costs
45	Warfarin dose	4.5	3.5	7.5	Assumption
46	Warfarin monitoring visits during maintenance	5	3	7	Assumption
47	Utility: Stable - not on therapy	0.78	0.69	1	UK Population norm, Kind 1999(112)
48	Utility Decrement: Stable on Warfarin Therapy	1.00	0.92	1.00	Kind 1999(112), Robinson 2001(100)
49	Utility: Stable - on other therapy	0.78	0.69	1.00	Assumed = not on therapy
50	Utility Decrement: Initiating Warfarin	1.00	0.92	1.00	Robinson 2001(100)
51	Utility: Minor Stroke	0.64	0.55	0.66	Robinson et al. 2001(100)
52	Utility: Post Minor Stroke	0.72	0.54	0.77	Hallan et al. 1999(96)
53	Utility: Major Stroke	0.19	0.14	0.24	Robinson et al. 2001(100)
54	Utility: Post Major Stroke	0.48	0.08	0.71	Hallan et al. 1999(96)
55	Utility: Systemic Embolism	0.66	0.66	0.69	Sullivan et al 2006(108)

	Sensitivity Analysis	Base case values	Low estimate	High estimate	Source
56	Utility: Minor Bleed	0.78	0.77	0.78	Sullivan et al 2006(108)
57	Utility: Major Bleed	0.60	0.57	0.63	Sullivan et al 2006(108)
58	Utility: Intracranial Bleed	0.60	0.02	1.00	Lenert & Soetikno 1997(109)
59	Utility: Post IC Bleed	0.74	0.08	0.77	Haacke 2006(95)
60	Other Therapy Monitoring Visits	1	0	2	Assumption
61	Cost of other monitoring	36	27	45	PSSRU 2010
62	% using PTS for warfarin clinics	9%	6%	11%	Assumption
63	MI base rate	[redacted]	[redacted]	[redacted]	ROCKET CSR
64	MI case fatality	[redacted]	[redacted]	[redacted]	Section 6.3.2
65	MI post-event mortality	2.7%	0.00%	6.75%	Hoit et al. 1986(93)
66	Minor Bleed RR for Warfarin	[redacted]	[redacted]	[redacted]	Section 5.9.1, Table 26
67	Time horizon	Lifetime	10	20	NICE guidelines(85)
68	Cost Warfarin Monitoring in Primary Care	27	5.75	48.75	Low CG36(17), high +25%
69	% Warfarin Monitoring in Primary Care	66.45%	0%	100%	Assumption

ASA = Aspirin, MI = myocardial infarction, IC = intracranial

For analyses based on parameters taken from the NMA, the list of variables included in one-way sensitivity analysis are shown in Table 71.

Table 71. Parameters tested in the one-way sensitivity analysis (NMA)

	Sensitivity Analysis	Base case values	Low estimate	High estimate	Source
1	Stroke Rate for warfarin	1.14%	0.86%	1.43%	AFI 1994(88)
2	Stroke RR for Riva	[redacted]	[redacted]	[redacted]	NMA
3	Stroke RR for Warfarin	[redacted]	[redacted]	[redacted]	NMA
4	Stroke RR for Aspirin	[redacted]	[redacted]	[redacted]	NMA
5	Minor Bleed Rate	0.61%	0.46%	0.76%	EAFT 1993(48)
6	Major Bleed Rate	0.12%	0.09%	0.14%	EAFT 1993(48)
7	IC Bleed Rate	0.03%	0.02%	0.04%	EAFT 1993(48)
8	Bleed RR for Riva	[redacted]	[redacted]	[redacted]	NMA
9	Bleed RR for Warfarin	[redacted]	[redacted]	[redacted]	NMA
10	Bleed RR for ASA	[redacted]	[redacted]	[redacted]	NMA
11	IC Bleed RR for Riva	[redacted]	[redacted]	[redacted]	NMA
12	IC Bleed RR for Warfarin	[redacted]	[redacted]	[redacted]	NMA
13	IC Bleed RR for ASA	[redacted]	[redacted]	[redacted]	NMA
14	SE rate (warfarin)	0.13%	0.09%	0.16%	AFI 1994(88)
15	MI RR for Warfarin (trial) ASA	[redacted]	[redacted]	[redacted]	NMA
16	MI base rate	0.49%	0.37%	0.62%	SAFT 2003(90)
17	Minor Bleed RR for Warfarin (trial) ASA	1.99	1.40	2.77	Hart 2007(138)

ASA = Aspirin, MI = myocardial infarction, IC = intracranial, NMA = network meta-analysis

Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analyses were conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. This was achieved through repeated sampling of mean parameter values from a series of assigned distribution types, based on the point estimates and the standard error statistics for each average parameter value.

Each set of samples from all the parameters generated a single estimate of expected costs, effects and net benefit generated by the model. The analyses were run over 1,000 iterations, so all the values the parameters are likely to take are represented in a range of outputs.

Table 72. PSA parameters and distributions – trial based analysis

Parameter name in the model	Definition	Distribution type	Source
PrStrokelowrisk	Probability of stroke - untreated low risk	LINKED	Linked to PrStrokemodrisk
PrStrokemodrisk	Pr of stroke - untreated mod risk	Beta	ROCKET data (Safety on Treatment analysis). Final Obj C table 35.
PrStrokehighrisk	Pr of stroke - untreated high risk	LINKED	Linked to PrStrokemodrisk
PrMajStroke	Pr that stroke is major	Beta	Hylek 2003(139)
PrMinStroke	Pr that stroke is minor	LINKED	Linked to PrMajStroke
RivaStrokeRR	RR for Rivaroxaban Tx	Log-normal	ROCKET (US PI, table 4). Upper and lower values are (95% CI) / Network Meta-analysis
WarfStrokeRR	RR for Warfarin Tx	Log-normal	ROCKET (US PI, table 4). Upper and lower values are (95% CI)/ Network Meta-analysis
ASAstrokeRR	RR for ASA Tx	Log-normal	Hart 2007(138) (converted from warf vs ASA RRR)/ Network Meta-analysis
PlacstrokeRR	RR for Placebo vs Warfarin	Log-normal	Network Meta-analysis
SEratelow	Pr of SE - untreated low risk	LINKED	Linked to SEratemod
SEratemod	Pr of SE - untreated mod risk	Beta	ROCKET Data (Safety on Treatment analysis). Final Obj C table 38.
SEratehigh	Pr of SE - untreated high risk	LINKED	Linked to SEratemod
RivaSERR	Systemic Embolism - RR for Rivaroxaban Tx	Log-normal	ROCKET (US PI, table 4). Upper and lower values are (95% CI)/ Network Meta-analysis
WarfSERR	Systemic Embolism - RR for Warfarin Tx	Log-normal	ROCKET (US PI, table 4). Upper and lower values are (95% CI)
ASAseRR	Systemic Embolism - RR for ASA Tx	Log-normal	Hart 2007(138) (converted from warf vs ASA RRR)

Parameter name in the model	Definition	Distribution type	Source
PlacSERR	Systemic Embolism - RR for Placebo vs Warfarin	Log-normal	Network Meta-analysis
Bleedminor	Pr of Minor EC Bleed - warfarin	Beta	ROCKET Data (Safety on Treatment analysis). Final Obj C table 45.
Bleedmajor	Pr of Major EC Bleed - warfarin	Beta	ROCKET Data (Safety on Treatment analysis). Final Obj C table 45.
BleedIC	Pr of IC Bleed - warfarin	Beta	ROCKET Data (Safety on Treatment analysis). Final Obj C table 47.
RivaBleedRR	Major bleed - RR for Rivaroxaban Tx	Log-normal	ROCKET (Final Obj C table 45.1). Upper and lower values are (95% CI)
WarfBleedRR	Major bleed - RR for Warfarin Tx	Log-normal	ROCKET (Final Obj C table 45.1). Upper and lower values are (95% CI)
ASABleedRR	Major bleed - RR for ASA Tx	Log-normal	Hart 2007(138) (converted from warf vs ASA RRR)
PlacBleedRR	Major bleed - RR for Placebo vs Warfarin	Log-normal	Network Meta-analysis
RivaICRR	IC bleed - RR for Rivaroxaban Tx	Log-normal	ROCKET (primary publication, table 2). Upper and lower values are (95% CI)
WarfICRR	IC bleed - RR for Warfarin Tx	Log-normal	ROCKET (primary publication, table 2). Upper and lower values are (95% CI)
ASAICRR	IC bleed - RR for ASA Tx	Log-normal	Hart 2007(138) (converted from warf vs ASA RRR)
PlacICRR	IC bleed - RR fo Placebo vs Warfarin	Log-normal	Network Meta-analysis
Strokedeath	Case-fatality of major stroke	Beta	Baseline from ROCKET Safety on treatment analysis, from both arms
Minorstrokedeath	Case-fatality of minor stroke	LINKED	Linked to Strokedeath
PostStrokeDeath	Post-major stroke mortality rate	Beta	Marini et al 2005(92)
PostMinorStrokeDeath	Post-minor stroke moratlity rate	LINKED	Linked to PostStrokeDeath
BleedDeath	Case-fatality of major bleed	Beta	Baseline data from ROCKET Safety on treatment analysis, from both arms

Parameter name in the model	Definition	Distribution type	Source
ICDeath	Case-fatality of IC bleed	Beta	Baseline data from ROCKET Safety on treatment analysis, from both arms
PostICDeath	Post-IC bleed mortality rate	Beta	Same as ischaemic stroke
DiscontinueRiva	Discontinuation Rate Rivaroxaban - initial	Beta	ROCKET data - Riv 3 months
DiscontinueWarf	Discontinuation Rate Warfarin - initial	Beta	ROCKET data - Warfarin 3 months
DiscontinueASA	Discontinuation Rate Aspirin - initial	Beta	Base case from Gallagher et al. 2008(13). Upper value based on discontinuation at 1 year (in Gallagher et al., 2008)
DiscontinueTrialWarf	Discontinuation Rate Warfarin (TRIAL) - initial	Beta	ROCKET data - Warfarin 3 months
Discontinue2Riva	Discontinuation Rate Rivaroxaban - subsequent	Beta	ROCKET data - Riv subseq
Discontinue2Warf	Discontinuation Rate Warfarin - subsequent	Beta	ROCKET data - Warf subseq
Discontinue2ASA	Discontinuation Rate Aspirin - subsequent	Beta	Base case from Gallagher et al. 2008(13). Upper value based on discontinuation at 1 year (in Gallagher et al. 2008(13))
Discontinue2TrialWarf	Discontinuation Rate Warfarin (TRIAL) - subsequent	Beta	ROCKET data - Warfarin 3 months
CHADS1	RR compared to CHADS 2 - CHADS 1	Log-Normal	Gage 2001(15)
CHADS3	RR compared to CHADS 2 - CHADS 3+	Log-Normal	Gage 2001(15)
WarfMoniCostUK	Cost Warfarin Monitoring Visit (first ever)	Gamma	NHS Reference Costs 09-10
WarfMoniCost2UK	Cost Warfarin Monitoring Visit (subsequent - weighted for Hybrid)	Gamma	NHS Reference Costs 09-10
WarfMoniCostGPUK	Cost GP-based warfarin monitoring	Gamma	Assume ±25% variation from baseline
OACmonitor	Cost Check-ups for other therapy	Gamma	Assume ±25% variation from baseline

Parameter name in the model	Definition	Distribution type	Source
PostSTrokeCost	Cost stroke Follow-on Care (per quarter)	Gamma	Assume ±25% variation from baseline
PostICcost	Cost IC Bleed Follow-on Care (per quarter)	Gamma	Assume ±25% variation from baseline
PrPTS	% Taking NHS Transport	Beta	pH associates Service evaluation(140)
warfdoseUK	Warfarin Daily Dose (mg)	Gamma	Assume ±25% variation from baseline
Aspdose	Aspirin Daily Dose (mg)	Gamma	Assume ±50% variation from baseline
maintmonitorvisit	Weighted number of visits during maintenance phase	Gamma	Assumption
reinitiatevisit	Number of visits for warfarin re-initiation	Gamma	Derived
Strokexsdays	Excess days for major stroke	Gamma	Assumption
UtilityOffTx	Utility Stable - not on therapy	Beta	UK Population norm, Kind 1999(112)
UtilityonTx	Utility Stable - on therapy	Beta	Assumed = not on therapy
Utilityminstroke	Utility Minor Stroke	Beta	Robinson et al. 2001(100)
Utilitypostminstroke	Utility Post Minor Stroke	Beta	Hallan et al. 1999(96)
Utilitymajstroke	Utility Major Stroke	Beta	Robinson et al. 2001(100)
Utilitypostmajstroke	Utility Post Major Stroke	Beta	Hallan et al. 1999(96)
UtilitySE	Utility Systemic Embolism	Beta	Sullivan et al. 2006(108)
Utilityminbleed	Utility Minor Bleed	Beta	Sullivan et al. 2006(108)
Utilitymajbleed	Utility Major Bleed	Beta	Sullivan et al. 2006(108) Value from Robinson et al. 2001(100) (0.841) not used as this is greater than the value used for stable patients on therapy (0.78).
UtilityIC	Utility Intracranial Bleed	Beta	Lenert & Soetikno 1997(109)
UtilitypostIC	Utility Post IC Bleed	Beta	Haacke et al. 2006(95)
PrMI	Untreated risk of MI	Beta	Based on US PI table 4 (also in table 31 from CSR), safety on treatment analysis

Parameter name in the model	Definition	Distribution type	Source
Mideath	Case fatality rate of MI	Beta	ROCKET Safety on treatment analysis, from both arms
PostMIDeath	Post MI mortality rate	Beta	Hoit et al. 1986(93). Post-discharge mortality. Base is for middle aged patients, upper value is for elderly patients. Lower value is set to 0 because of the high uncertainty around these values.
RivaMIRR	RR for Rivaroxaban Tx	Log-normal	ROCKET (US PI, table 4). Upper and lower values are (95% CI)
WarfMIRR	RR for Warfarin Tx	Log-normal	ROCKET (US PI, table 4). Upper and lower values are (95% CI)
ASAMIRR	RR for ASA Tx	Log-normal	Connolly et al. 2009(62)
PlacMIRR	RR for Placebo vs Warfarin	Log-normal	Network Meta-analysis
RivaBleedMinRR	RR for Rivaroxaban Tx	Log-normal	ROCKET (primary publication, table 2). Upper and lower values are (95% CI)
WarfBleedMinRR	RR for Warfarin Tx	Log-normal	Hart et al. 2007(138)
ASABleedMinRR	RR for ASA Tx	Log-normal	Aguilar & Hart 2005(141)
PlacBleedMinRR	RR for Placebo vs Warfarin	Log-normal	Network Meta-analysis

Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 73. Summary of model results compared with clinical data

Outcome	Rivaroxaban		Warfarin	
	Clinical trial result (SoT) Rate per 100 person years	Model events per year for cohort of 100*	Clinical trial result (SoT) Rate per 100 person years	Model events per year for cohort of 100*
Mortality	1.87	3.34	2.21	3.41
Ischaemic Stroke	1.34	1.27	1.42	1.27
MI	0.91	0.84	1.12	0.84
SE	0.04	0.08	0.19	0.19
Total Bleeds	14.9	12.9	14.5	13.1

*Based on two-year model run to approximately match ROCKET median follow-up time; model uses statistically significantly different relative risks only.

Mortality rates in the model were higher than in the trial, due to the inclusion of UK general mortality in the model. We note that the UK general mortality at age 73 is 3.4% for males and 2.2% for females per year, suggesting that observed trial mortality (1.87-2.21 per 100) may understate mortality likely in an unselected population with AF.

Overall mortality was 0.34 per 100 person years lower in the rivaroxaban arm than in the warfarin arm in the trial. In the model overall mortality was only 0.07 per 100 person years lower in the rivaroxaban arm compared to the warfarin arm. Although the study found lower mortality with rivaroxaban than with warfarin, the difference did not achieve statistical significance. General mortality was therefore set to be equal in the two arms in the model and the remaining mortality differences in the model result from differences between arms in stroke and bleeding events.

Ischaemic stroke and MI event rates were slightly lower in the model compared to the study. For both cases these events differences between groups did not achieve statistical significance in the trial and these events are modelled as having equal risk in both arms. The study reports events per 100 patient years of exposure: the model reports events per year for 100 patients starting therapy. Events in the model should therefore be slightly lower as patients die and the number at risk declines.

Bleeding events occurred in fewer patients in the model than in the trial. In addition to reduced patient exposure, the model did not capture minor bleeds that might occur in patients who experienced other, more severe, events. This simplification was introduced to prevent a minor bleed event leading to a change in pathway for a

patient who would otherwise remain in a post stroke or post IC bleed state. As a consequence the model has slightly understated the number of these events.

In the trial, bleeding events occurred slightly more frequently in the rivaroxaban arm than the warfarin arm. However this was not statistically significant. The only significant difference in bleeding included in the model was in the rate of IC bleeding, which favoured rivaroxaban, As the model considers only significant differences, the overall bleed rate in the model slightly favour rivaroxaban.

Systemic embolism rates in treated patients are very low and in the model these events are influenced by relatively high risk in a small number of patients who have discontinued studied therapy.

Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 74 shows the proportion of the model cohort occupying each aggregated health state per year for the intervention and the comparator arm. The health states, which have been aggregated to represent major clinical outcomes, comprise the following health states:

- Total Strokes = Major stroke + minor stroke + Major stroke (untreated) + minor stroke (untreated)
- Total Bleeds = Major bleed + minor bleed + IC bleed + Major bleed (untreated) + minor bleed (untreated) + IC bleed (untreated)
- Total MI = Myocardial infarction
- Total SE = Systemic embolism + systemic embolism (untreated)

Table 74. Proportion of the cohort per health state over time, per treatment arm

Year	Total Strokes rivaroxaban	Total Bleeds rivaroxaban	Total MI rivaroxaban	Total SE rivaroxaban	Total Strokes warfarin	Total Bleeds warfarin	Total MI warfarin	Total SE warfarin
1	0.0143	0.1379	0.0101	0.0006	0.0143	0.1402	0.0102	0.0019
2	0.0149	0.1208	0.0089	0.0010	0.0148	0.1224	0.0089	0.0019
3	0.0172	0.1081	0.0080	0.0013	0.0172	0.1091	0.0080	0.0022
4	0.0171	0.0971	0.0073	0.0014	0.0170	0.0978	0.0073	0.0021
5	0.0166	0.0876	0.0067	0.0014	0.0165	0.0880	0.0067	0.0020
6	0.0159	0.0791	0.0062	0.0014	0.0158	0.0793	0.0061	0.0019
7	0.0151	0.0714	0.0057	0.0014	0.0150	0.0715	0.0057	0.0018
8	0.0158	0.0643	0.0052	0.0014	0.0157	0.0644	0.0052	0.0018
9	0.0147	0.0577	0.0048	0.0013	0.0146	0.0576	0.0048	0.0017
10	0.0135	0.0514	0.0044	0.0012	0.0134	0.0514	0.0044	0.0015
11	0.0123	0.0456	0.0040	0.0011	0.0122	0.0456	0.0040	0.0014
12	0.0110	0.0402	0.0036	0.0010	0.0109	0.0401	0.0036	0.0012
13	0.0114	0.0351	0.0033	0.0010	0.0113	0.0350	0.0032	0.0012
14	0.0100	0.0304	0.0029	0.0009	0.0099	0.0303	0.0029	0.0011
15	0.0088	0.0260	0.0026	0.0008	0.0087	0.0259	0.0025	0.0009
16	0.0075	0.0219	0.0022	0.0006	0.0074	0.0219	0.0022	0.0008
17	0.0063	0.0182	0.0019	0.0005	0.0063	0.0181	0.0019	0.0006
18	0.0061	0.0149	0.0016	0.0005	0.0060	0.0148	0.0016	0.0006
19	0.0050	0.0120	0.0013	0.0004	0.0050	0.0120	0.0013	0.0005

Year	Total Strokes rivaroxaban	Total Bleeds rivaroxaban	Total MI rivaroxaban	Total SE rivaroxaban	Total Strokes warfarin	Total Bleeds warfarin	Total MI warfarin	Total SE warfarin
20	0.0041	0.0095	0.0011	0.0003	0.0040	0.0095	0.0011	0.0004
21	0.0032	0.0074	0.0009	0.0003	0.0032	0.0074	0.0009	0.0003
22	0.0025	0.0057	0.0007	0.0002	0.0025	0.0057	0.0007	0.0002
23	0.0019	0.0043	0.0005	0.0001	0.0019	0.0043	0.0005	0.0002
24	0.0014	0.0032	0.0004	0.0001	0.0014	0.0031	0.0004	0.0001
25	0.0011	0.0023	0.0003	0.0001	0.0010	0.0023	0.0003	0.0001
26	0.0008	0.0016	0.0002	0.0001	0.0007	0.0016	0.0002	0.0001
27	0.0005	0.0011	0.0002	0.0000	0.0005	0.0011	0.0002	0.0000
28	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
29	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
30	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

MI = Myocardial infarction, IC = Intracranial, SE = Systemic embolism

Table 75, Figure 19, Table 76 and Figure 20 illustrate the Markov traces for 73-year old patients treated with rivaroxaban or warfarin.

Table 75. Markov trace: rivaroxaban patients 73 years of age

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15	HS16	HS17	HS18	HS19	HS20	HS21	HS22
0	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.0309	0.7004	0.0013	0.0014	0.0050	0.0047	0.0218	0.0051	0.0009	0.0016	0.0001	0.1808	0.0005	0.0005	0.0037	0.0009	0.0002	0.0005	0.0001	0.0024	0.0067	0.0309
2	0.0275	0.5613	0.0010	0.0012	0.0115	0.0103	0.0175	0.0041	0.0008	0.0030	0.0001	0.2703	0.0007	0.0008	0.0052	0.0012	0.0002	0.0011	0.0002	0.0021	0.0133	0.0667
3	0.0246	0.4555	0.0010	0.0011	0.0184	0.0158	0.0142	0.0033	0.0007	0.0040	0.0001	0.3237	0.0010	0.0011	0.0061	0.0014	0.0003	0.0017	0.0003	0.0019	0.0180	0.1057
4	0.0222	0.3750	0.0009	0.0010	0.0250	0.0205	0.0117	0.0027	0.0006	0.0045	0.0000	0.3516	0.0011	0.0012	0.0066	0.0015	0.0003	0.0023	0.0003	0.0018	0.0212	0.1479
5	0.0200	0.3128	0.0008	0.0009	0.0308	0.0241	0.0097	0.0023	0.0005	0.0048	0.0000	0.3613	0.0012	0.0013	0.0067	0.0016	0.0003	0.0028	0.0003	0.0016	0.0233	0.1929
6	0.0180	0.2640	0.0007	0.0008	0.0357	0.0268	0.0082	0.0019	0.0004	0.0050	0.0000	0.3578	0.0012	0.0013	0.0066	0.0015	0.0003	0.0031	0.0003	0.0015	0.0245	0.2402
7	0.0163	0.2251	0.0006	0.0007	0.0397	0.0285	0.0070	0.0016	0.0004	0.0049	0.0000	0.3454	0.0011	0.0012	0.0064	0.0015	0.0003	0.0034	0.0003	0.0014	0.0250	0.2891
8	0.0146	0.1930	0.0006	0.0007	0.0432	0.0299	0.0060	0.0014	0.0004	0.0048	0.0000	0.3258	0.0012	0.0013	0.0060	0.0014	0.0003	0.0035	0.0003	0.0013	0.0248	0.3395
9	0.0131	0.1662	0.0006	0.0006	0.0458	0.0305	0.0052	0.0012	0.0003	0.0046	0.0000	0.3022	0.0011	0.0012	0.0056	0.0013	0.0003	0.0036	0.0003	0.0012	0.0241	0.3911
10	0.0116	0.1434	0.0005	0.0006	0.0472	0.0304	0.0045	0.0010	0.0003	0.0043	0.0000	0.2763	0.0010	0.0011	0.0051	0.0012	0.0002	0.0036	0.0003	0.0011	0.0231	0.4431
11	0.0103	0.1238	0.0005	0.0005	0.0476	0.0295	0.0039	0.0009	0.0003	0.0040	0.0000	0.2494	0.0009	0.0010	0.0046	0.0011	0.0002	0.0034	0.0002	0.0010	0.0218	0.4951
12	0.0090	0.1066	0.0004	0.0005	0.0471	0.0280	0.0033	0.0008	0.0003	0.0037	0.0000	0.2222	0.0008	0.0009	0.0041	0.0009	0.0002	0.0033	0.0002	0.0009	0.0203	0.5465
13	0.0078	0.0914	0.0005	0.0005	0.0461	0.0267	0.0028	0.0007	0.0002	0.0034	0.0000	0.1953	0.0008	0.0009	0.0036	0.0008	0.0002	0.0030	0.0002	0.0008	0.0186	0.5955
14	0.0068	0.0778	0.0004	0.0005	0.0444	0.0249	0.0024	0.0006	0.0002	0.0030	0.0000	0.1695	0.0007	0.0008	0.0031	0.0007	0.0002	0.0028	0.0002	0.0007	0.0168	0.6435
15	0.0057	0.0657	0.0004	0.0004	0.0419	0.0228	0.0020	0.0005	0.0002	0.0027	0.0000	0.1452	0.0006	0.0007	0.0027	0.0006	0.0001	0.0025	0.0002	0.0006	0.0150	0.6894
16	0.0048	0.0546	0.0003	0.0004	0.0385	0.0203	0.0017	0.0004	0.0002	0.0024	0.0000	0.1219	0.0005	0.0006	0.0022	0.0005	0.0001	0.0022	0.0001	0.0005	0.0131	0.7346
17	0.0040	0.0448	0.0003	0.0003	0.0347	0.0177	0.0014	0.0003	0.0001	0.0020	0.0000	0.1009	0.0004	0.0005	0.0019	0.0004	0.0001	0.0019	0.0001	0.0004	0.0113	0.7765
18	0.0032	0.0363	0.0003	0.0003	0.0309	0.0154	0.0011	0.0003	0.0001	0.0017	0.0000	0.0821	0.0004	0.0005	0.0015	0.0003	0.0001	0.0016	0.0001	0.0004	0.0095	0.8138
19	0.0026	0.0289	0.0002	0.0002	0.0270	0.0132	0.0009	0.0002	0.0001	0.0014	0.0000	0.0657	0.0003	0.0004	0.0012	0.0003	0.0001	0.0013	0.0001	0.0003	0.0079	0.8476
20	0.0020	0.0227	0.0002	0.0002	0.0231	0.0110	0.0007	0.0002	0.0001	0.0012	0.0000	0.0517	0.0003	0.0003	0.0009	0.0002	0.0000	0.0010	0.0001	0.0003	0.0065	0.8773
21	0.0016	0.0176	0.0001	0.0002	0.0193	0.0090	0.0005	0.0001	0.0001	0.0009	0.0000	0.0400	0.0002	0.0002	0.0007	0.0002	0.0000	0.0008	0.0001	0.0002	0.0052	0.9029
22	0.0012	0.0133	0.0001	0.0001	0.0158	0.0072	0.0004	0.0001	0.0000	0.0008	0.0000	0.0304	0.0002	0.0002	0.0006	0.0001	0.0000	0.0006	0.0000	0.0002	0.0041	0.9245
23	0.0009	0.0099	0.0001	0.0001	0.0127	0.0056	0.0003	0.0001	0.0000	0.0006	0.0000	0.0227	0.0001	0.0001	0.0004	0.0001	0.0000	0.0005	0.0000	0.0001	0.0032	0.9425
24	0.0006	0.0073	0.0001	0.0001	0.0099	0.0042	0.0002	0.0001	0.0000	0.0004	0.0000	0.0166	0.0001	0.0001	0.0003	0.0001	0.0000	0.0004	0.0000	0.0001	0.0024	0.9570
25	0.0005	0.0052	0.0001	0.0001	0.0076	0.0032	0.0002	0.0000	0.0000	0.0003	0.0000	0.0119	0.0001	0.0001	0.0002	0.0001	0.0000	0.0003	0.0000	0.0001	0.0018	0.9686
26	0.0003	0.0036	0.0000	0.0000	0.0056	0.0023	0.0001	0.0000	0.0000	0.0002	0.0000	0.0083	0.0000	0.0000	0.0002	0.0000	0.0000	0.0002	0.0000	0.0000	0.0013	0.9775
27	0.0002	0.0025	0.0000	0.0000	0.0042	0.0016	0.0001	0.0000	0.0000	0.0002	0.0000	0.0058	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0009	0.9840
28	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
29	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
30	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

HS1: Anticoagulant initiation; HS2: Stable AF treated; HS3: Minor Stroke; HS4: Major Stroke; HS5: Post-minor stroke on treatment; HS6: Post-major stroke on treatment; HS7: Minor bleed; HS8: Major bleed; HS9: IC bleed; HS10: Post-IC bleed ; HS11: Systemic embolism; HS12: Stable AF untreated; HS13: Minor stroke untreated; HS14: Major stroke untreated; HS15: Minor bleed untreated; HS16: Major bleed untreated; HS17: IC bleed untreated; HS18: Post IC bleed untreated; HS19: Systemic embolism untreated; HS20: Myocardial infarction HS21: Post myocardial infarction; HS22: Death

Figure 19. Markov trace: rivaroxaban patients 73 years of age

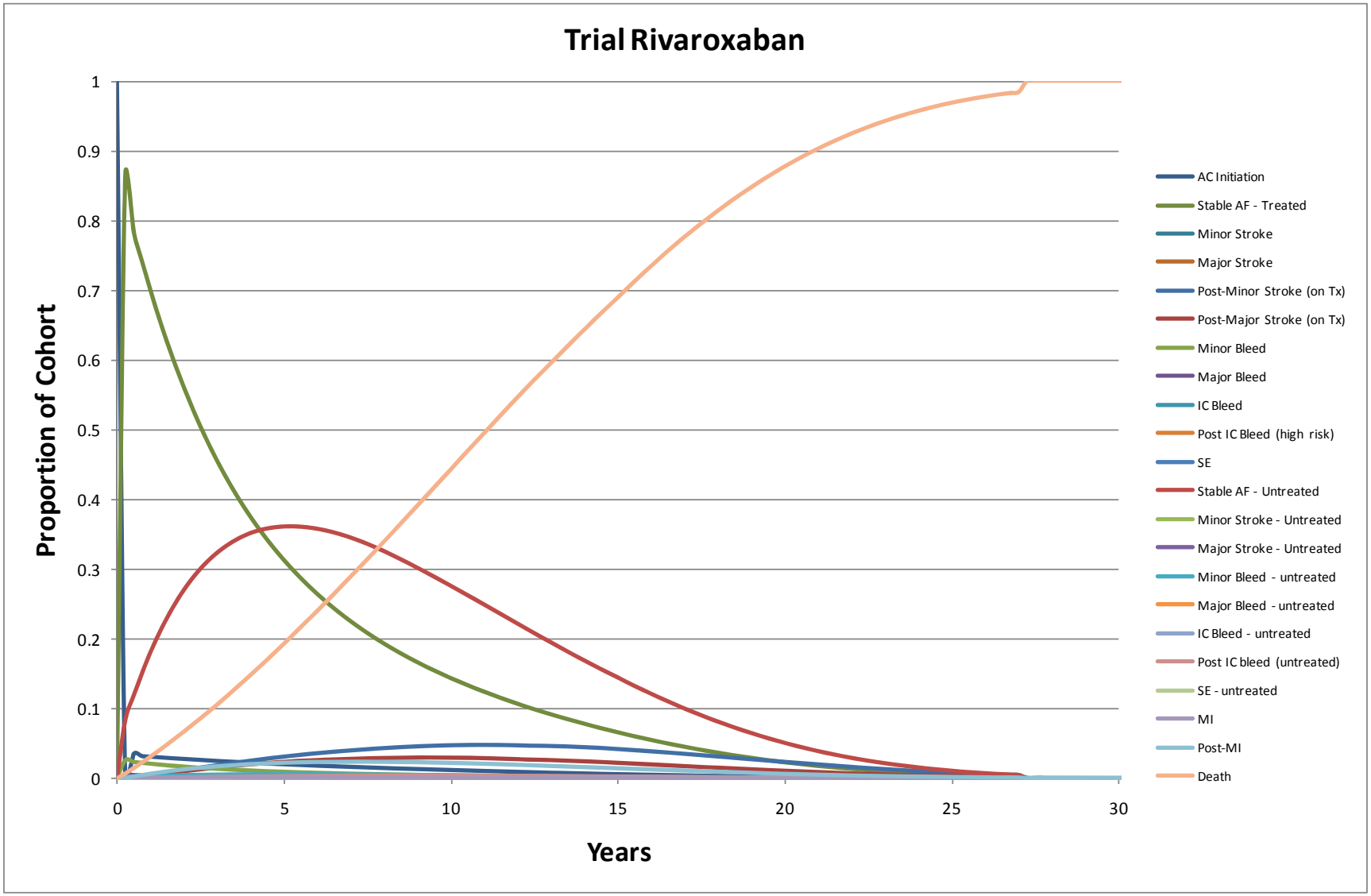
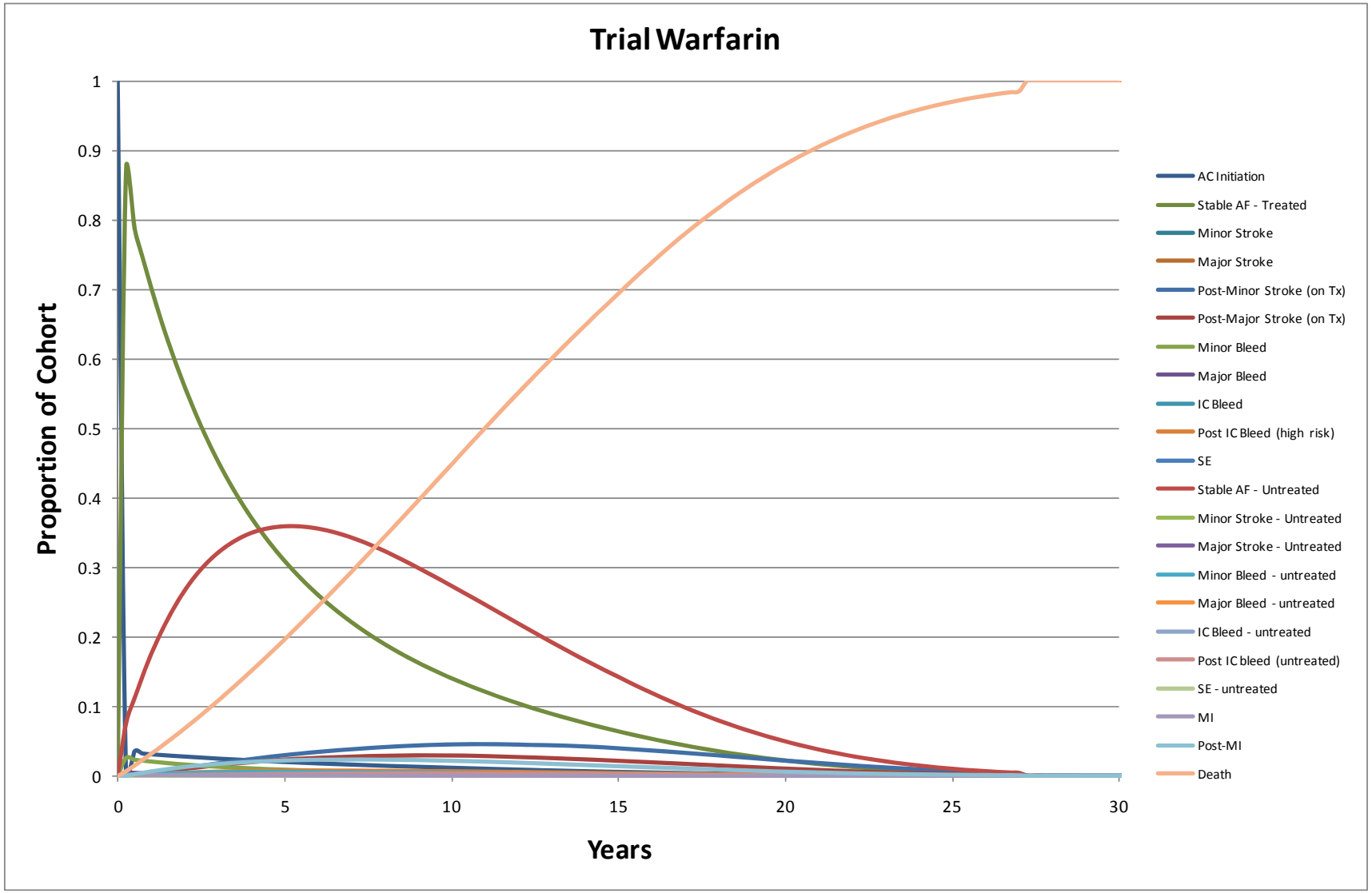


Table 76. Markov trace: warfarin patients 73 years of age

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15	HS16	HS17	HS18	HS19	HS20	HS21	HS22
0	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.0311	0.7036	0.0013	0.0014	0.0050	0.0047	0.0219	0.0051	0.0014	0.0024	0.0004	0.1749	0.0005	0.0005	0.0036	0.0008	0.0002	0.0006	0.0001	0.0024	0.0067	0.0316
2	0.0276	0.5613	0.0011	0.0012	0.0114	0.0102	0.0175	0.0041	0.0012	0.0046	0.0003	0.2664	0.0007	0.0008	0.0051	0.0012	0.0003	0.0014	0.0002	0.0021	0.0133	0.0682
3	0.0247	0.4537	0.0010	0.0011	0.0183	0.0157	0.0141	0.0033	0.0010	0.0060	0.0003	0.3208	0.0010	0.0011	0.0061	0.0014	0.0003	0.0021	0.0003	0.0019	0.0179	0.1079
4	0.0222	0.3721	0.0009	0.0010	0.0248	0.0203	0.0116	0.0027	0.0008	0.0068	0.0002	0.3492	0.0011	0.0012	0.0065	0.0015	0.0003	0.0027	0.0003	0.0018	0.0212	0.1507
5	0.0199	0.3094	0.0008	0.0009	0.0305	0.0239	0.0096	0.0022	0.0007	0.0072	0.0002	0.3589	0.0012	0.0013	0.0067	0.0015	0.0003	0.0032	0.0003	0.0016	0.0232	0.1962
6	0.0180	0.2605	0.0007	0.0008	0.0354	0.0265	0.0081	0.0019	0.0007	0.0074	0.0001	0.3555	0.0012	0.0013	0.0066	0.0015	0.0003	0.0036	0.0003	0.0015	0.0243	0.2440
7	0.0162	0.2216	0.0006	0.0007	0.0392	0.0282	0.0069	0.0016	0.0006	0.0073	0.0001	0.3429	0.0011	0.0012	0.0063	0.0015	0.0003	0.0039	0.0003	0.0014	0.0247	0.2932
8	0.0145	0.1896	0.0006	0.0007	0.0426	0.0296	0.0059	0.0014	0.0005	0.0071	0.0001	0.3232	0.0012	0.0013	0.0059	0.0014	0.0003	0.0040	0.0003	0.0013	0.0245	0.3439
9	0.0130	0.1631	0.0006	0.0006	0.0451	0.0301	0.0051	0.0012	0.0005	0.0068	0.0001	0.2995	0.0011	0.0012	0.0055	0.0013	0.0003	0.0040	0.0003	0.0012	0.0238	0.3956
10	0.0115	0.1406	0.0005	0.0006	0.0465	0.0299	0.0044	0.0010	0.0005	0.0064	0.0001	0.2736	0.0010	0.0011	0.0050	0.0012	0.0002	0.0040	0.0003	0.0011	0.0228	0.4478
11	0.0102	0.1212	0.0005	0.0005	0.0468	0.0290	0.0038	0.0009	0.0004	0.0059	0.0001	0.2467	0.0009	0.0010	0.0045	0.0011	0.0002	0.0038	0.0002	0.0010	0.0215	0.4997
12	0.0089	0.1043	0.0004	0.0005	0.0462	0.0276	0.0033	0.0008	0.0004	0.0054	0.0001	0.2197	0.0008	0.0009	0.0040	0.0009	0.0002	0.0036	0.0002	0.0009	0.0199	0.5511
13	0.0078	0.0893	0.0005	0.0005	0.0452	0.0262	0.0028	0.0006	0.0003	0.0049	0.0001	0.1929	0.0008	0.0009	0.0035	0.0008	0.0002	0.0033	0.0002	0.0008	0.0183	0.5999
14	0.0067	0.0760	0.0004	0.0005	0.0435	0.0245	0.0024	0.0006	0.0003	0.0044	0.0001	0.1672	0.0007	0.0008	0.0031	0.0007	0.0002	0.0030	0.0002	0.0007	0.0165	0.6477
15	0.0057	0.0641	0.0004	0.0004	0.0410	0.0224	0.0020	0.0005	0.0003	0.0039	0.0000	0.1432	0.0006	0.0007	0.0026	0.0006	0.0001	0.0027	0.0002	0.0006	0.0147	0.6933
16	0.0047	0.0532	0.0003	0.0003	0.0376	0.0199	0.0017	0.0004	0.0002	0.0034	0.0000	0.1201	0.0005	0.0006	0.0022	0.0005	0.0001	0.0024	0.0001	0.0005	0.0128	0.7383
17	0.0039	0.0436	0.0003	0.0003	0.0338	0.0173	0.0014	0.0003	0.0002	0.0030	0.0000	0.0993	0.0004	0.0005	0.0018	0.0004	0.0001	0.0020	0.0001	0.0004	0.0110	0.7797
18	0.0032	0.0353	0.0003	0.0003	0.0301	0.0151	0.0011	0.0003	0.0002	0.0025	0.0000	0.0807	0.0004	0.0004	0.0015	0.0003	0.0001	0.0017	0.0001	0.0004	0.0093	0.8167
19	0.0025	0.0282	0.0002	0.0002	0.0263	0.0129	0.0009	0.0002	0.0001	0.0021	0.0000	0.0645	0.0003	0.0004	0.0012	0.0003	0.0001	0.0014	0.0001	0.0003	0.0077	0.8501
20	0.0020	0.0221	0.0002	0.0002	0.0224	0.0107	0.0007	0.0002	0.0001	0.0017	0.0000	0.0508	0.0003	0.0003	0.0009	0.0002	0.0000	0.0011	0.0001	0.0002	0.0063	0.8794
21	0.0015	0.0171	0.0001	0.0002	0.0187	0.0087	0.0005	0.0001	0.0001	0.0014	0.0000	0.0392	0.0002	0.0002	0.0007	0.0002	0.0000	0.0009	0.0001	0.0002	0.0051	0.9047
22	0.0012	0.0129	0.0001	0.0001	0.0153	0.0070	0.0004	0.0001	0.0001	0.0011	0.0000	0.0298	0.0002	0.0002	0.0005	0.0001	0.0000	0.0007	0.0000	0.0002	0.0040	0.9260
23	0.0009	0.0096	0.0001	0.0001	0.0122	0.0054	0.0003	0.0001	0.0001	0.0008	0.0000	0.0222	0.0001	0.0001	0.0004	0.0001	0.0000	0.0005	0.0000	0.0001	0.0031	0.9437
24	0.0006	0.0070	0.0001	0.0001	0.0096	0.0041	0.0002	0.0001	0.0000	0.0006	0.0000	0.0162	0.0001	0.0001	0.0003	0.0001	0.0000	0.0004	0.0000	0.0001	0.0023	0.9579
25	0.0005	0.0050	0.0000	0.0001	0.0073	0.0031	0.0002	0.0000	0.0000	0.0005	0.0000	0.0116	0.0001	0.0001	0.0002	0.0000	0.0000	0.0003	0.0000	0.0001	0.0017	0.9693
26	0.0003	0.0035	0.0000	0.0000	0.0054	0.0022	0.0001	0.0000	0.0000	0.0003	0.0000	0.0081	0.0000	0.0000	0.0001	0.0000	0.0000	0.0002	0.0000	0.0000	0.0012	0.9780
27	0.0002	0.0024	0.0000	0.0000	0.0040	0.0016	0.0001	0.0000	0.0000	0.0003	0.0000	0.0056	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0009	0.9844
28	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
29	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
30	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

HS1: Anticoagulant initiation; HS2: Stable AF treated; HS3: Minor Stroke; HS4: Major Stroke; HS5: Post-minor stroke on treatment; HS6: Post-major stroke on treatment; HS7: Minor bleed; HS8: Major bleed; HS9: IC bleed; HS10: Post-IC bleed; HS11: Systemic embolism; HS12: Stable AF untreated; HS13: Minor stroke untreated; HS14: Major stroke untreated; HS15: Minor bleed untreated; HS16: Major bleed untreated; HS17: IC bleed untreated; HS18: Post IC bleed untreated; HS19: Systemic embolism untreated; HS20: Myocardial infarction HS21: Post myocardial infarction; HS22: Death

Figure 20. Markov trace: warfarin patients 73 years of age



Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The table below shows the cumulative QALYs for the two treatments arms analysed

Table 77. QALY accrued over time: rivaroxaban

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15	HS16	HS17	HS18	HS19	HS20	HS21	HS22
0	0.1948	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.0060	0.1364	0.0002	0.0001	0.0009	0.0006	0.0042	0.0008	0.0001	0.0003	0.0000	0.0352	0.0001	0.0000	0.0007	0.0001	0.0000	0.0001	0.0000	0.0004	0.0011	0.0000
2	0.0054	0.1093	0.0002	0.0001	0.0021	0.0012	0.0034	0.0006	0.0001	0.0006	0.0000	0.0526	0.0001	0.0000	0.0010	0.0002	0.0000	0.0002	0.0000	0.0003	0.0023	0.0000
3	0.0048	0.0887	0.0002	0.0001	0.0033	0.0019	0.0027	0.0005	0.0001	0.0007	0.0000	0.0630	0.0002	0.0001	0.0012	0.0002	0.0000	0.0003	0.0000	0.0003	0.0031	0.0000
4	0.0043	0.0730	0.0001	0.0000	0.0045	0.0025	0.0023	0.0004	0.0001	0.0008	0.0000	0.0685	0.0002	0.0001	0.0013	0.0002	0.0000	0.0004	0.0001	0.0003	0.0036	0.0000
5	0.0039	0.0609	0.0001	0.0000	0.0055	0.0029	0.0019	0.0003	0.0001	0.0009	0.0000	0.0704	0.0002	0.0001	0.0013	0.0002	0.0000	0.0005	0.0001	0.0003	0.0040	0.0000
6	0.0035	0.0514	0.0001	0.0000	0.0064	0.0032	0.0016	0.0003	0.0001	0.0009	0.0000	0.0697	0.0002	0.0001	0.0013	0.0002	0.0000	0.0006	0.0001	0.0002	0.0042	0.0000
7	0.0032	0.0438	0.0001	0.0000	0.0071	0.0034	0.0014	0.0002	0.0001	0.0009	0.0000	0.0673	0.0002	0.0001	0.0012	0.0002	0.0000	0.0006	0.0001	0.0002	0.0043	0.0000
8	0.0028	0.0376	0.0001	0.0000	0.0078	0.0036	0.0012	0.0002	0.0001	0.0009	0.0000	0.0634	0.0002	0.0001	0.0012	0.0002	0.0000	0.0007	0.0001	0.0002	0.0042	0.0000
9	0.0025	0.0324	0.0001	0.0000	0.0082	0.0037	0.0010	0.0002	0.0001	0.0008	0.0000	0.0589	0.0002	0.0001	0.0011	0.0002	0.0000	0.0007	0.0000	0.0002	0.0041	0.0000
10	0.0023	0.0279	0.0001	0.0000	0.0085	0.0037	0.0009	0.0002	0.0000	0.0008	0.0000	0.0538	0.0002	0.0001	0.0010	0.0002	0.0000	0.0007	0.0000	0.0002	0.0040	0.0000
11	0.0020	0.0241	0.0001	0.0000	0.0086	0.0036	0.0007	0.0001	0.0000	0.0007	0.0000	0.0486	0.0001	0.0000	0.0009	0.0002	0.0000	0.0006	0.0000	0.0002	0.0037	0.0000
12	0.0018	0.0208	0.0001	0.0000	0.0085	0.0034	0.0006	0.0001	0.0000	0.0007	0.0000	0.0433	0.0001	0.0000	0.0008	0.0001	0.0000	0.0006	0.0000	0.0001	0.0035	0.0000
13	0.0015	0.0178	0.0001	0.0000	0.0083	0.0032	0.0006	0.0001	0.0000	0.0006	0.0000	0.0380	0.0001	0.0000	0.0007	0.0001	0.0000	0.0006	0.0000	0.0001	0.0032	0.0000
14	0.0013	0.0152	0.0001	0.0000	0.0080	0.0030	0.0005	0.0001	0.0000	0.0006	0.0000	0.0330	0.0001	0.0000	0.0006	0.0001	0.0000	0.0005	0.0000	0.0001	0.0029	0.0000
15	0.0011	0.0128	0.0001	0.0000	0.0075	0.0028	0.0004	0.0001	0.0000	0.0005	0.0000	0.0283	0.0001	0.0000	0.0005	0.0001	0.0000	0.0005	0.0000	0.0001	0.0026	0.0000
16	0.0009	0.0106	0.0001	0.0000	0.0069	0.0024	0.0003	0.0001	0.0000	0.0004	0.0000	0.0237	0.0001	0.0000	0.0004	0.0001	0.0000	0.0004	0.0000	0.0001	0.0022	0.0000
17	0.0008	0.0087	0.0000	0.0000	0.0062	0.0021	0.0003	0.0000	0.0000	0.0004	0.0000	0.0197	0.0001	0.0000	0.0004	0.0001	0.0000	0.0003	0.0000	0.0001	0.0019	0.0000
18	0.0006	0.0071	0.0000	0.0000	0.0056	0.0019	0.0002	0.0000	0.0000	0.0003	0.0000	0.0160	0.0001	0.0000	0.0003	0.0001	0.0000	0.0003	0.0000	0.0001	0.0016	0.0000
19	0.0005	0.0056	0.0000	0.0000	0.0049	0.0016	0.0002	0.0000	0.0000	0.0003	0.0000	0.0128	0.0001	0.0000	0.0002	0.0000	0.0000	0.0002	0.0000	0.0000	0.0014	0.0000
20	0.0004	0.0044	0.0000	0.0000	0.0042	0.0013	0.0001	0.0000	0.0000	0.0002	0.0000	0.0101	0.0000	0.0000	0.0002	0.0000	0.0000	0.0002	0.0000	0.0000	0.0011	0.0000
21	0.0003	0.0034	0.0000	0.0000	0.0035	0.0011	0.0001	0.0000	0.0000	0.0002	0.0000	0.0078	0.0000	0.0000	0.0001	0.0000	0.0000	0.0002	0.0000	0.0000	0.0009	0.0000
22	0.0002	0.0026	0.0000	0.0000	0.0028	0.0009	0.0001	0.0000	0.0000	0.0001	0.0000	0.0059	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0007	0.0000
23	0.0002	0.0019	0.0000	0.0000	0.0023	0.0007	0.0001	0.0000	0.0000	0.0001	0.0000	0.0044	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0005	0.0000
24	0.0001	0.0014	0.0000	0.0000	0.0018	0.0005	0.0000	0.0000	0.0000	0.0001	0.0000	0.0032	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0004	0.0000
25	0.0001	0.0010	0.0000	0.0000	0.0014	0.0004	0.0000	0.0000	0.0000	0.0001	0.0000	0.0023	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0003	0.0000
26	0.0001	0.0007	0.0000	0.0000	0.0010	0.0003	0.0000	0.0000	0.0000	0.0000	0.0000	0.0016	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000
27	0.0000	0.0005	0.0000	0.0000	0.0007	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0011	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000
28	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
29	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
30	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

HS1: Anticoagulant initiation; HS2: Stable AF treated; HS3: Minor Stroke; HS4: Major Stroke; HS5: Post-minor stroke on treatment; HS6: Post-major stroke on treatment; HS7: Minor bleed; HS8: Major bleed; HS9: IC bleed; HS10: Post-IC bleed; HS11: Systemic embolism; HS12: Stable AF untreated; HS13: Minor stroke untreated; HS14: Major stroke untreated; HS15: Minor bleed untreated; HS16: Major bleed untreated; HS17: IC bleed untreated; HS18: Post IC bleed untreated; HS19: Systemic embolism untreated; HS20: Myocardial infarction HS21: Post myocardial infarction; HS22: Death

Table 78. QALY accrued over time: warfarin

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15	HS16	HS17	HS18	HS19	HS20	HS21	HS22
0	0.1948	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.0061	0.1370	0.0002	0.0001	0.0009	0.0006	0.0042	0.0008	0.0002	0.0004	0.0001	0.0341	0.0001	0.0000	0.0007	0.0001	0.0000	0.0001	0.0000	0.0004	0.0011	0.0000
2	0.0054	0.1093	0.0002	0.0001	0.0021	0.0012	0.0034	0.0006	0.0002	0.0008	0.0000	0.0519	0.0001	0.0000	0.0010	0.0002	0.0000	0.0003	0.0000	0.0003	0.0023	0.0000
3	0.0048	0.0884	0.0002	0.0001	0.0033	0.0019	0.0027	0.0005	0.0001	0.0011	0.0000	0.0625	0.0002	0.0001	0.0012	0.0002	0.0000	0.0004	0.0000	0.0003	0.0031	0.0000
4	0.0043	0.0725	0.0001	0.0000	0.0045	0.0024	0.0022	0.0004	0.0001	0.0013	0.0000	0.0680	0.0002	0.0001	0.0013	0.0002	0.0000	0.0005	0.0001	0.0003	0.0036	0.0000
5	0.0039	0.0603	0.0001	0.0000	0.0055	0.0029	0.0019	0.0003	0.0001	0.0013	0.0000	0.0699	0.0002	0.0001	0.0013	0.0002	0.0000	0.0006	0.0001	0.0003	0.0040	0.0000
6	0.0035	0.0507	0.0001	0.0000	0.0064	0.0032	0.0016	0.0003	0.0001	0.0014	0.0000	0.0692	0.0002	0.0001	0.0013	0.0002	0.0000	0.0007	0.0001	0.0002	0.0042	0.0000
7	0.0032	0.0432	0.0001	0.0000	0.0071	0.0034	0.0013	0.0002	0.0001	0.0013	0.0000	0.0668	0.0002	0.0001	0.0012	0.0002	0.0000	0.0007	0.0001	0.0002	0.0042	0.0000
8	0.0028	0.0369	0.0001	0.0000	0.0077	0.0036	0.0011	0.0002	0.0001	0.0013	0.0000	0.0629	0.0002	0.0001	0.0012	0.0002	0.0000	0.0007	0.0001	0.0002	0.0042	0.0000
9	0.0025	0.0318	0.0001	0.0000	0.0081	0.0036	0.0010	0.0002	0.0001	0.0012	0.0000	0.0583	0.0002	0.0001	0.0011	0.0002	0.0000	0.0007	0.0000	0.0002	0.0041	0.0000
10	0.0022	0.0274	0.0001	0.0000	0.0084	0.0036	0.0008	0.0002	0.0001	0.0012	0.0000	0.0533	0.0002	0.0001	0.0010	0.0002	0.0000	0.0007	0.0000	0.0002	0.0039	0.0000
11	0.0020	0.0236	0.0001	0.0000	0.0084	0.0035	0.0007	0.0001	0.0001	0.0011	0.0000	0.0481	0.0001	0.0000	0.0009	0.0002	0.0000	0.0007	0.0000	0.0002	0.0037	0.0000
12	0.0017	0.0203	0.0001	0.0000	0.0083	0.0033	0.0006	0.0001	0.0001	0.0010	0.0000	0.0428	0.0001	0.0000	0.0008	0.0001	0.0000	0.0007	0.0000	0.0001	0.0034	0.0000
13	0.0015	0.0174	0.0001	0.0000	0.0081	0.0032	0.0005	0.0001	0.0001	0.0009	0.0000	0.0376	0.0001	0.0000	0.0007	0.0001	0.0000	0.0006	0.0000	0.0001	0.0031	0.0000
14	0.0013	0.0148	0.0001	0.0000	0.0078	0.0029	0.0005	0.0001	0.0000	0.0008	0.0000	0.0326	0.0001	0.0000	0.0006	0.0001	0.0000	0.0006	0.0000	0.0001	0.0028	0.0000
15	0.0011	0.0125	0.0001	0.0000	0.0074	0.0027	0.0004	0.0001	0.0000	0.0007	0.0000	0.0279	0.0001	0.0000	0.0005	0.0001	0.0000	0.0005	0.0000	0.0001	0.0025	0.0000
16	0.0009	0.0104	0.0001	0.0000	0.0068	0.0024	0.0003	0.0001	0.0000	0.0006	0.0000	0.0234	0.0001	0.0000	0.0004	0.0001	0.0000	0.0004	0.0000	0.0001	0.0022	0.0000
17	0.0008	0.0085	0.0000	0.0000	0.0061	0.0021	0.0003	0.0000	0.0000	0.0005	0.0000	0.0193	0.0001	0.0000	0.0004	0.0001	0.0000	0.0004	0.0000	0.0001	0.0019	0.0000
18	0.0006	0.0069	0.0000	0.0000	0.0054	0.0018	0.0002	0.0000	0.0000	0.0005	0.0000	0.0157	0.0001	0.0000	0.0003	0.0001	0.0000	0.0003	0.0000	0.0001	0.0016	0.0000
19	0.0005	0.0055	0.0000	0.0000	0.0047	0.0016	0.0002	0.0000	0.0000	0.0004	0.0000	0.0126	0.0001	0.0000	0.0002	0.0000	0.0000	0.0003	0.0000	0.0000	0.0013	0.0000
20	0.0004	0.0043	0.0000	0.0000	0.0040	0.0013	0.0001	0.0000	0.0000	0.0003	0.0000	0.0099	0.0000	0.0000	0.0002	0.0000	0.0000	0.0002	0.0000	0.0000	0.0011	0.0000
21	0.0003	0.0033	0.0000	0.0000	0.0034	0.0011	0.0001	0.0000	0.0000	0.0003	0.0000	0.0076	0.0000	0.0000	0.0001	0.0000	0.0000	0.0002	0.0000	0.0000	0.0009	0.0000
22	0.0002	0.0025	0.0000	0.0000	0.0028	0.0008	0.0001	0.0000	0.0000	0.0002	0.0000	0.0058	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0007	0.0000
23	0.0002	0.0019	0.0000	0.0000	0.0022	0.0007	0.0001	0.0000	0.0000	0.0002	0.0000	0.0043	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0005	0.0000
24	0.0001	0.0014	0.0000	0.0000	0.0017	0.0005	0.0000	0.0000	0.0000	0.0001	0.0000	0.0032	0.0000	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0004	0.0000
25	0.0001	0.0010	0.0000	0.0000	0.0013	0.0004	0.0000	0.0000	0.0000	0.0001	0.0000	0.0023	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0003	0.0000
26	0.0001	0.0007	0.0000	0.0000	0.0010	0.0003	0.0000	0.0000	0.0000	0.0001	0.0000	0.0016	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000
27	0.0000	0.0005	0.0000	0.0000	0.0007	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0011	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000
28	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
29	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
30	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

HS1: Anticoagulant initiation; HS2: Stable AF treated; HS3: Minor Stroke; HS4: Major Stroke; HS5: Post-minor stroke on treatment; HS6: Post-major stroke on treatment; HS7: Minor bleed; HS8: Major bleed; HS9: IC bleed; HS10: Post-IC bleed; HS11: Systemic embolism; HS12: Stable AF untreated; HS13: Minor stroke untreated; HS14: Major stroke untreated; HS15: Minor bleed untreated; HS16: Major bleed untreated; HS17: IC bleed untreated; HS18: Post IC bleed untreated; HS19: Systemic embolism untreated; HS20: Myocardial infarction HS21: Post myocardial infarction; HS22: Death

Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results:

The disaggregated outcomes for total strokes, total bleeds, total MI and total SE are presented in Table 70. These costs have been estimated in the following manner:

- Total Strokes = Major stroke + minor stroke + Major stroke (untreated) + minor stroke (untreated)
- Total Bleeds = Major bleed + minor bleed + IC bleed + Major bleed (untreated) + minor bleed (untreated) + IC bleed (untreated)
- Total MI = Myocardial infarction
- Total SE = Systemic embolism + systemic embolism (untreated)

Table 79. Summary of LY and QALY gained by clinical outcome, rivaroxaban

Clinical outcome	LY rivaroxaban	QALY rivaroxaban
Total Strokes	0.0623	0.0252
Total Bleeds	0.2887	0.2126
Total MIs	0.0238	0.0154
Total SE	0.0051	0.0034

Table 80. Summary of LY and QALY gained by clinical outcome, warfarin

Clinical outcome	LY warfarin	QALY warfarin
Total Strokes	0.0618	0.0250
Total Bleeds	0.2901	0.2131
Total MIs	0.0236	0.0153
Total SE	0.0071	0.0047

Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 81. Summary of QALY gain by health state

Health State	QALY rivaroxaban	QALY warfarin	Increment
Anticoagulant initiation	0.362	0.3618	0.0002
Stable AF treated	2.9301	2.9113	0.0188
Minor Stroke	0.0064	0.0064	0.0000

Health State	QALY rivaroxaban	QALY warfarin	Increment
Major Stroke	0.0021	0.0021	0.0000
Post-minor stroke on treatment	0.366	0.3595	0.0065
Post-major stroke on treatment	0.1557	0.1534	0.0023
Minor bleed	0.0908	0.0903	0.0005
Major bleed	0.0162	0.0162	0.0000
IC bleed	0.0037	0.0055	-0.0018
Post-IC bleed	0.0383	0.0565	-0.0182
Systemic embolism	0.0003	0.0014	-0.0011
Stable AF untreated	2.7704	2.7378	0.0326
Minor stroke untreated	0.008	0.0079	0.0001
Major stroke untreated	0.0026	0.0026	0.0000
Minor bleed untreated	0.0516	0.051	0.0006
Major bleed untreated	0.0092	0.0091	0.0001
IC bleed untreated	0.0019	0.002	-0.0001
Post IC bleed untreated	0.0267	0.0303	-0.0036
Systemic embolism untreated	0.0022	0.0022	0.0000
Myocardial infraction	0.0123	0.0122	0.0001
Post myocardial infraction	0.1805	0.1783	0.0022
Death	0	0	0.0000
TOTAL	7.037	6.9978	0.0392

Please note differences reported between disaggregated and aggregated results are related to rounding differences

Table 82. Summary of costs by health state

Health State	Cost rivaroxaban	Cost warfarin	Increment
Anticoagulant initiation	£423.12	£357.22	65.90
Stable AF treated	£2,883.07	£2,190.74	692.33
Minor Stroke	£121.36	£121.23	0.13
Major Stroke	£555.76	£553.88	1.88
Post-minor stroke on treatment	£410.46	£314.19	96.27
Post-major stroke on treatment	£1,820.02	£1,736.66	83.36
Minor bleed	£148.88	£152.35	-3.47
Major bleed	£114.89	£115.26	-0.37

IC bleed	£162.67	£242.09	-79.42
Post-IC bleed	£291.34	£433.34	-142.00
Systemic embolism	£3.65	£15.39	-11.74
Stable AF untreated	£21.14	£20.89	0.25
Minor stroke untreated	£151.05	£150.00	1.05
Major stroke untreated	£691.73	£685.33	6.40
Minor bleed untreated	£34.04	£33.64	0.40
Major bleed untreated	£53.59	£52.96	0.63
IC bleed untreated	£80.79	£83.90	-3.11
Post IC bleed untreated	£175.69	£199.78	-24.09
Systemic embolism untreated	£22.23	£22.52	-0.29
Myocardial infraction	£414.67	£409.31	5.36
Post myocardial infraction	£360.43	£309.80	50.63
Death	£0.00	£0.00	0.00
TOTAL	8,941	8,200	740.10

Please note differences reported between disaggregated and aggregated results are related to rounding differences

Base-case analysis

Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

In the base case analysis rivaroxaban was associated with improved life expectancy (0.051) and improved quality-adjusted life expectancy (0.039) compared with warfarin, based on statistically significant treatment effects from the SOT analysis of the ROCKET AF trial. Rivaroxaban was associated with increased lifetime direct medical costs (£740 per patient). The incremental cost-utility ratio was £18,883 per QALY gained (Table 83), which would represent good value for money, assuming a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained.

Table 83. Base–case results: trial population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SOT data	8,200	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial SOT data	8,941	9.272	7.037	740	0.051	0.039	18,883	18,883

Any differences between the ICERs presented and the ICERs estimated from the Incremental costs and Incremental QALY above are due to rounding of the estimates from the cost-effectiveness model

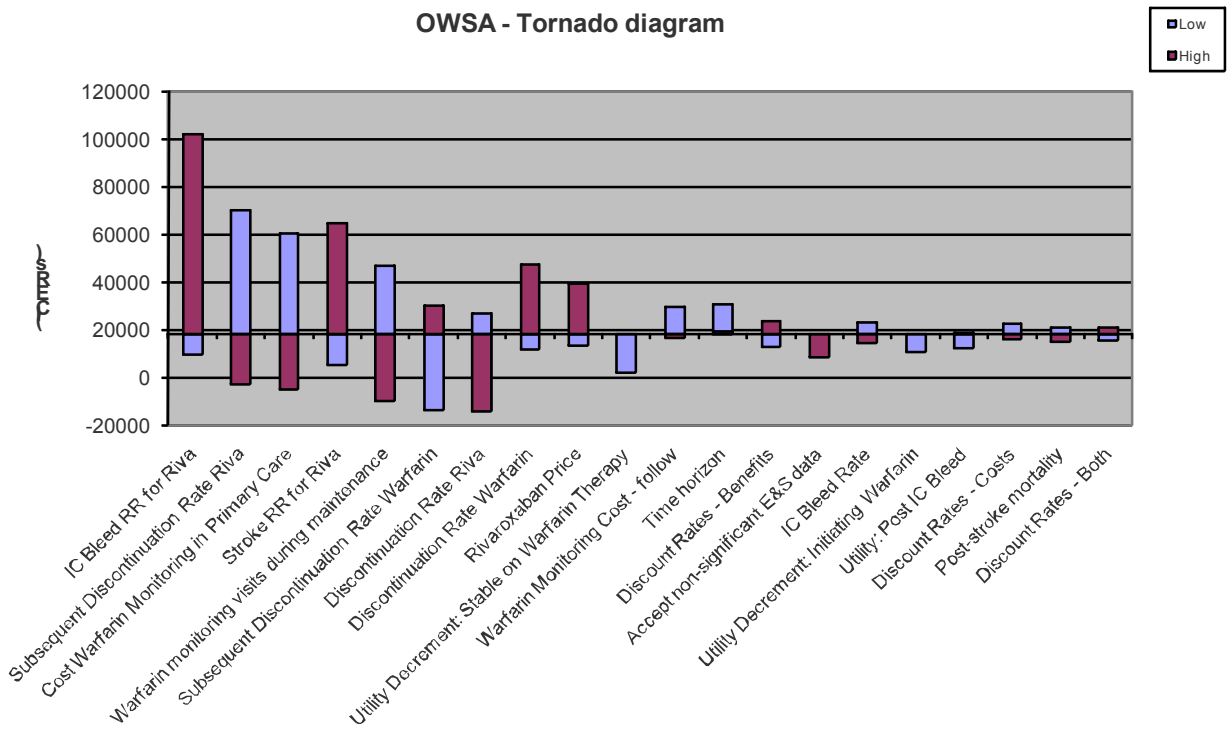
Sensitivity analyses

Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Sensitivity analysis was performed by means of one-way sensitivity analysis, where one parameter or group of related parameters was varied relative to its base case value and the results compared. Parameters tested included utility values, adverse event rates, treatment adherence rates, relative risk values for rivaroxaban treatment, time horizons and discount rates (for detailed list of parameters included refer to section 6.6).

As indicated in the tornado diagrams in Figure 21, results were most sensitive to the intracranial bleeding relative risk for rivaroxaban, the rate of discontinuation for rivaroxaban, the cost of warfarin monitoring in Primary Care and the relative risk of stroke for rivaroxaban. Using the point estimates from the ROCKET AF trial regardless of their significance reduced the ICER of rivaroxaban compared with warfarin. Discount rates used for the analysis had relatively little impact on overall cost-effectiveness outcomes.

Figure 21. OWSA – Tornado diagram for rivaroxaban compared with warfarin based on the SOT population of the ROCKET AF trial using only statistically significant treatment effects



Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis results, derived by sampling from input parameter distributions, indicated that rivaroxaban may be associated with cost savings and increased quality-adjusted life expectancy compared with warfarin (Figure 22). Probabilistic sensitivity analysis also indicated that rivaroxaban would be considered cost-effective versus warfarin across a range of hypothetical willingness-to-pay thresholds (Figure 23).

Figure 22. Cost-effectiveness plane for rivaroxaban compared with warfarin, 1000 runs

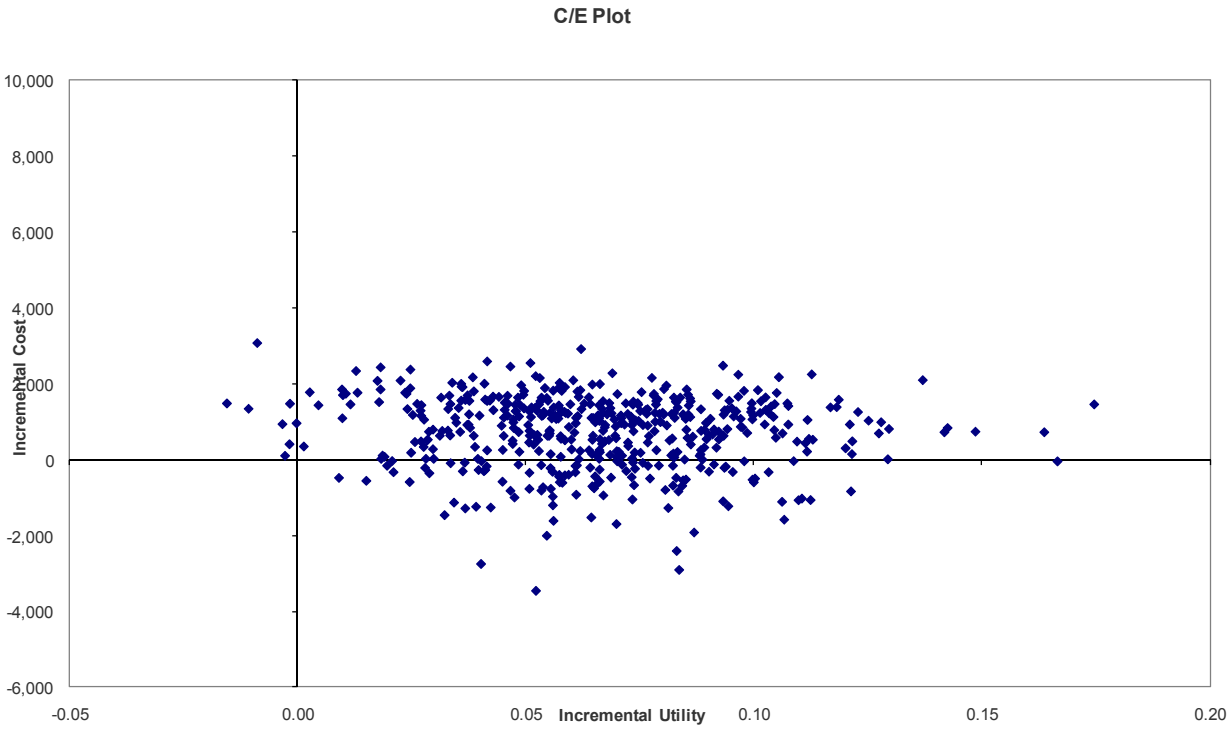
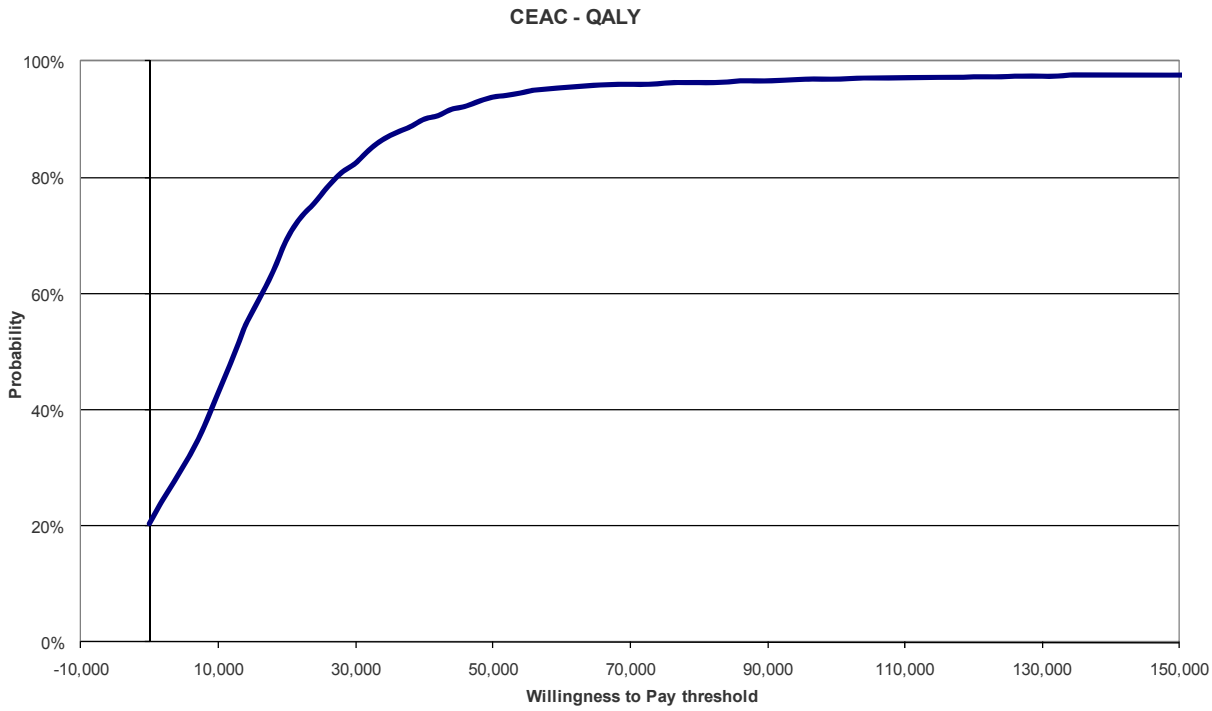


Figure 23. Cost-effectiveness acceptability curve for rivaroxaban compared with warfarin , 1000 runs



Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Analysis based upon intention to treat population to site notification from ROCKET AF

In an alternative scenario where efficacy data were derived from the intention to Treat (ITT) analysis of the ROCKET AF trial, rivaroxaban was associated with increased lifetime direct medical costs (£745 per patient). Rivaroxaban was also associated with greater health outcomes in term of life expectancy (0.055) and quality-adjusted life expectancy (0.042).

Table 84. Scenario 1: trial population (ITT – significant values only)

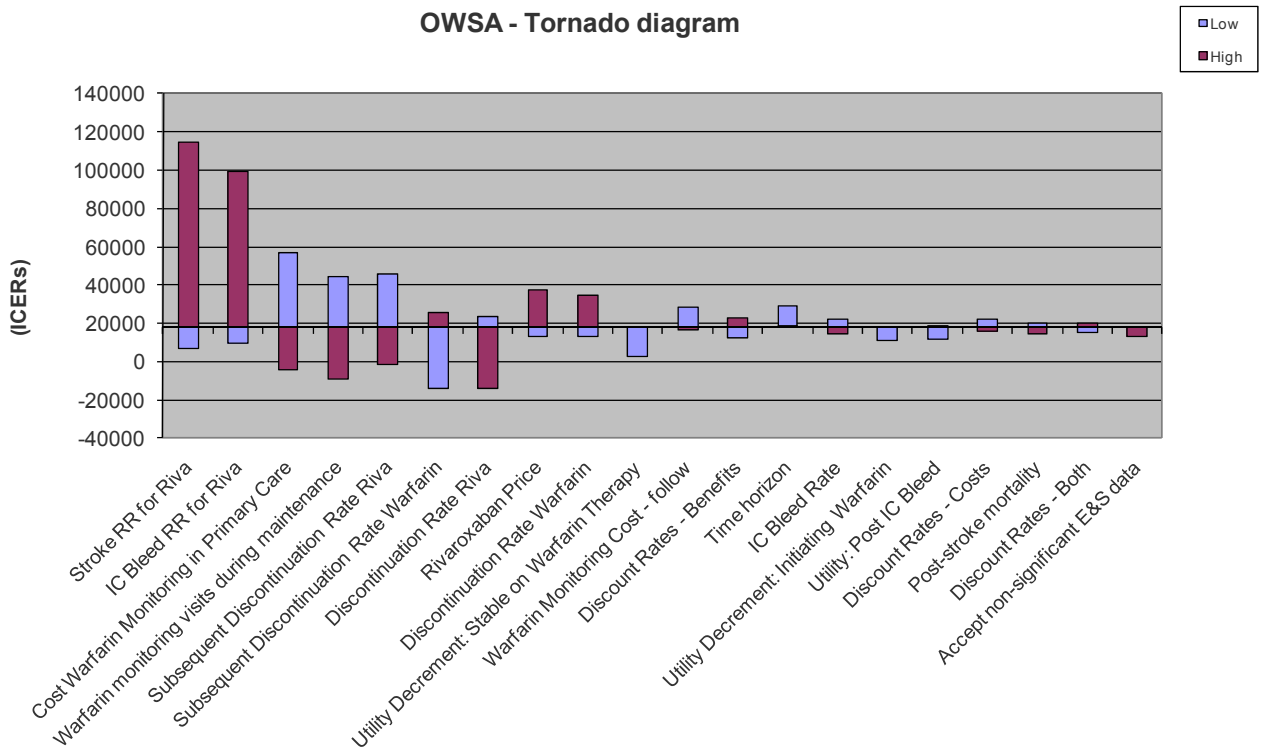
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial ITT data	8,737	9.146	6.917					
Rivaroxaban based on the ROCKET AF trial ITT data	9,482	9,201	6.959	745	0.055	0.042	17,927	17,927

Any differences between the ICERs presented and the ICERs estimated from the Incremental costs and Incremental QALY above are due to rounding of the estimates from the cost-effectiveness model

OWSA

Sensitivity analysis was performed by means of one-way sensitivity analysis. As indicated in the tornado diagrams in Figure 24, results were most sensitive to the stroke relative risk for rivaroxaban, the intracranial bleeding relative risk for rivaroxaban, the cost of warfarin monitoring in Primary Care and the number of monitoring visits required for warfarin during the maintenance period. Discount rates used for the analysis had little impact on overall cost-effectiveness outcomes.

Figure 24. OWSA – Rivaroxaban compared with warfarin based on the ITT analysis of the ROCKET AF trial



PSA

Probabilistic sensitivity analysis results indicated that rivaroxaban may be associated with cost savings and increased quality-adjusted life expectancy compared with warfarin in the ITT population. Probabilistic sensitivity analysis also indicated that rivaroxaban would be considered cost-effective versus warfarin across a range of hypothetical willingness-to-pay thresholds.

Figure 25. Cost-effectiveness plane for rivaroxaban when compared with warfarin based on the ITT analysis of the ROCKET AF trial

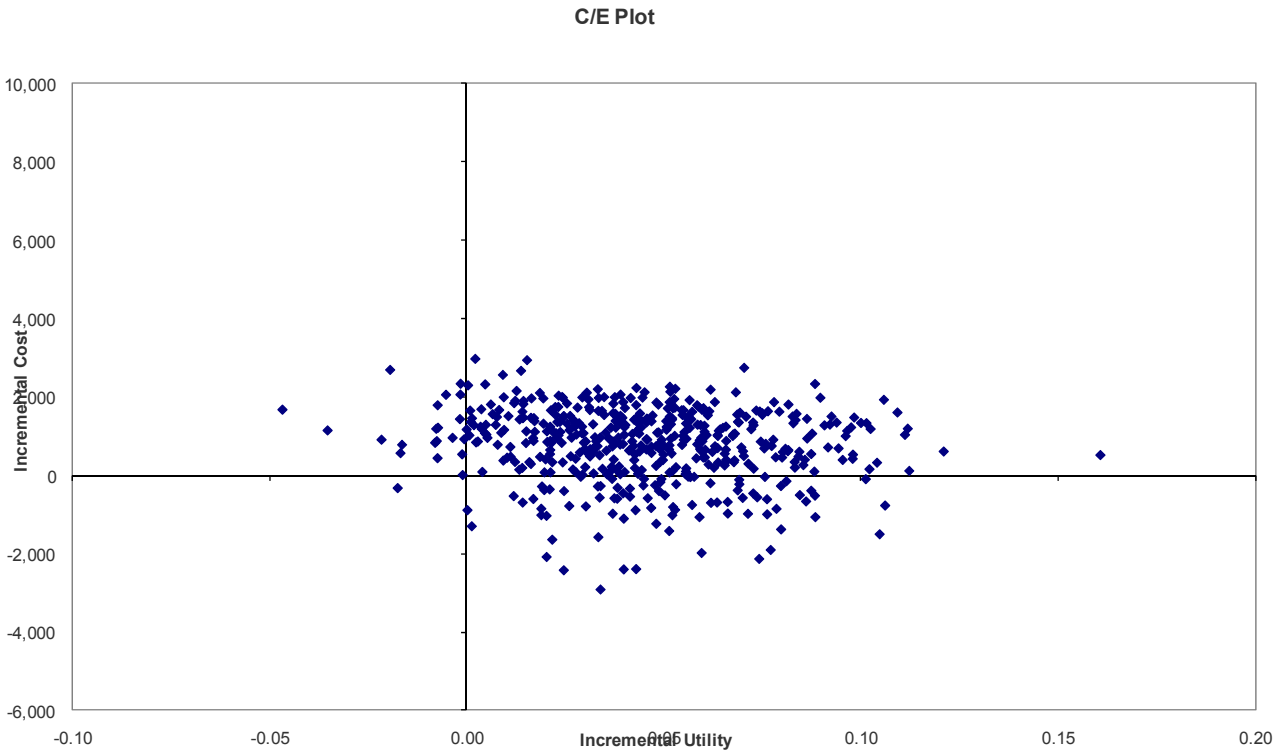
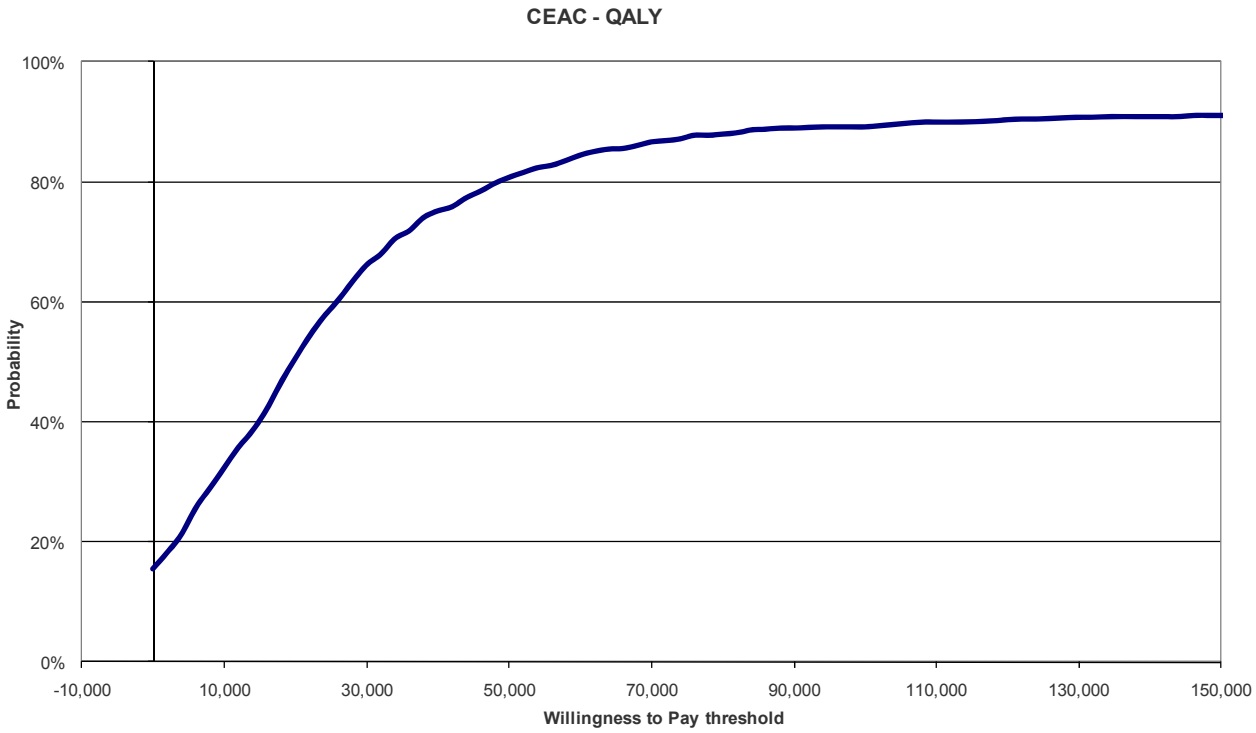


Figure 26. Cost-effectiveness acceptability curve for rivaroxaban when compared with warfarin based on the ITT analysis of the ROCKET AF trial



An additional scenario was included comparing rivaroxaban with warfarin, including all point estimates from the SOT dataset regardless of their significance

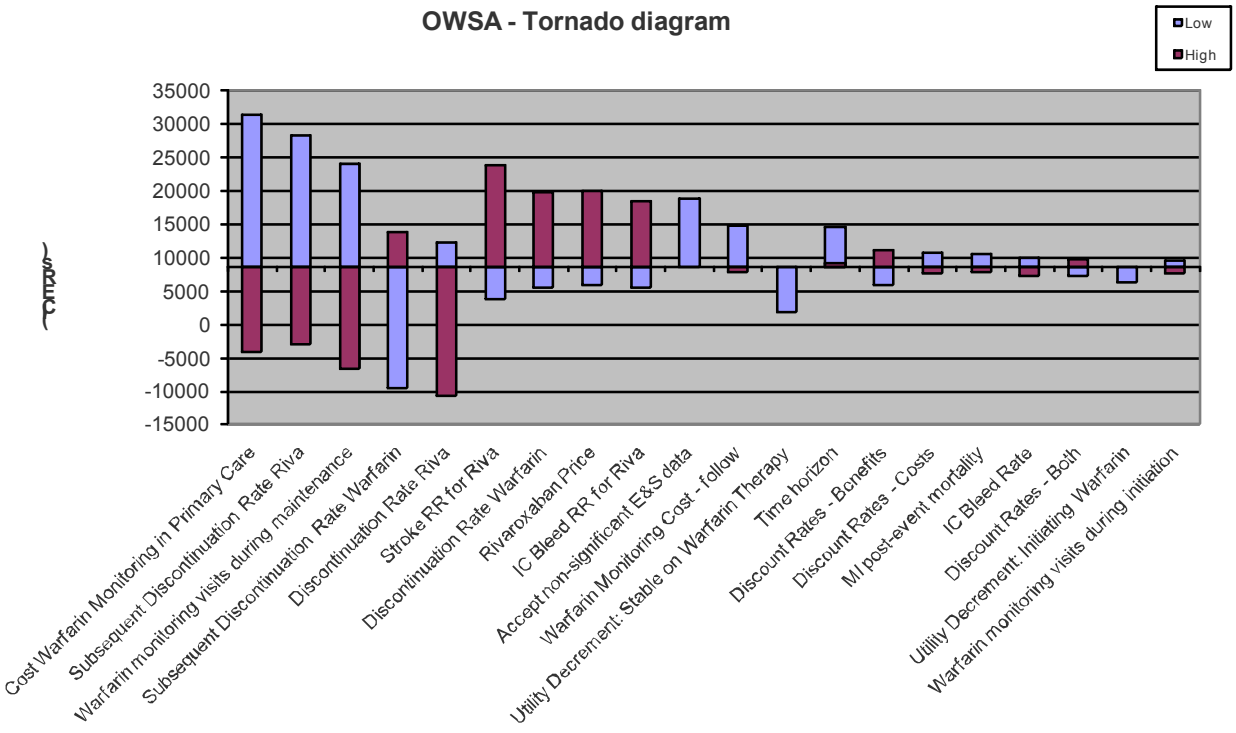
Table 85. Scenario 2: trial population (SOT – point estimates)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial sot data (point estimates)	8,200	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial sot data (point estimates)	8,834	9.308	7.071	633	0.087	0.073	8,732	8,732

OWSA

Sensitivity analysis was performed by means of one-way sensitivity analysis. As indicated in the tornado diagrams in Figure 27, results were most sensitive to the cost of warfarin monitoring in primary care, the subsequent discontinuation rate for rivaroxaban, the number of warfarin monitoring visits during the maintenance phase and the subsequent discontinuation rate for warfarin.

Figure 27. OWSA – Rivaroxaban compared with warfarin based on the SOT analysis of the ROCKET AF trial – point estimates



What were the main findings of each of the sensitivity analyses?

For the base case (SoT – significant values only) and the ITT (significant values only) analyses, the sensitivity analyses found that the analysis was sensitive to clinical parameters including the relative risks of IC bleed and stroke; the cost of warfarin monitoring including number of visits and unit cost; and discontinuation rate of the therapies compared.

However, the point estimate-based SoT OWSA indicated that the results showed only modest changes to variation in input parameter values. The only parameter to increase the ICER above £30,000 was the cost of warfarin monitoring in primary care.

PSA for both of the above analyses also indicate that the model results are robust. The CEAC indicate that the likelihood of rivaroxaban being cost-effective at a willingness-to-pay threshold of £30,000 ranged between 75% to 80%.

What are the key drivers of the cost-effectiveness results?

The cost-effectiveness model is primarily driven by:

- IC bleed rate
    - The IC bleed rate (as well as the relative risk of IC bleeds) is a key driver for the base case results, as it is the only efficacy endpoint that was statistically significantly different between rivaroxaban and warfarin. Rivaroxaban had a lower rate of IC bleeds (better safety) compared to warfarin, and therefore a low rate of IC bleeds will mean that the benefit derived by preventing IC bleeds is small and drives the ICER up.
- Warfarin monitoring visits during maintenance phase;
    - This is a key driver in all analyses comparing rivaroxaban to warfarin as this determines the cost of warfarin monitoring, which accounts for the majority of warfarin-related costs incurred by the healthcare system. A higher cost of warfarin monitoring driven by more frequent visits yields a lower ICER.
- Subsequent discontinuation rate for rivaroxaban.
    - When the subsequent discontinuation rate of rivaroxaban is increased or decreased independently, this directly impacts on the efficacy of therapy, as on average, there will be fewer patients on therapy. This leads to a lower efficacy benefit. At the same time, fewer patients on therapy means that the cost of therapy is also decreased. As the overall efficacy benefit is fairly small, small changes in the overall cost and benefits cause large changes in the ICER.

Validation

Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

There are two types of validation that can generally be conducted for an economic model. Extensive external validation was undertaken in consultation with experts in atrial fibrillation and health economics, as described below.

The cost-effectiveness model has been validated in the following manner:

- A review of key literature in the field of SPAF economic modelling was conducted prior to formulating the model design concept.
- The initial design of the cost-effectiveness model was extensively discussed with the involvement of key experts in clinical aspects of SPAF.
- The model design and the results of the economic evaluation were presented to leading health economic experts throughout the period of model development.
- Within the validated model framework, the model was populated with the results of the most recently available evidence synthesis for SPAF treatments.
- The assumptions of extrapolating key outcomes of interest beyond the time horizon of the clinical trials is the common practice in the economic modelling of chronic conditions, including non-valvular atrial fibrillation.
- Results of the model were compared against other published studies and found to be comparable.

A second type of validation is around internal validity, to ensure that outputs are logical and accurate within the framework set by the model. This was ensured by quality control of the model by the model developers, as well as a model audit performed by an external health economist (Peter Lindgren i3 Innovus).

Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Patients poorly controlled on warfarin

The first subgroup considered is a subgroup of the indicated population, who are not well controlled on warfarin and therefore require frequent monitoring visits. A real-world evaluation was conducted at a single secondary care based anti-coagulation clinic(22). In the database, 26 patients (18.6%) required more than 2 visits per month in the maintenance phase. The average number of visits per month for these patients – assuming that the number of visits is in the middle of the range for each category in Table 86 – was 3.0. This group is referred to as "not well controlled" in analyses. Note that 9 patients (6.4%) required more than 3 visits per month (mean number of visits 3.9 per month).

Figure 28. Identification of warfarin patients who are not well controlled and high resource users

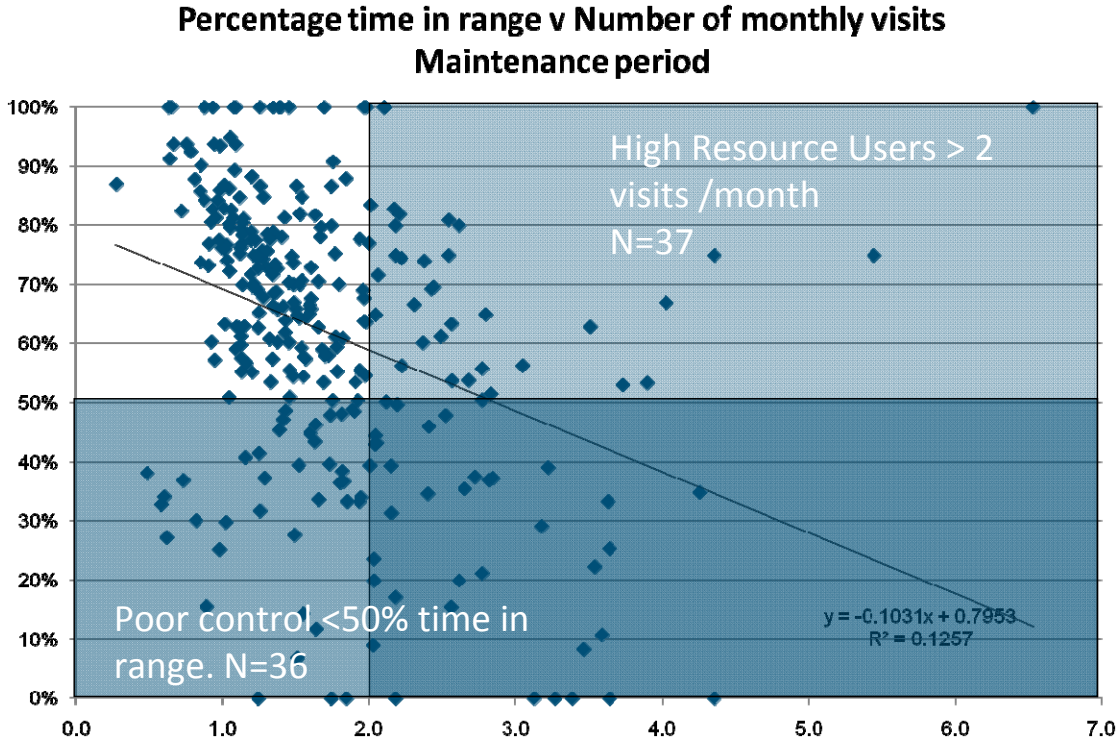


Table 86. Frequency of INR monitoring in warfarin patients on maintenance therapy

No. visits per month in maintenance phase	No. (n=140)	%
>0<1	22	16%
1<2	92	66%
2<3	17	12%
3<4	6	4%
4<5	2	1%
≥ 5	1	1%

Current warfarin practice includes drug monitoring to ensure that patients are within therapeutic range. The frequency of monitoring depends on the stability of INR measurement in warfarin patients. While some patients have constant, stable INR readings and can therefore be monitored infrequently, others struggle to stay in the therapeutic range and require more frequent monitoring. In this scenario efficacy and safety were identical to the base case.

People who have not previously been treated with warfain

A second subgroup considered AF patients who have not previously been treated with warfarin (Section 0). Patients who need to be initiated on anticoagulation therapy may benefit from not having to go through a phase of continuous INR monitoring until stabilization with warfarin is achieved.

Warfain unsuitable

A third subgroup was defined as epidemiological data shows that there are a large proportion of patients who are eligible for OAC, but who are not currently prescribed(4;5). These patients may not be on OAC for one of several reasons, including:

- Patients have discontinued from previous OAC use
- Patients are contraindicated to warfarin
- Patients are deemed unable to keep track of warfarin intake and keep up with monitoring requirements, due to physical or mental impairments
- Patients have an excessive risk of bleeding

Rivaroxaban may be able to answer the need for anti-coagulation for the first three of these groups of patients. While the ROCKET AF trial did not include a non-anti-coagulant arm, this analysis was considered essential. A network meta-analysis was undertaken to derive the relative treatment effects of rivaroxaban compared with aspirin and no treatment. All odds ratios were produced versus the no treatment arm.

Alternative comparator - dabigatran

A fourth subgroup considered alternative new oral anticoagulants to rivaroxaban, such as dabigatran. As this product has recently gained a licence for the prevention of stroke in patients with AF (4th August 2011), it was anticipated that this may be a competitor to rivaroxaban, therefore a subgroup analysis was undertaken. As the NMA did not identify any significant differences between rivaroxaban and dabigatran, and given the substantial heterogeneity between the ROCKET AF trial (rivaroxaban) and the RE-LY trial (dabigatran) the deterministic analysis for this comparison applied equal RRs for each treatment.

Please clearly define the characteristics of patients in the subgroup.

Patients included in the first subgroup matched the patients included in the base case analysis as derived from the safety on treatment population from the ROCKET AF trial, with the exception of increased frequency of monitoring visits for patients receiving warfarin. The second subgroup considered patients who have not previously been treated with oral anticoagulants and may benefit from rivaroxaban as it does not require INR stabilization. This was a pre-specified sub group in the ROCKET AF trial.

Sub group 3 is defined as:

- Those patients who have previously taken warfarin but have discontinued for reasons other than bleeding, and
- Those patients for whom clinicians would have preferred to prescribe an OAC but who they assessed as being unable to comply with warfarin management because of difficulties in dose adjustments, attending for monitoring visits, polypharmacy, or lifestyle factors.

Sub group 4 is the sub set of patients for whom rivaroxaban can be seen as an alternative to dabigatran.

The relative efficacy estimates from the network meta-analysis used for subgroups 3 and 4 are provided in section 6.3. Analyses of rivaroxaban against aspirin, no treatment or dabigatran were undertaken on a patient cohort with a baseline $CHADS_2$ risk profile from a UK observational study(13).

Please describe how the statistical analysis was undertaken.

No further statistical analyses were required for subgroup one or two. Further description of the NMA used for the analyses in subgroup three and subgroup four is provided in sections 6.3 and 6.4.

What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

<u>Subgroup 1</u> - patients not well controlled on warfarin

In this scenario rivaroxaban was associated with improved life expectancy (0.051) and improved quality-adjusted life expectancy (0.039) compared with warfarin. Rivaroxaban was associated with fewer lifetime direct medical costs (savings of

£1,482 per patient), which was driven by the costs offset by rivaroxaban when compared with warfarin, assuming a higher than average number of monitoring visits for the latter therapy (Table 87).

Table 87. Subgroup 1: patients not well controlled on warfarin

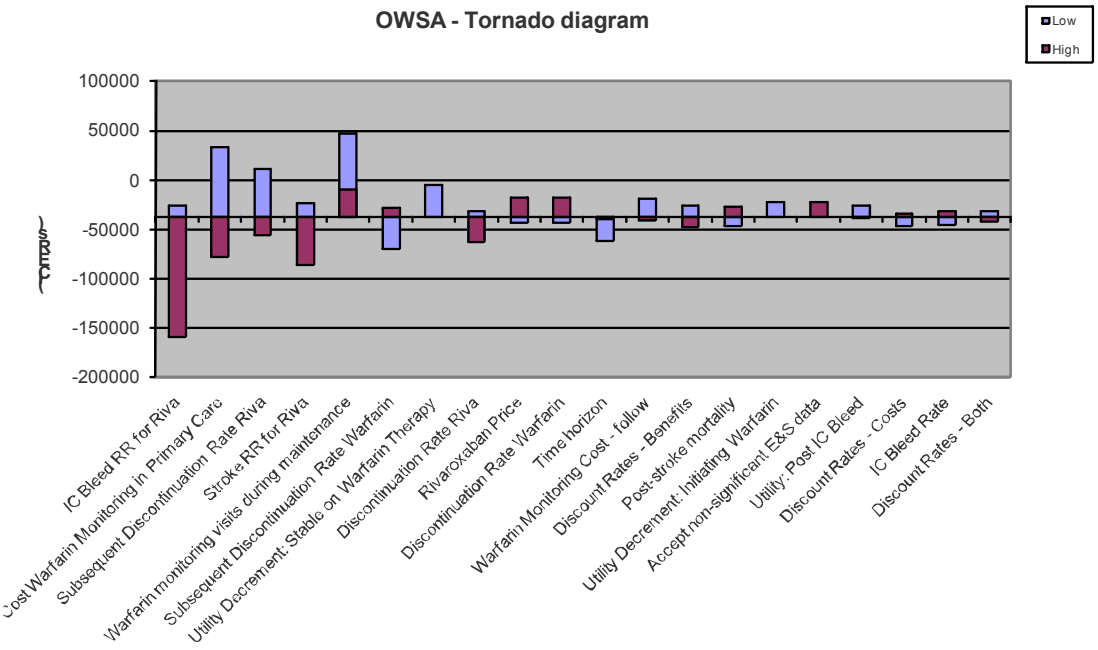
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban based on the ROCKET AF trial SOT data – poor control	8,941	9.272	7.037					
Warfarin based on the ROCKET AF trial SOT data poor control	10,423	9.221	6.998	1,482	0.051	0.039	Rivaroxaban dominates	Rivaroxaban dominates

Any differences between the ICERs presented and the ICERs estimated from the Incremental costs and Incremental QALY above are due to rounding of the estimates from the cost-effectiveness model

OWSA

Sensitivity analysis was performed by means of one-way sensitivity analysis. As indicated in the tornado diagrams in Figure 29 results were most sensitive to the intracranial bleeding relative risk for rivaroxaban, the costs of warfarin monitoring in primary care the rate of discontinuation for patients on rivaroxaban and the relative risk of stroke for rivaroxaban. Discount rates and had little impact on overall cost-effectiveness outcomes.

Figure 29. Subgroup1: Patients who are not well controlled on warfarin



PSA

Probabilistic sensitivity analysis results indicated that rivaroxaban may be associated with cost savings and increased quality-adjusted life expectancy compared with warfarin (Figure 30). Probabilistic sensitivity analysis also indicated that rivaroxaban would be considered cost-effective versus warfarin across a range of hypothetical willingness-to-pay thresholds (Figure 31).

Figure 30. Cost-effectiveness plane for rivaroxaban compared with warfarin in patients who are not well controlled on warfarin

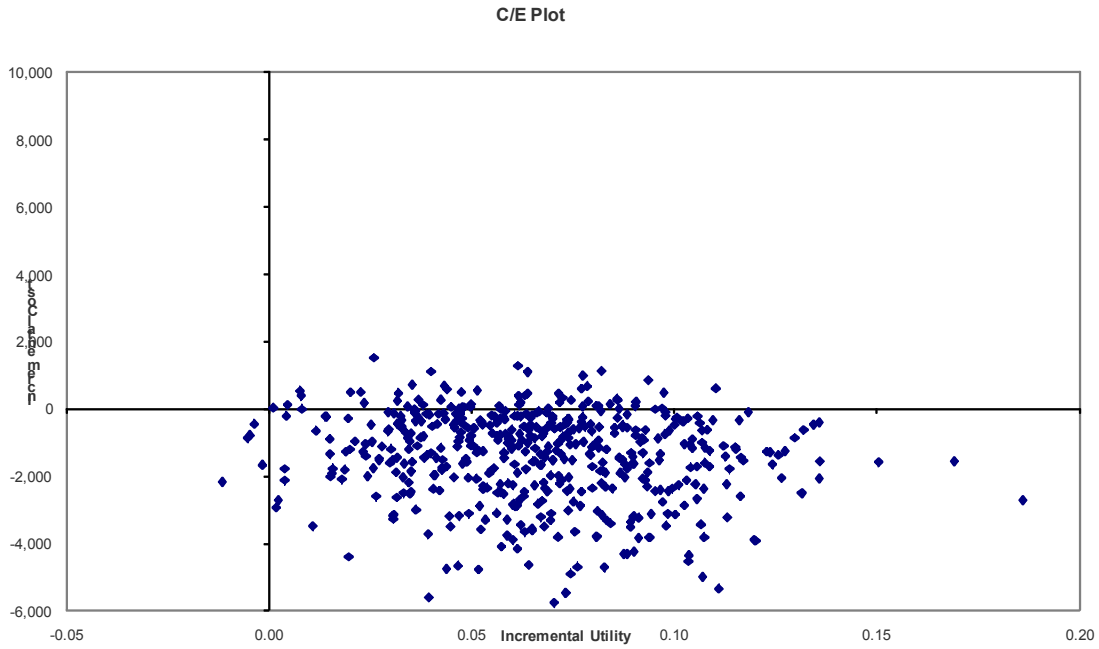
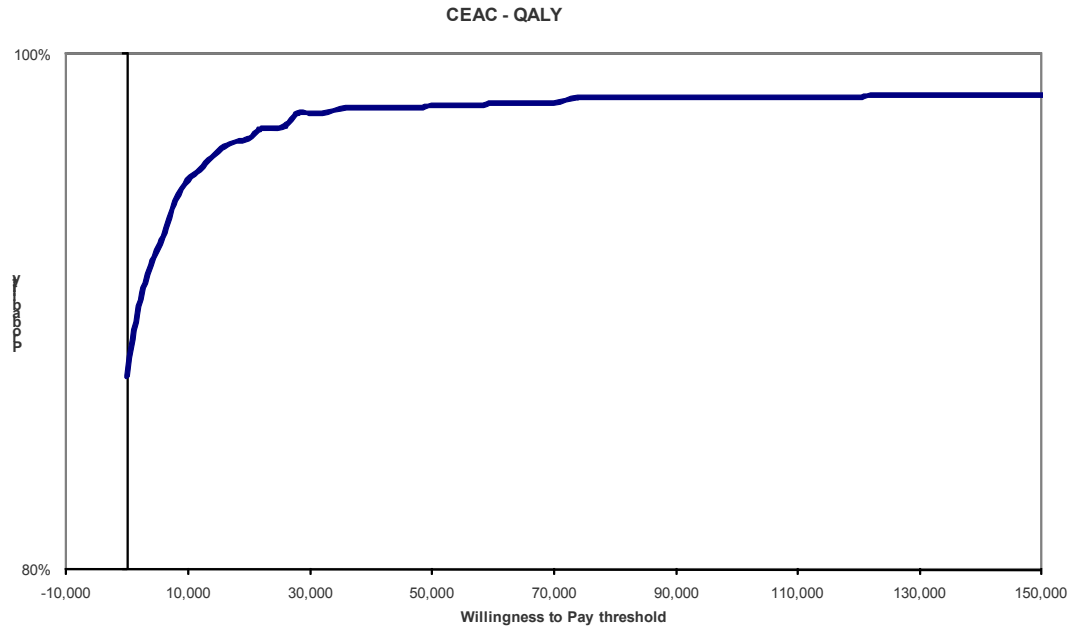


Figure 31. Cost-effectiveness acceptability curve for rivaroxaban compared with warfarin in patients who are not well controlled on warfarin



Subgroup 2 – Patients who have not previously been treated with warfarin

In this scenario rivaroxaban was associated with improved life expectancy (0.051) and improved quality-adjusted life expectancy (0.039) compared with warfarin. Rivaroxaban was associated with additional lifetime direct medical costs (£607 per patient) (Table 88).

Table 88. Subgroup 2: patients who have not previously been treated with warfarin

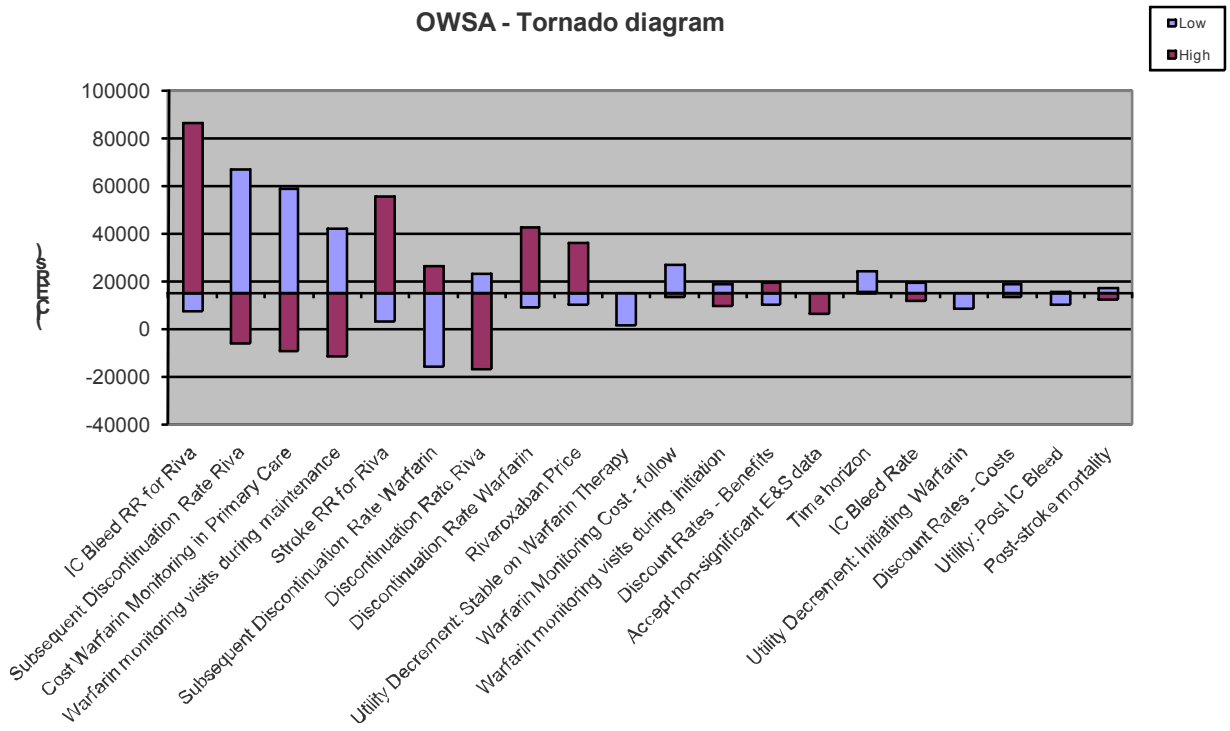
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SOT data – warfarin naive	8,333	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial SOT data – warfarin naive	8,941	9.272	7.037	607	0.051	0.039	15,494	15,494

Any differences between the ICERs presented and the ICERs estimated from the Incremental costs and Incremental QALY above are due to rounding of the estimates from the cost-effectiveness model

OWSA

Sensitivity analysis was performed by means of one-way sensitivity analysis. As indicated in the tornado diagrams in Figure 32 results were most sensitive to the intracranial relative risk for rivaroxaban, the costs of warfarin monitoring in Primary Care, the discontinuation rate for rivaroxaban and the number of monitoring during the maintenance period. Discount rates and had little impact on overall cost-effectiveness outcomes.

Figure 32. Subgroup 2: Patients who have not previously been treated with warfarin



PSA

Probabilistic sensitivity analysis results indicated that rivaroxaban may be associated with cost savings and increased quality-adjusted life expectancy compared with when warfarin (Figure 33). Probabilistic sensitivity analysis also indicated that rivaroxaban would be considered cost-effective versus warfarin across a range of hypothetical willingness-to-pay thresholds (Figure 34).

Figure 33. Cost-effectiveness plane for rivaroxaban compared with warfarin in patients who not previously been treated with warfarin

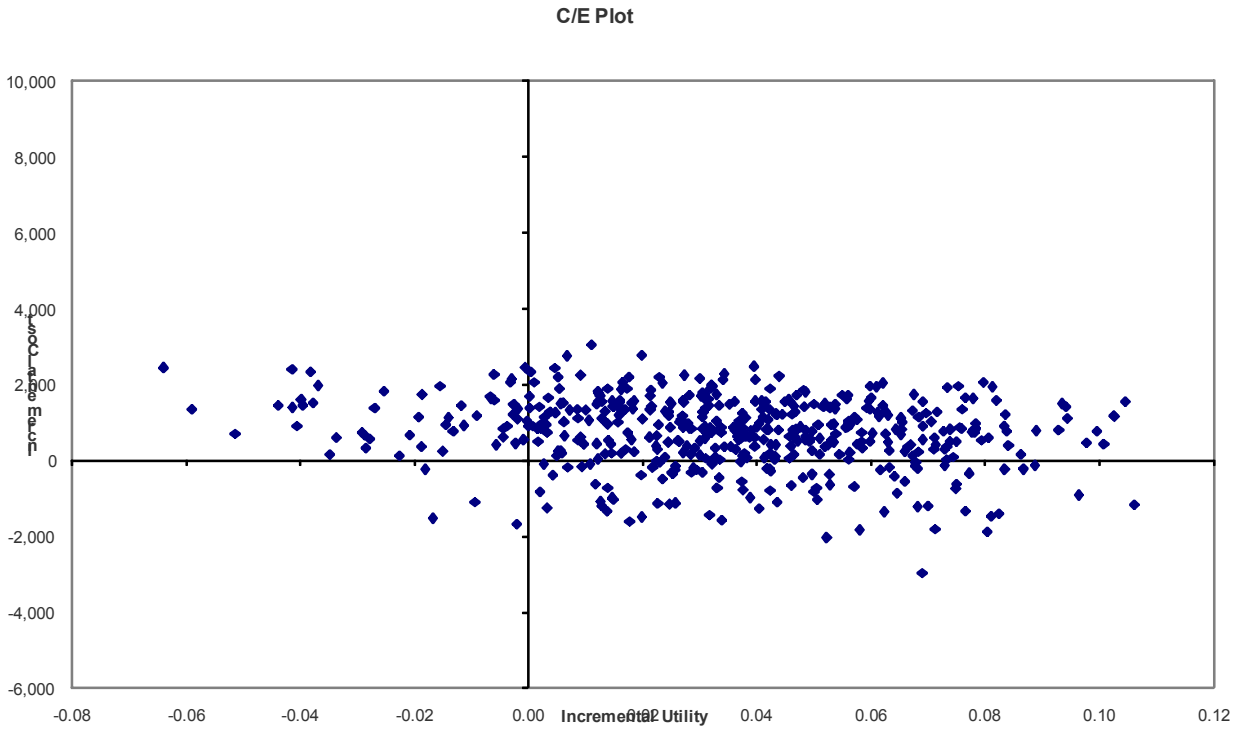
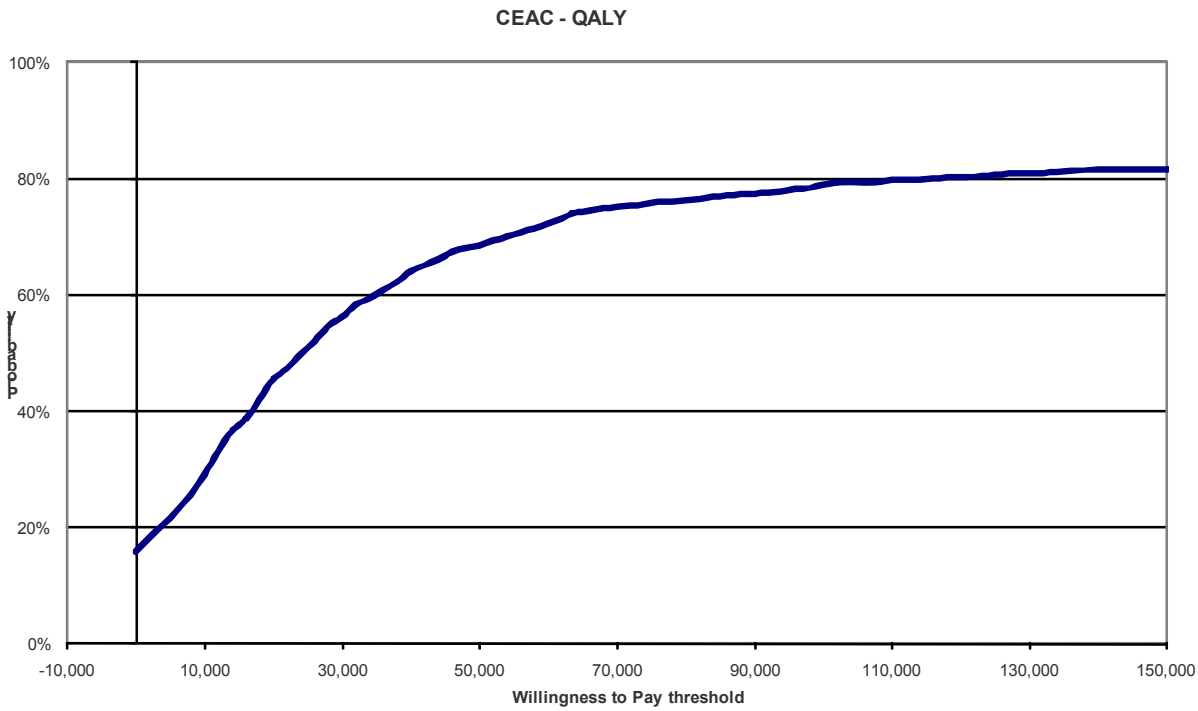


Figure 34. Cost-effectiveness acceptability curve for rivaroxaban compared with warfarin in patients who not previously been treated with warfarin



Subgroup 3 – warfarin unsuitable

When comparing rivaroxaban, aspirin and no treatment for management of atrial fibrillation patients, aspirin was the treatment associated with the lowest overall cost, as patients not receiving any prophylaxis experienced a higher number of embolic events and myocardial infarctions. The occurrence of these events reduced the overall QALY associated with no treatment, which led to "no treatment" being a dominated alternative in this comparison. Rivaroxaban was associated with improved life expectancy (0.369) and improved quality-adjusted life expectancy (0.424) compared with aspirin. Rivaroxaban was associated with increased lifetime direct medical costs (£883 per patient). The incremental cost-utility ratio was £2,083 per QALY gained (Table 89), which would represent good value for money, assuming a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained.

Table 89. Subgroup 3: warfarin unsuitable

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Aspirin based on data from NMA	10,367	8.782	6.409					
No therapy based on data from NMA	10,753	8.654	6.285	386	-0.128	-0.124	Dominated	Dominated
Rivaroxaban based on data from NMA	11,249	9.151	6.833	883	0.369	0.424	2,083	2,083

Any differences between the ICERs presented and the ICERs estimated from the Incremental costs and Incremental QALY above are due to rounding of the estimates from the cost-effectiveness model

OWSA

Sensitivity analysis was performed by means of one-way sensitivity analysis. As indicated in the tornado diagram in Figure 35, results were most sensitive to the intracranial bleeding relative risk for rivaroxaban followed by stroke relative risk for rivaroxaban and the stroke relative risk when compared with aspirin. When one-way sensitivity analysis was conducted comparing rivaroxaban with no treatment, the drivers of the model were the relative risk of stroke for rivaroxaban, the intracranial bleeding relative risk for rivaroxaban, and the relative risk of mortality following a stroke.

Figure 35. OWSA – Rivaroxaban compared with aspirin based on the NMA

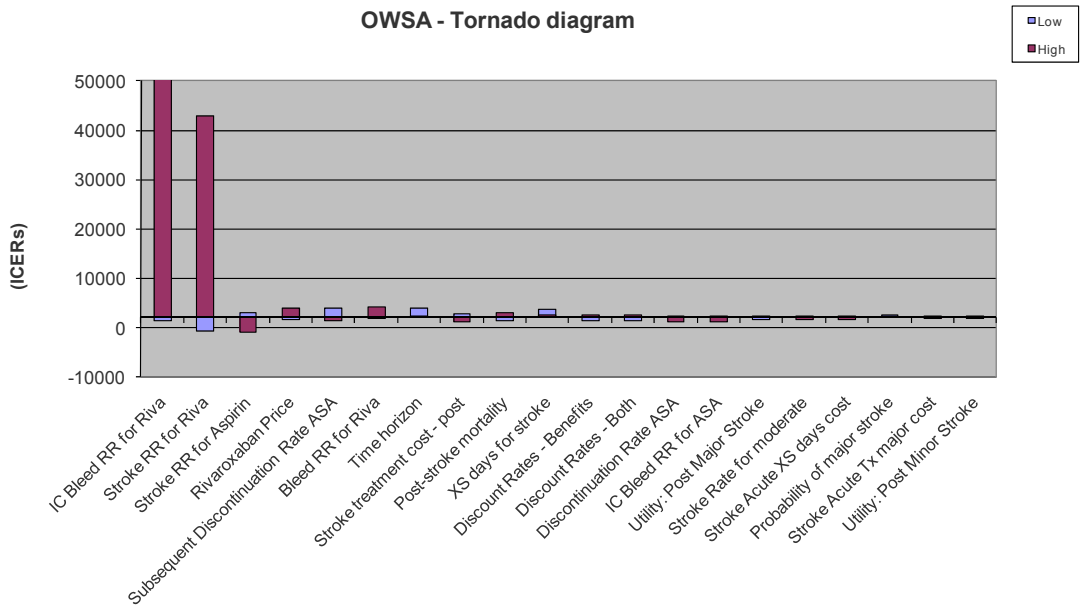
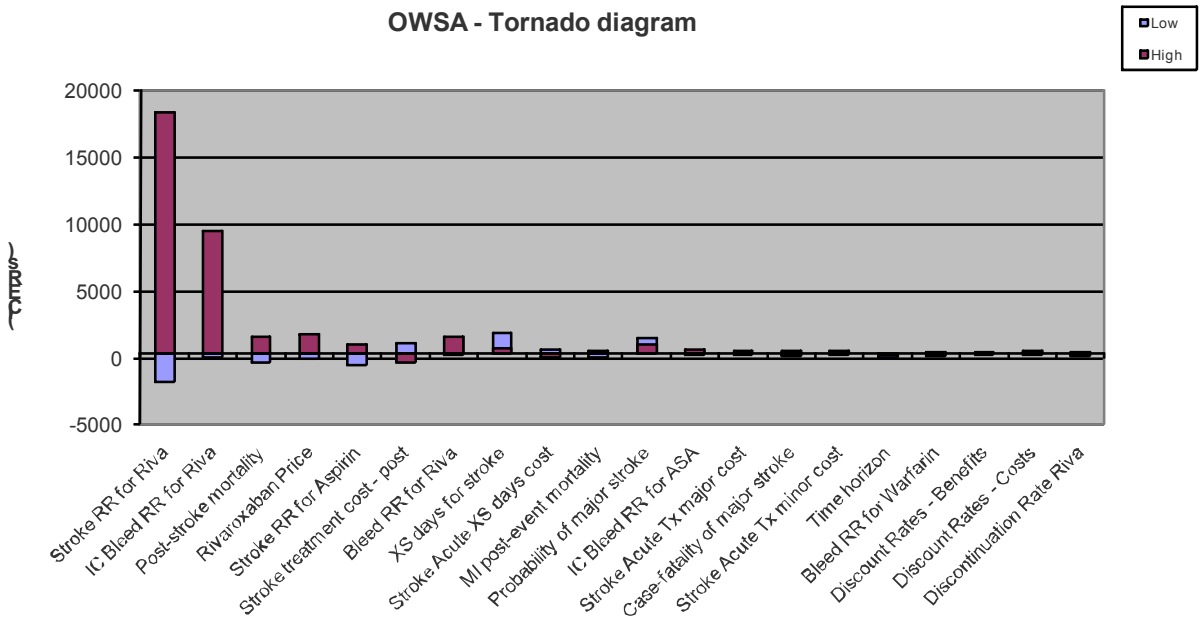


Figure 36. OWSA – Rivaroxaban compared with no treatment based on the NMA



PSA

Probabilistic sensitivity analysis also indicated that rivaroxaban would be considered cost-effective versus aspirin or no treatment across a range of hypothetical willingness-to-pay thresholds (Figure 39 and Figure 40). Probabilistic sensitivity analysis results indicated that rivaroxaban may be associated with cost savings and increased quality-adjusted life expectancy compared with aspirin (Figure 37) or no treatment (Figure 38).

Figure 37. Cost-effectiveness plane for rivaroxaban when compared with aspirin based on the NMA

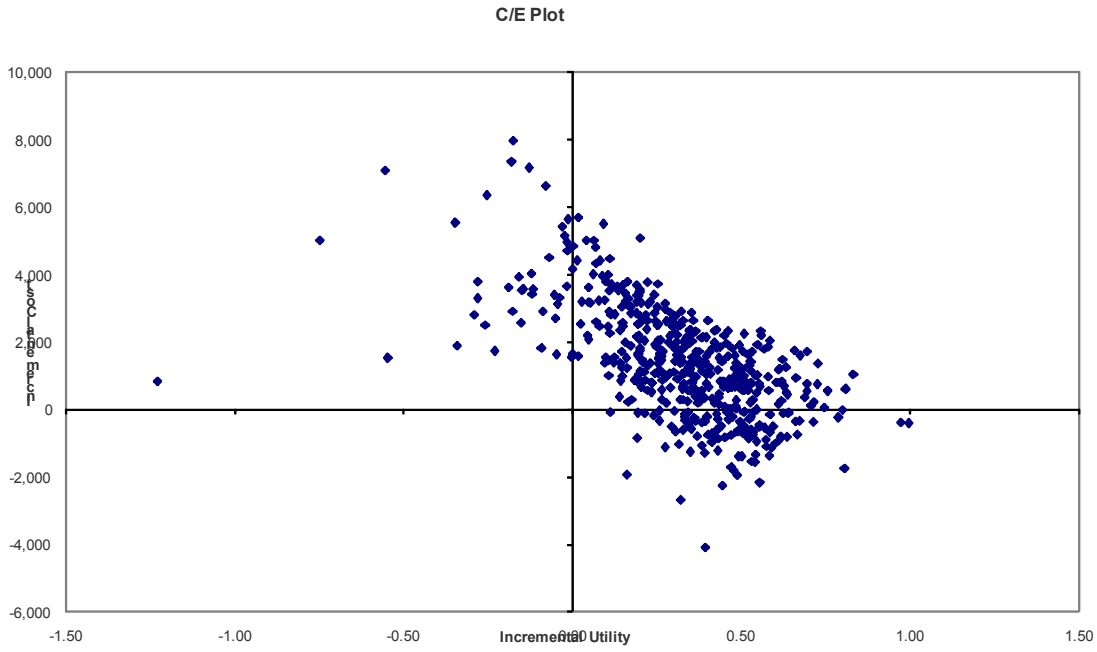


Figure 38. Cost-effectiveness plane for rivaroxaban when compared with no treatment based on the NMA

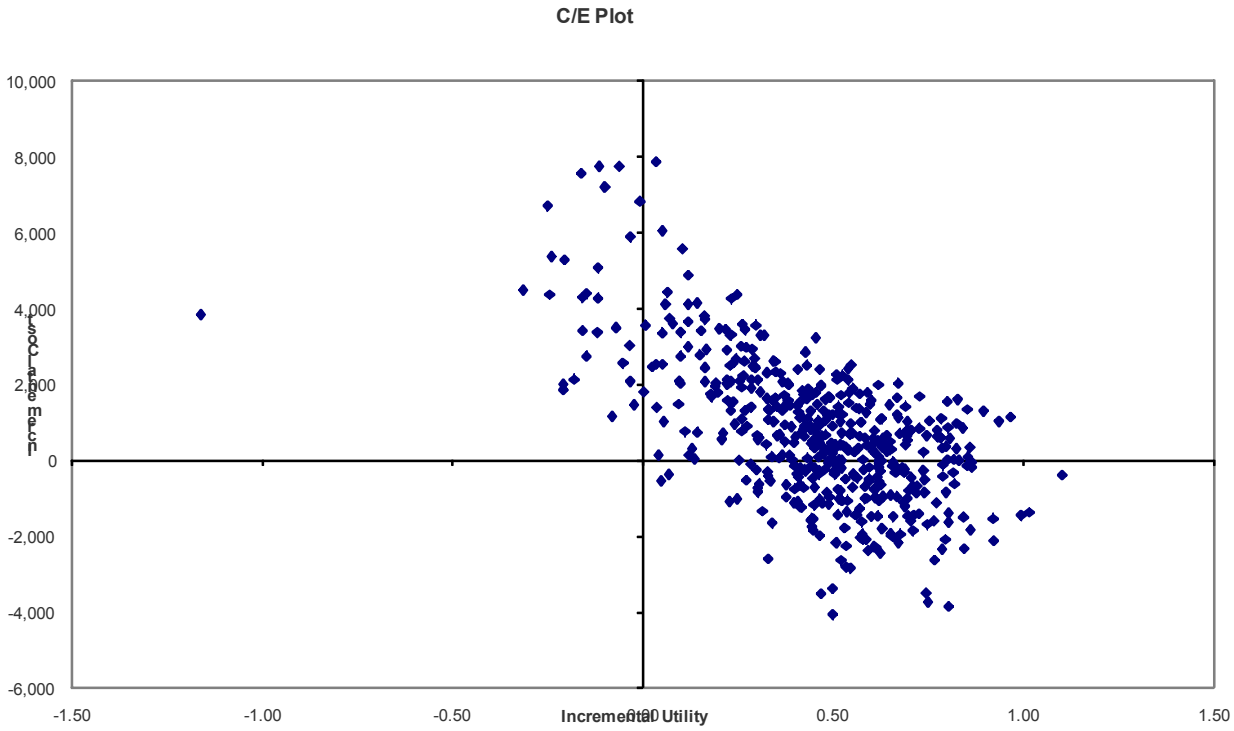


Figure 39. Cost-effectiveness acceptability curve for rivaroxaban compared with aspirin based on the NMA

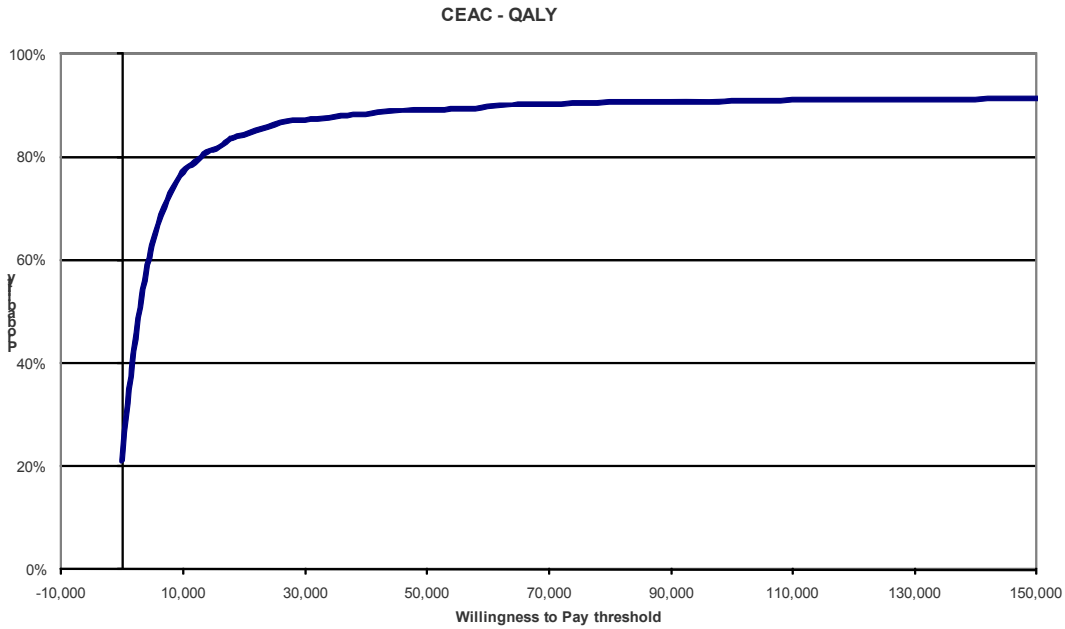
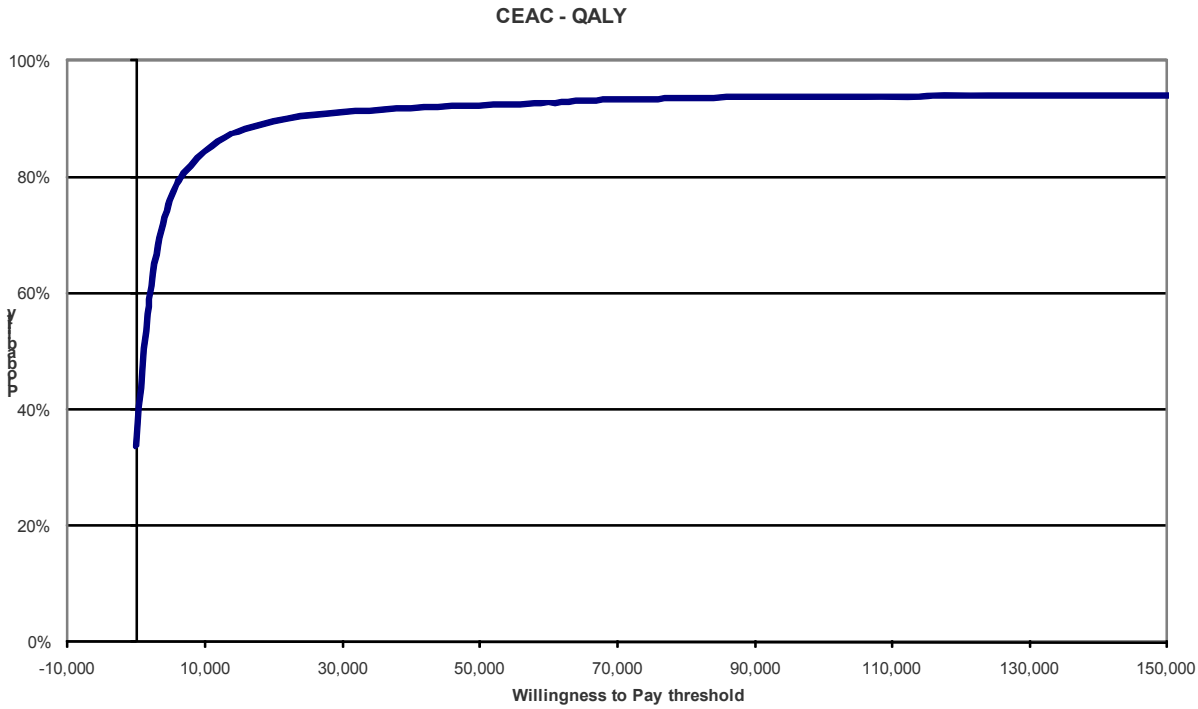


Figure 40. Cost-effectiveness acceptability curve for rivaroxaban compared with no treatment based on the NMA



Subgroup 4 - dabigatran

Rivaroxaban and dabigatran were compared using a cost minimisation approach. Results are presented in Table 90.

Table 90. Subgroup 4: dabigatran

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban based on NMA	12,397	9.056	6.712					
Dabigatran based on NMA	13,310	9.056	6.712	913	0	0	Extended dominance	Extended dominance

Any differences between the ICERs presented and the ICERs estimated from the Incremental costs and Incremental QALY above are due to rounding of the estimates from the cost-effectiveness model

Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

All relevant subgroups were considered in the analysis.

Interpretation of economic evidence

Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published economic literature regarding the cost-effectiveness of rivaroxaban for the prevention of stroke in patients with atrial fibrillation.

Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes. The ROCKET AF trial included a large proportion of patients with characteristics consistent with those patients in practice requiring anticoagulation. Furthermore, the inclusion of the NMA has allowed comparison to alternative treatments commonly used in practice.

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the economic evaluation lies in the comprehensive model structure fed by a robust clinical trial and extensive research to populate it.

The model was developed over the course of the ROCKET Phase III study in consultation with UK clinical and health economic experts, ensuring that the model clinical pathway is in line with UK clinical practice.

One of the key drivers of this evaluation is the cost of warfarin monitoring. As there is wide variation in the published literature as well as in clinical practice around warfarin monitoring, an extensive research project was undertaken to quantify the costs of warfarin monitoring in the UK. A service evaluation and national survey were conducted to obtain the models of anti-coagulation, quantify its distribution and collect resource use data for each type of model.

The main weakness of the evaluation lies in the lack of data around certain parameters which were not found in spite of a thorough systematic review. This was particularly true in the endpoints of systemic embolism, bleeding events and follow-on care costs for major events, where the individual clinical variation makes it difficult to assign an average cost per event.

What further analyses could be undertaken to enhance the robustness/completeness of the results?

Extensive sensitivity analyses, both one-way and probabilistic, were undertaken to test the robustness of the results. Further evidence generation programmes may improve the overall robustness of the analysis by increasing the accuracy of the input values.

Section C – Implementation

Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Annual estimates of atrial fibrillation prevalence from 2007 to 2010 for England(8) and Wales(9) were obtained from each country's Quality and Outcomes Frameworks (QOF) disease register. These figures indicated an increasing prevalence of atrial fibrillation over this time period. Therefore, the linear trend observed was used to estimate atrial fibrillation prevalence for the years 2012 to 2016 in both countries. Table 91 outlines the projected prevalence figures used in the budget impact model. It was assumed that all prevalent atrial fibrillation patients were diagnosed since QOF prevalence estimates were from general practitioner records.

Table 91. Projected prevalence of atrial fibrillation 2012-2016

Country	2012	2013	2014	2015	2016
England	1.46%	1.49%	1.53%	1.56%	1.60%
Wales	1.72%	1.74%	1.76%	1.78%	1.80%
Weighted prevalence	**1.47%**	**1.50%**	**1.54%**	**1.57%**	**1.61%**

In order to estimate the number of patients with atrial fibrillation the projected prevalence figures were applied to the projected total population estimates for England and Wales (ONS 2007-2010 population estimates)(142). Consistent with the expected license for rivaroxaban the population was restricted to non-valvular atrial fibrillation (NVAF). This estimation was based on data from the UK study by Stewart

et al (2001)(3) who reported that 93% of all atrial fibrillation patients have NVAF. Total NVAF patient estimates are reported in Table 92.

Table 92. Projected numbers of NVAF patients over 5 years in England and Wales

	2012	2013	2014	2015	2016
Population in England and Wales	55,993,805	56,387,650	56,781,482	57,175,519	57,575,709
Number of AF patients	822,825	848,089	873,627	899,442	925,630
Number of NVAF patients	**765,228**	**788,723**	**812,473**	**836,481**	**860,836**

Consistent with the expected indication of rivaroxaban, the population included was further limited to a patient population with a $CHADS_2$ score ≥ 1. Based upon data from a UK observational study this was estimated to represent 87.43% of all NVAF patients (Gallagher 2008)(13). Projected numbers of NVAF patients with a $CHADS_2$ score ≥ 1 are outlined in Table 93. This represents the proposed licensed population included within the analysis.

Table 93. Projected numbers of NVAF patients with $CHADS_2$ score ≥ 1 in England and Wales

	2012	2013	2014	2015	2016
Number of NVAF patients	765,228	788,723	812,473	836,481	860,836
Number of NVAF patients with $CHADS_2$ score ≥ 1	**669,003**	**689,544**	**710,308**	**731,297**	**752,590**

Within the proposed licensed population, there are a number of distinctive patient groups:

- Patients prescribed warfarin who are well controlled within the target therapeutic INR range
- Patients poorly controlled on warfarin
- Patients who have discontinued warfarin and instead receive aspirin or no treatment. Warfarin may not be suitable for some patients due to:
    - Hypersensitivity
    - Bleeding complications

    - Inability to comply with warfarin therapeutic regimen and regular INR monitoring
    - Other reasons

- Patients who according to stroke risk are eligible for an oral anticoagulant but are instead prescribed aspirin or no treatment

We expect a low likelihood of clinicians switching patients well controlled on warfarin to another oral anticoagulant. Two types of patient were identified as being the most likely to be prioritised by clinicians for rivaroxaban treatment:

- Patients poorly controlled warfarin
- Patients who have discontinued warfarin and instead receive aspirin or no treatment but who may be appropriate for rivaroxaban.
    - Those who have discontinued warfarin for reasons other than bleeding complications (patients who discontinue warfarin due to bleeding complications would also be unsuitable for rivaroxaban)
    - Those patients who are anticipated to have difficulty complying with warfarin regimen and the regular INR monitoring involved e.g. housebound patients with cognitive impairment

Estimation of patient population prescribed warfarin who are poorly controlled on warfarin

Patients in this cohort incur higher healthcare costs as they would require more frequent INR monitoring than well controlled patients. Since rivaroxaban treatment does not involve INR monitoring, there is a potential for cost saving within the healthcare system.

Using data from DeWilde et al (2006)(5), it was estimated that 49.7% of NVAF patients with a $CHADS_2$ score ≥ 1 receive warfarin. Nineteen percent (18.6%) of these patients were assumed to be poorly controlled on warfarin, based on results observed from a real-world study in a single secondary care anticoagulation clinic(22). Table 94 shows the projected number of NVAF patients with $CHADS_2$ score ≥ 1 over 5 years who would not be well controlled on warfarin.

Table 94. Projected numbers of NVAF patients with $CHADS_2$ score ≥ 1 over 5 years who are not well controlled on warfarin

	2012	2013	2014	2015	2016
NVAF patients with $CHADS_2$ ≥ 1	669,003	689,544	710,308	731,297	752,590
Patients on warfarin	332,597	342,809	353,131	363,566	374,152
Patients poorly controlled on warfarin (18.6%)	**61,863**	**63,762**	**65,682**	**67,623**	**69,592**

Estimation of patient population unsuitable for warfarin, but who may be appropriate for rivaroxaban

As outlined above, the population of patients unsuitable for warfarin but appropriate for rivaroxaban comprises several subgroups:

Patients discontinuing warfarin treatment

The number of patients hypersensitive to warfarin has been estimated at 0.6% (Samsa et al 2000)(143). It was assumed that these patients would fall within the group “those who have discontinued warfarin for reasons other than bleeding complications”.

Results from the DeWilde et al (2006)(5) study were used to estimate that 8.1% of the prevalent population had previously discontinued warfarin treatment (Table 95). Evans et al (2000)(144) was used to estimate the proportion of these patients that would most likely be appropriate for rivaroxaban and exclude discontinuations related to bleeding (Table 96). Evans et al (2000)(144) was identified as the most representative data source available as it reported results from an AF study population with a history of stroke and predominantly over the age of 70.The authors reported that, of patients who discontinue warfarin, 34% discontinued treatment due to bleeding complications, with the remaining 66.2% of patients discontinuing for a variety of reasons. Table 96 outlines the reasons for warfarin discontinuation and the corresponding proportion of patients.

Table 95. Proportion of patients discontinuing warfarin from DeWilde (2006)(5)

	Number of patients	Percentage
Patients not receiving treatment after discontinuation	302	2.7%
Patients receiving antiplatelets after discontinuation	611	5.4%
Total cohort	**11,238**	**8.1%**

Table 96. Reasons for warfarin discontinuation (Evans et al 2000)(144)

Reason for warfarin discontinuation	Percentage of patients
Bleeding complications	33.8%
Choice/compliance/logistics	50%
Other reasons	16.2%
Total excluding bleeding	**66.2%**

Overall, the percentage of patients who have discontinued warfarin and who may be suitable for rivaroxaban (having not experienced warfarin related bleeding complications) was estimated to be 5.4% of the eligible atrial fibrillation population (Table 97).

Table 97. Estimation of the proportion of patients suitable for rivaroxaban following warfarin discontinuation

Patient cohort	% of Patients
Relative % NVAF discontinued from warfarin	8.1%
Relative % of patients discontinuing warfarin for reasons other than bleeding complications	66.2%
Overall percentage of patients discontinuing warfarin for reasons other than bleeding complications	**5.4%** (8.1%*66.2%)

Patients with anticipated difficulty in complying with warfarin and its monitoring

The proportion of patients anticipated to be unable to comply with warfarin and INR monitoring has been estimated to represent 8.1% of the eligible atrial fibrillation population. Sudlow et al (1998)(145) reported the proportion of atrial fibrillation patients assessed as unable to comply with warfarin treatment and therefore inappropriate for initiation. These values were reported by age group and sex and have therefore been weighted by the respective demographics of $CHADS_2 \geq 1$ patients reported in a UK observational study (Gallagher 2008)(13). Table 98 illustrates the derivation of this estimate.

Table 98. Derivation of age and sex-weighted proportion of patients unable to comply with warfarin treatment

Age	Women		Men		Total
	≥75	<75*	≥75	<75*	
Patients unable to comply with VKA treatment (Sudlow 1998)(145) (%)*	14.55%	7.14%	9.64%	0%	-
Patients per age and sex group (Gallaghar 2008)(13) (%)	32.2%	12.7%	25.7%	29.4%	100%
Age-weighted % of patients not complying with treatment	4.7%	0.9%	2.5%	0.0%	**8.1%**

**Sudlow et al (1998)(145) reported patient percentages for those ≥75 and those aged 65-74. It was assumed that the percentage of 65-74 year-old patients unable to comply was applicable to all patients below the age of 75 from Gallaghar et al (2008)(13)*

Summary of population potentially prioritised as suitable for rivaroxaban

The overall percentage of patients unsuitable for warfarin, but who may be appropriate for rivaroxaban was calculated as 13.45% of eligible patients. This represents the total of patient who have discontinued warfarin for reasons other than bleeding complications (5.4%) and the percentage of patients identified as unable to comply with warfarin (8.1%). Table 99 shows the projected numbers of patients for these two subgroups and their respective total. In 2012 it was estimated that a total of 89,965 patients would be unsuitable for warfarin, but may be suitable for rivaroxaban.

Table 99. Projected number of patients unsuitable for warfarin treatment but suitable for rivaroxaban

Patient cohort	2012	2013	2014	2015	2016
Patients discontinuing warfarin for reasons other than bleeding complications	35,989	37,094	38,211	39,341	40,486
Patients unable to comply with warfarin	53,976	55,633	57,309	59,002	60,720
Total patients unsuitable for warfarin but suitable for rivaroxaban (n)	**89,965**	**92,728**	**95,520**	**98,342**	**101,206**

The combination of patients not well controlled on warfarin treatment and those unsuitable for warfarin but may be appropriate for rivaroxaban gives the total number of patients who will most likely be prioritised by clinicians for rivaroxaban treatment as demonstrated in Table 100. In 2012 this was estimated to represent 151,828 patients.

Table 100. Projected number of eligible patients likely to be prioritised for rivaroxaban treatment by physicians

Patient cohort	2012	2013	2014	2015	2016
Patients not well controlled on warfarin (n)	61,863	63,762	65,682	67,623	69,592
Patients unsuitable for warfarin but suitable for rivaroxaban (n)	89,965	92,728	95,520	98,342	101,206
Total patients likely to be prioritised for rivaroxaban treatment (n)	**151,828**	**156,490**	**161,202**	**165,966**	**170,798**

What assumption(s) were made about current treatment options and uptake of technologies?

To help understand the economic impact of rivaroxaban uptake and use, cost savings were estimated under two scenarios; a world with rivaroxaban and a world without rivaroxaban. Two pre-existing treatment options, warfarin and aspirin, were included as current treatment options in the analysis; in addition to a no treatment option. Using data from a UK study by DeWilde et al (2006)(5), estimations were made for the distribution of these treatment options across $CHADS_2 \geq 1$ patients, as shown in Table 101. Note a PRODIGY risk score of moderate or greater was considered equivalent to a $CHADS_2 \geq 1$.

Table 101. Current treatment options and uptake in the eligible population

Treatment	Current uptake
Warfarin	49.7%
Aspirin (antiplatelet)	34.5%
No treatment	15.8%

In anticipation of dabigatran uptake following approval of the stroke prevention indication this has also been included as a scenario analysis in the estimates for the market share in a world without rivaroxaban. Given the novel nature of this technology it was assumed that uptake of dabigatran would increase over the next 5 years.

What assumption(s) were made about market share (when relevant)?

The estimated market shares in a world without rivaroxaban are reported in Table 102. These values are based on those reported by DeWilde 2006(5) with an adjustment to reflect that a proportion of the non warfarin treated population will most likely be contraindicated to rivaroxaban due to prior bleeding events on warfarin.

Based on data from Evans et al (2000)(144) this was estimated to represent 3% of potentially eligible patients.

Table 102. Projected market share for the total eligible population – world without rivaroxaban*

	2012	2013	2014	2015	2016
Warfarin	51.1%	51.1%	51.1%	51.1%	51.1%
Aspirin	33.6%	33.6%	33.6%	33.6%	33.6%
Rivaroxaban	0%	0%	0%	0%	0%
No Treatment	15.3%	15.3%	15.3%	15.3%	15.3%

* *Total market share reported may deviate from 100% due to rounding differences.*

The availability of the new oral anticoagulants, such as rivaroxaban, represents a potentially important change in the approach to the management of NVAF. However, it was considered that the uptake of these new treatments would most likely be higher in two specific patient groups:

- Patients poorly controlled on warfarin treatment
- Patients unsuitable for warfarin, but who may be appropriate for rivaroxaban

In a world with rivaroxaban, it was anticipated that a proportion of patients who would have been treated with warfarin, aspirin or no treatment would instead be managed with rivaroxaban (Table 103).

Table 103. Projected market share for the total eligible population – world with rivaroxaban*

	2012	2013	2014	2015	2016
Warfarin	50.5%	50.0%	48.5%	45.9%	44.5%
Aspirin	33.1%	32.4%	31.2%	29.8%	27.9%
Rivaroxaban	1.4%	2.9%	6.1%	10.8%	15.0%
No Treatment	15.1%	14.8%	14.2%	13.6%	12.7%

**Total market share reported may deviate from 100% due to rounding differences.*

Scenario analysis to assess the potential impact of the prior approval of dabigatran for use in the NHS in England and Wales

Dabigatran has recently received marketing authorisation for the prevention of stroke in NVAF. Therefore, as a scenario analysis, a budget impact analysis was undertaken including dabigatran in the world with and without rivaroxaban. For the world without rivaroxaban the market share uptake of dabigatran was assumed to rise (displacing warfarin, aspirin and no treatment) over the next 5 years (Table 104).

For the analysis including rivaroxaban it was assumed that rivaroxaban would capture up to half of the market share projected for dabigatran (Table 105). Reflecting a later marketing authorisation for rivaroxaban in the management of NVAF, the market share estimates for 2012 and 2013 are lower than those estimated for dabigatran.

Table 104. Projected market share for the total eligible population – world without rivaroxaban (scenario analysis)*

	2012	2013	2014	2015	2016
Warfarin	50.5%	50.0%	48.5%	45.9%	44.5%
Aspirin	33.1%	32.4%	31.2%	29.8%	27.9%
Dabigatran	1.4%	2.9%	6.1%	10.8%	15.0%
Rivaroxaban	0.0%	0.0%	0.0%	0.0%	0.0%
No Treatment	15.1%	14.8%	14.2%	13.6%	12.7%

** Total market share reported may deviate from 100% due to rounding differences.*

Table 105. Projected market share for the total eligible population – world with rivaroxaban (scenario analysis)*

	2012	2013	2014	2015	2016
Warfarin	50.5%	50.0%	48.5%	45.9%	44.5%
Aspirin	33.1%	32.4%	31.2%	29.8%	27.9%
Dabigatran	1.0%	1.6%	3.1%	5.4%	7.5%
Rivaroxaban	0.4%	1.3%	3.1%	5.4%	7.5%
No Treatment	15.1%	14.8%	14.2%	13.6%	12.7%

** Total market share reported may deviate from 100% due to rounding differences.*

In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

It is likely that the availability of warfarin will reduce overhead costs associated with the monitoring of warfarin. However, since not all warfarin will be displaced by rivaroxaban, estimates of cost savings related to overheads could not be made. Therefore, the presented cost savings relating to warfarin monitoring are likely to represent conservative estimates.

What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Drug and monitoring costs were sourced as described in section 6.5.1. This included patient transport costs for the 8.55% of patients monitored in secondary care and who were estimated to require this resource. Warfarin monitoring costs were differentiated between well controlled and poorly controlled patients. Costs for patients well controlled on warfarin were estimated by considering the mean number of visits to anticoagulation clinics applied in the cost-effectiveness model. This was differentiated into well and poorly controlled patients using 18.6% as the relative size of the poorly controlled population and required 9 visits per quarter. These cost parameters are summarised in Table 106.

Table 106. Costs of warfarin monitoring per quarter and number of visits to anticoagulation clinics

	Visits (n)	Cost (£, per quarter)
Mean visits/quarter	5	136
Weighted estimate per quarter well managed patients	4.09	111
Weighted estimate per quarter poorly controlled patients	9	244

Were there any estimates of resource savings? If so, what were they?

Displacement of warfarin by rivaroxaban amongst poorly controlled patients will be associated with a reduction in INR monitoring costs in both primary and secondary care. There will also be a transport cost saving amongst those patients whose INR was monitored in secondary care and require NHS transport to attend appointments.

What is the estimated annual budget impact for the NHS in England and Wales?

Results from the base case budget impact analysis

Table 107 and Table 108 present the estimated expenditure for the years 2012 – 2016 for a world with and without rivaroxaban, respectively. The net budget impact is presented in Table 109. The budget impact analysis indicates that the net cost incurred due to the uptake of rivaroxaban in the year 2016 would be approximately £34 million and that the cumulative cost over 5 years would be approximately £77

million. These costs are contingent upon rivaroxaban displacing warfarin, aspirin and no treatment as options in the management of atrial fibrillation.

When compared to poorly controlled warfarin patients, rivaroxaban is cost saving. The projected increase in expenditure can therefore be attributed to the use of rivaroxaban amongst patients unsuitable for warfarin who were previously on aspirin or no treatment. Given the excess risk of ischaemic stroke amongst these patients it is likely that consideration of event costs would offset this budget impact.

Table 107. Estimated expenditure for the NHS in England and Wales in a world without rivaroxaban

	2012	2013	2014	2015	2016
Drug Costs	15,909,153	16,397,622	16,891,388	17,390,521	17,896,864
Monitoring Costs	180,355,032	185,892,587	191,490,192	197,148,643	202,888,825
Total Costs*	**196,264,185**	**202,290,210**	**208,381,580**	**214,539,164**	**220,785,689**

** Total expenditure reported may deviate from individual components due to rounding differences.*

Table 108. Estimated expenditure for the NHS in England and Wales in a world with rivaroxaban

	2012	2013	2014	2015	2016
Drug Costs	22,467,742	30,763,523	48,386,767	74,256,188	99,393,261
Monitoring Costs	176,128,231	178,424,167	173,539,135	160,845,692	155,339,800
Total Costs*	**198,595,973**	**209,187,689**	**221,925,903**	**235,101,880**	**254,733,061**

** Total expenditure reported may deviate from individual components due to rounding differences.*

Table 109. Estimated net budget impact of rivaroxaban uptake for the NHS in England and Wales

	2012	2013	2014	2015	2016
Drug Costs	6,558,589	14,365,900	31,495,379	56,865,667	81,496,397
Monitoring Costs	-4,226,801	-7,468,421	-17,951,057	-36,302,951	-47,549,025
Total Costs*	**2,331,788**	**6,897,480**	**13,544,323**	**20,562,716**	**33,947,372**

* *Net budget impact reported may deviate from individual components due to rounding differences.*

Results from the scenario analysis to assess the potential impact of the prior approval of dabigatran for use in the NHS in England and Wales

In a scenario including dabigatran use within the analysis population Table 110 and Table 111 present the estimated expenditures for the years 2012 – 2016 for a world with and without rivaroxaban, respectively. The net budget impact is presented in Table 112. The budget impact analysis indicates that the net cost savings due to the uptake of rivaroxaban in the year 2016 would be approximately £8 million and that

the cumulative cost saving over 5 years would be approximately £19 million. These savings are contingent upon rivaroxaban displacing the more expensive alternative dabigatran for stroke prevention in AF, with no direct displacement of warfarin and hence no additional savings on monitoring costs. This scenario analysis demonstrates that rivaroxaban would result in substantial cost savings to the NHS in England and Wales by directly displacing dabigatran for use under the licensed indication.

Table 110. Estimated expenditure for the NHS in England and Wales in a world without rivaroxaban

	2012	2013	2014	2015	2016
Drug Costs	23,821,179	33,713,391	54,866,921	85,988,210	116,170,118
Monitoring Costs	176,128,231	178,424,167	173,539,135	160,845,692	155,339,800
Total Costs*	**199,949,410**	**212,137,557**	**228,406,057**	**246,833,902**	**271,509,918**

* *Total expenditure reported may deviate from individual components due to rounding differences.*

Table 111. Estimated expenditure for the NHS in England and Wales in a world with rivaroxaban

	2012	2013	2014	2015	2016
Drug Costs	23,424,632	32,416,146	51,626,844	80,122,199	107,781,689
Monitoring Costs	176,128,231	178,424,167	173,539,135	160,845,692	155,339,800
Total Costs*	**199,552,863**	**210,840,313**	**225,165,980**	**240,967,891**	**263,121,489**

* *Total expenditure reported may deviate from individual components due to rounding differences.*

Table 112. Estimated net budget impact of rivaroxaban uptake for the NHS in England and Wales

	2012	2013	2014	2015	2016
Drug Costs	-396,547	-1,297,245	-3,240,077	-5,866,011	-8,388,428
Monitoring Costs	0	0	0	0	0
Total Costs*	**-396,547**	**-1,297,245**	**-3,240,077**	**-5,866,011**	**-8,388,428**

* *Net budget impact reported may deviate from individual components due to rounding differences.*

Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Any impact of novel anticoagulants as a class upon fixed over head costs associated with provision of INR monitoring clinics was not considered. Furthermore, conservatively the potential impact of rivaroxaban upon a reduction in events has not been included.

8 References

Reference List

(1) National Institute for Health and Clinical Excellence. Atrial Fibrillation. The management of atrial fibrillation. Clinical Guideline Number 36. 2006.

(2) European Society of Cardiology. Guidelines for the management of atrial fibrillation. http://www escardio org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT pdf 2010 August 29 [cited 2010 Oct 29];

(3) Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart 2001 Nov;86(5):516-21.

(4) de Lusignan S, van Vlymen J, Hague N, Thana L, Dzregah B, Chan T. Preventing stroke in people with atrial fibrillation: a cross-sectional study. J Public Health (Oxf) 2005;27(1):85-92.

(5) DeWilde S, Carey IM, Emmas C, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart 2006 Aug;92(8):1064-70.

(6) Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994-1998: analysis of data from the general practice research database. Heart 2001 Sep;86(3):284-8.

(7) Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. Heart 2007 May;93(5):606-12.

(8) NHS The Information Centre. Quality and Outcomes Framework (QOF) for April 2009 - March 2010, England. http://www ic nhs uk/webfiles/QOF/2009-10/Prevalence%20tables/QOF0910_National_Prevalence xls 2010 [cited 2011 Jul 5];

(9) Health in Wales. QOF prevalence charts 2009-10 350. http://www wales nhs uk/sites3/Documents/480/LHB%20Prevalence%20Charts xls 2011 [cited 2011 Jul 5];

(10) Bayer plc. Atrial Fibrillation and Cardioembolic Stroke. http://www thrombosisadviser co uk/scripts/pages/en/knowing-the-risk/atrial-fibrillation-and-cardioembolic-stroke/index php 2011 [cited 2011 Jun 23];

(11) Frost L, Engholm G, Johnsen S, Moller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. Arch Intern Med 2001 Jan 22;161(2):272-6.

(12) StatsWales - Welsh Assembly Government. QOF disease registers 2009-10. http://www statswales wales gov uk/TableViewer/tableView aspx?ReportId=24813 2010 [cited 2011 Jul 5];

(13) Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? J Thromb Haemost 2008 Sep;6(9):1500-6.

(14) Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J 2006 Aug;27(16):1979-2030.

(15) Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001 Jun 13;285(22):2864-70.

(16) NHS Improvement Programme. Heart and Stroke Improvement. Commissioning for Stroke Prevention in Primary Care - The Role of Atrial Fibrillation. http://www improvement nhs uk/heart/Portals/0/documents2009/AF_Commissioning_Guide_v2 pdf 2009 [cited 2010 Mar 22];

(17) National Institute for Health and Clinical Excellence. Atrial Fibrillation. The management of atrial fibrillation. Costing Report. Implementing NICE guidance in England. Clinical Guideline number 36. 2006.

(18) Department of Health. NHS reference costs 2009-2010. http://www dh gov uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123 459 2011 January 13 [cited 2011 Jun 23];

(19) Curtis L. Unit Costs of Health and Social Care 2010. Personal Social Services Research Unit (PSSRU). http://www pssru ac uk/pdf/uc/uc2010/uc2010 pdf 2010 [cited 2011 May 20];

(20) Bayer plc., pH associates. Data on File. Survey of anticoagulation services in the UK. 2011.

(21) NHS evidence Clinical Knowledge Summaries. Anticoagulation - oral. http://www cks nhs uk/anticoagulation_oral/view_whole_topic 2010 [cited 2011 Jun 30];

(22) Bayer plc, pH Assciates, P Rose, R James, O Chapman. Data on file. A real world evaluation to describe the characteristics, outcomes and resource use associated with patients being managed by a secondary care based anticoagulation service. 2011.

(23) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. New England Journal of Medicine 2011 Aug 10;null.

(24) ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J 2010 Mar;159(3):340-7.

(25) Johnson & Johnson Pharmaceutical Research & Development. Clinical Protocol: A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group Multicenter, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Once Daily Oral Rivaroxaban (BAY 59-7939) With Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in

Subjects With Non-Valvular Atrial Fibrillation. 2006 Oct 4. Report No.: EDMS-PSDB-5429061:2.0.

(26) Johnson & Johnson Pharmaceutical Research & Development. Clinical Study Report: A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group Multicenter, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Once Daily Oral Rivaroxaban (BAY 59-7939) With Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Non-Valvular Atrial Fibrillation. The ROCKET AF Trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). 2010 Dec 23. Report No.: EDMS-PSDB-7123167:2:0.

(27) Patel MR. Stroke prevention using the oral direct factor Xa inhibitor rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation (ROCKET AF). 2010 p. 2215-26.

(28) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Supplementary Appendix to Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011. DOI:10.1056/NEJMoa1009638. http://www nejm org/doi/suppl/10 1056/NEJMoa1009638/suppl_file/nejmoa1009638_appendix pdf 2011 August 10 [cited 2011 Aug 11];

(29) Masatsugu H, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. J-ROCKET AF: THE SAFETY AND EFFICACY OF RIVAROXABAN FOR PREVENTION OF STROKE IN JAPANESE PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION. http://www isth2011 com/prgrm-common/abstracts 2011 July 25Presented at ISTH 2011 Congress in Kyoto (July 2011)

(30) Kirchof P, Auricchio A, Bax J, Crijns H, Camm J, Diener H-C, et al. Outcome parameters for trials in atrial fibrillation: executive summary. European Heart Journal 2007;28:2803-17.

(31) Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. J Am Coll Cardiol 1991;18:349-55.

(32) Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361(12):1139-51.

(33) Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009 May;157(5):805-10, 810.

(34) Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.

(35) Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993 Mar 1;69(3):236-9.

(36) Bayer plc. Data on file. 2011.

(37) International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials. E9. http://www ema europa eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928 pdf 1998 September [cited 2011 Aug 11];

(38) U.S.Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Draft Guidance for Industry. Non-Inferiority Clinical Trials. http://www fda gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140 pdf 2010 [cited 2011 Aug 11];

(39) International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Choice of control group and related issues in clinical trials. E10. http://www ich org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline pdf 2000 July 20 [cited 2011 May 11];

(40) Hacke W, Hankey G, For the ROCKET-AF Committees. Rivaroxaban versus warfarin in patients with AF and prior cerebrovascular disease: Results from the ROCKET-AF trial. 20 European Stroke Conference; May 24-27 2011; Hamburg,Germany . 2011. 22-6-2011.
Ref Type: Abstract

(41) Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). J Thromb Haemost 2010 Oct;8(10):2182-91.

(42) Oxford Outcomes. Rivaroxaban versus alternative comparators for stroke prevention in atrial fibrillation treatment: a systematic review- Protocol. 2010 Oct 1.

(43) Oxford Outcomes. Rivaroxaban versus alternative comparators in stroke prevention in atrial fibrillation treatment: a systematic review. 2011 May 6.

(44) Prevention of stroke in atrial fibrillation. N Engl J Med 1990 Aug 16;323(7):481-4.

(45) Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989 Jan 28;1(8631):175-9.

(46) 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. N Engl J Med 1990 Nov 29;323(22):1505-11.

(47) 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. N Engl J Med 1992 Nov 12;327(20):1406-12.

(48) EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993 Nov 20;342(8882):1255-62.

(49) Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation. LASAF Pilot Study Group. Am Heart J 1999 Jul;138(1 Pt 1):137-43.

(50) 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. Stroke 2006 Feb 1;37(2):447-51.

(51) Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994 Mar 19;343(8899):687-91.

(52) Chesebro JHW. Bleeding during antithrombotic therapy in patients with atrial fibrillation. Archives of Internal Medicine 1996 Feb 26;156(4):26.

(53) 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. Arch Intern Med 1998 Jul 27;158(14):1513-21.

(54) 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.

(55) 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. Eur J Intern Med 2006 Jan;17(1):48-52.

(56) 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.

(57) Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. 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.

(58) Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370(9586):493-503.

(59) 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 Cardiovasc Disord 2003 Aug 26;3:9.

(60) Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007 Nov 1;100(9):1419-26.

(61) Connolly S, Yusuf S, Budaj A, Camm J, Chrolavicius S, Commerford PJ, et al. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006 Jun;151(6):1187-93.

(62) Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009 May 14;360(20):2066-78.

(63) Oxford Outcomes. Network meta-analysis incorporating results of the ROCKET trial (Stroke prevention in atrial fibrillation). 2011 May 7.

(64) Goto S, Bhatt DL, Rother J, Alberts M, Hill MD, Ikeda Y, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. Am Heart J 2008 Nov;156(5):855-63, 863.

(65) Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van WC. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. CMAJ 2008 Jul 29;179(3):235-44.

(66) Ghate SR, Biskupiak JE, Ye X, Hagan M, Kwong WJ, Fox ES, et al. Hemorrhagic and thrombotic events associated with generic substitution of warfarin in patients with atrial fibrillation: a retrospective analysis. Ann Pharmacother 2011 Jun;45(6):701-12.

(67) Murdoch DL, O'Neill K, Jackson J, McMahon A, Rumley A, Wallace I, et al. Are atrial fibrillation guidelines altering management? A community based study. Scott Med J 2005 Nov;50(4):166-9.

(68) Ogilvie IM, Welner SA, Cowell W, Lip GY. Characterization of the proportion of untreated and antiplatelet therapy treated patients with atrial fibrillation. Am J Cardiol 2011 Jul 1;108(1):151-61.

(69) Ogilvie IM, Welner SA, Cowell W, Lip GY. Ischaemic stroke and bleeding rates in 'real-world' atrial fibrillation patients. Thromb Haemost 2011 Jul 4;106(1):34-44.

(70) 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.

(71) Bousser MG, Bouthier J, Buller HR, Cohen AT, Crijns H, Davidson BL, 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.

(72) Oldgren J, Ezekowitz MD, Alings M, Diener HC, Reilly PA, Yusuf S, et al. DABIGATRAN VERSUS WARFARIN AND IMPACT OF CHAD2-VASC SCORE ON OUTCOME IN ATRIAL FIBRILLATION PATIENTS: A RE-LY SUBGROUP ANALYSIS. Journal of the American College of Cardiology 2011 Apr 5;57(14_Suppl_S):E7.

(73) Abdelhafiz AH, Wheeldon NM. Results of an open-label, prospective study of anticoagulant therapy for atrial fibrillation in an outpatient anticoagulation clinic. Clin Ther 2004;26(9):1470-8.

(74) Burton C, Isles C, Norrie J, Hanson R, Grubb E. The safety and adequacy of antithrombotic therapy for atrial fibrillation: a regional cohort study. Br J Gen Pract 2006;56(530):697-702.

(75) Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. Arch Intern Med 2001;161(17):2125-8.

(76) Evans A, Perez I, Yu G, Kalra L. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? Stroke 2001;32(12):2828-32.

(77) Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart 2005;91(4):472-7.

(78) Yousef ZR, Tandy SC, Tudor V, Jishi F, Trent RJ, Watson DK, et al. Warfarin for non-rheumatic atrial fibrillation: five year experience in a district general hospital. Heart 2004;90(11):1259-62.

(79) Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. Journal of the American Medical Association 1995 Dec 20;274(23):1839-45.

(80) Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thromb Haemost 2011 May;105(5):908-19.

(81) Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Annals of Internal Medicine 2011;(1):January.

(82) Lightowlers S, McGuire A. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. Stroke 1998 Sep;29(9):1827-32.

(83) Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation 2011 Jun 7;123(22):2562-70.

(84) Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009 May 30;373(9678):1849-60.

(85) National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. http://www nice org uk/media/B52/A7/TAMethodsGuideUpdatedJune2008 pdf 2008 June [cited 2011 Aug 15];

(86) Boehringer Ingelheim International GmbH. Pradaxa Summary of Product Characteristics. http://ec europa eu/health/documents/community-register/2011/20110801104049/anx_104049_en pdf 2011 March 8 [cited 2011 Aug 16];

(87) Briggs AHE, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. 2006.

(88) Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994 Jul 11;154(13):1449-57.

(89) Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003 Aug 27;290(8):1049-56.

(90) 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. J Intern Med 2003 Jul;254(1):95-101.

(91) Office for National Statistics. Interim Lifetables. http://www statistics gov uk/hub/release-calendar/index html?newquery=*&title=Interim+Life+Tables&pagetype=calendar-entry&lday=&lmonth=&lyear=&uday=&umonth=&uyear= 2010 [cited 2011 Aug 15];

(92) Marini C, De SF, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005 Jun;36(6):1115-9.

(93) Hoit BD, Gilpin EA, Henning H, Maisel AA, Dittrich H, Carlisle J, et al. Myocardial infarction in young patients: an analysis by age subsets. Circulation 1986 Oct;74(4):712-21.

(94) Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991 Aug;22(8):983-8.

(95) Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. Stroke 2006 Jan;37(1):193-8.

(96) Hallan S, Asberg A, Indredavik B, Wideroe TE. Quality of life after cerebrovascular stroke: a systematic study of patients' preferences for different functional outcomes. J Intern Med 1999 Sep;246(3):309-16.

(97) Sanders GD, Hlatky MA, Every NR, McDonald KM, Heidenreich PA, Parsons LS, et al. Potential cost-effectiveness of prophylactic use of the implantable cardioverter defibrillator or amiodarone after myocardial infarction. Ann Intern Med 2001 Nov 20;135(10):870-83.

(98) Kato T, Yamashita T, Sagara K, Iinuma H, Fu LT. Progressive nature of paroxysmal atrial fibrillation. Observations from a 14-year follow-up study. Circ J 2004 Jun;68(6):568-72.

(99) Peinado R, Arribas F, Ormaetxe JM, Badia X. Variation in quality of life with type of atrial fibrillation. Rev Esp Cardiol 2010 Dec;63(12):1402-9.

(100) Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. J Health Serv Res Policy 2001 Apr;6(2):92-8.

(101) Berg J, Lindgren P, Nieuwlaat R, Bouin O, Crijns H. Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. Quality of Life Research 2010 Apr;19(3):381-90.

(102) Guedon-Moreau L, Capucci A, Denjoy I, Morgan CC, Perier A, Leplege A, et al. Impact of the control of symptomatic paroxysmal atrial fibrillation on health-related quality of life. Europace 2010 May;12(5):634-42.

(103) Kamel H, Hegde M, Johnson DR, Gage BF, Johnston SC. Cost-effectiveness of outpatient cardiac monitoring to detect atrial fibrillation after ischemic stroke (Provisional abstract). Stroke 2010;41:1514-20.

(104) Radholm K, Ostgren CJ, Alehagen U, Falk M, Wressle E, Marcusson J, et al. Atrial fibrillation (AF) and co-morbidity in elderly. A population based survey of 85 years old subjects. Archives of Gerontology and Geriatrics 2011;(3):May-June.

(105) Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Archives of Internal Medicine 1996;156:1829-36.

(106) Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. Stroke 1998 Jun;29(6):1083-91.

(107) Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. Lancet 2000;355(9208):956-62.

(108) Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. Pharmacoeconomics 2006;24(10):1021-33.

(109) Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc 1997 Jan;4(1):49-56.

(110) Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Medical Care 2005;43(7):736.

(111) Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. J Epidemiol Community Health 2003 Aug;57(8):622-7.

(112) Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D, discussion paper 172. York: Centre for Health Economics. http://www york ac uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172 pdf 1999

(113) Protheroe J, Fahey T, Montgomery AA, Peters TJ. The impact of patients' preferences on the treatment of atrial fibrillation: Observational study of patient based decision analysis
294. British Medical Journal 320(7246)()(pp 1380-1384), 2000 Date of Publication: 20 May 2000 2000;(7246):1380-4.

(114) Robinson MB, Thompson E, Black NA. A model for estimating the cost-utility of clinical audit. The example of thrombolysis for suspected acute myocardial infarction. Int J Technol Assess Health Care 1998;14(1):161-71.

(115) O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. Journal of the American Medical Association 2005;293(6):699-706.

(116) Catherwood E, Teng MP, Melby DP. Cost-effectiveness of current management strategies in atrial fibrillation. Cardiac electrophysiology review 2001;5(2-3):254-62.

(117) Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med 2004 Nov 16;141(10):745-52.

(118) BMJ Group, the Royal Pharmaceutical Society of Great Britain. British National Formulary, March 2011 (Edition 61). Available at http://www bnf org 2011 [cited 2011 May 20];

(119) National Institute for Health and Clinical Excellence. Anticoagulation therapy service - commissioning and benchmarking tool. http://www nice org uk/usingguidance/commissioningguides/anticoagulationtherapyservice/commissioningtool jsp?domedia=1&mid=B33E47E2-19B9-E0B5-D4CBD4C979603284 2010 June 2 [cited 2011 Aug 15];

(120) Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology 1997 Apr;48(4):891-5.

(121) Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998 Oct 16;82(8A):2N-9N.

(122) Lin H-J, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation: The Framingham study
1525. Stroke 27(10)()(pp 1760-1764), 1996 Date of Publication: Oct 1996 1996;(10):1760-4.

(123) Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. Age Ageing 2009 Jan;38(1):27-32.

(124) National Clinical Guideline Centre - Acute and Chronic Conditions (formerly the National Collaborating Centre for Acute Care). Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. 2010.

(125) Abdelhafiz AH, Wheeldon NM. Use of resources and cost implications of stroke prophylaxis with warfarin for patients with nonvalvular atrial fibrillation. The American journal of geriatric pharmacotherapy 2003;1(2):53-60.

(126) Jowett S, Bryan S, Mahe I, Brieger D, Carlsson J, Kartman B, et al. A multinational investigation of time and traveling costs in attending anticoagulation clinics. Value in Health 2008;11:207-12.

(127) Kerr M. Department of Health Atrial Fibrillation cost benefit analysis. 2008.

(128) Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. Health Technol Assess 2007 Oct;11(38):iii-66.

(129) McCahon D, Murray ET, Jowett S, Sandhar HS, Holder RL, Hussain S, et al. Patient self management of oral anticoagulation in routine care in the UK. J Clin Pathol 2007 Nov;60(11):1263-7.

(130) Parry D, Bryan S, Gee K, Murray E, Fitzmaurice D. Patient costs in anticoagulation management: a comparison of primary and secondary care. British Journal of General Practice 2001;51:972-6.

(131) National Audit Office. Progress in improving stroke care: modelling paper. Report on the findings from our modelling of stroke care provision. 2010.

(132) National Institute for Health and Clinical Excellence. Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (CG68). Costing report. Implementing NICE guidance. London; 2008.

(133) National Institute for Health and Clinical Excellence. Clinical Knowledge Summaries (CKS): Anticoagulation - oral - Management. http://www cks nhs uk/anticoagulation_oral/management/scenario_anticoagulation_oral 2009 March

(134) Baglin T, Keeling DM, Watson HG. Guidelines on oral anticoagulation (warfarin): third edition - 2005 update. British Soc Haematol 2005;132:277-85.

(135) Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):160S-98S.

(136) Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):454S-545S.

(137) Cooper A, Skinner J, Nherera L, Feder G, Richie G, Kathoria M, et al. *Clinical Guidelines and Evidence Review for Post Myocardial Infarction: Secondary prevention in primary and secondary care for patients following a myocardial infarction*. 2007.

(138) Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007 Jun 19;146(12):857-67.

(139) Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003 Sep 11;349(11):1019-26.

(140) Bayer plc., pH associates. Data on File. A series of local service evaluations to describe patient pathways and estimated resource use associated with different models of anticoagulation care. 2011.

(141) Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev 2005;(4):CD001925.

(142) Office for National Statistics. Population estimates for UK, England and Wales, Scotland and Northern Ireland - current datasets. http://www statistics gov uk/statbase/Product asp?vlnk=15106 2011 June 30 [cited 2011 Aug 15];

(143) Samsa GP, Matchar DB, Goldstein LB, Bonito AJ, Lux LJ, Witter DM, et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. Arch Intern Med 2000 Apr 10;160(7):967-73.

(144) Evans A, Perez I, Yu G, Kalra L. Secondary stroke prevention in atrial fibrillation: lessons from clinical practice. Stroke 2000 Sep;31(9):2106-11.

(145) Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. Lancet 1998 Oct 10;352(9135):1167-71.

(146) National Institute for Health and Clinical Excellence. Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (CG68). 2008.

(147) National Audit Office. Economic burden of stroke in England [online]. www nao org uk 2005 [cited 2011 Apr 4];

9 Appendices

Appendix 1

Please see attached to the covering email to this submission.

Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following databases were searched to identify potentially eligible trials from published sources:

MEDLINE and MEDLINE in process (OVID SP) 1950 to 2nd February 2011

EMBASE (OVID SP) 1988 to 2nd February 2011

The Cochrane Central Register of Controlled Trials (CENTRAL) to 2nd February 2011

The date on which the search was conducted was 2nd February 2011

All databases were searched from their date of inception to the date of the search, 2nd February 2011.

Search strategies used, including all the search terms:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>

1. atrial fibrillation/ (25706)
2. ((atrial or auricular) adj fibrillation).tw. (28106)
3. 1 or 2 (34798)
4. coumarins/ or acenocoumarol/ (9907)
5. warfarin/ (11640)
6. (warfarin$ or coumadin$ or marevan or acenocoumarol or nicoumalone or phenprocoumon or sinthrome or phenindione or fluindione or vitamin k antagonist$ or vka).tw. (14336)
7. or/4-6 (27339)
8. Platelet Aggregation Inhibitors/ (20745)
9. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw. (31582)
10. (aspirin? or aspirinine or aspisol or aspro or acetylsalicylic acid$ or acetyl?salicylic acid or acetysal or acylpyrin? or aloxiprimum or colfarit or dispril or dispirin or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).mp. (47827)
11. (indobufen or ibustrin or k 3920).mp. (160)
12. (clopidogrel or iscover or pcr 4099 or plavix or sc 25989c or sc 25990c or sr 25989).mp. (5697)
13. or/8-12 (79531)

14. idraparinux.nm. (55)
15. (idraparinux or org 34006 or org34006 or sanorg 34006 or sanorg34006 or sr 34006 or sr34006).mp. (124)
16. (ximelagatran or xi melagatran or exanta or h 376 95).mp. (524)
17. (dabigatran or bibr 1048 or pradaxa).mp. (316)
18. (apixaban or bms 562247 or bms562247).mp. (113)
19. (rivaroxaban or bay 59 7939 or xarelto).mp. (270)
20. or/14-19 (1053)
21. 7 or 13 or 20 (104029)
22. randomised controlled trial.pt. (295289)
23. controlled clinical trial.pt. (80688)
24. randomised controlled trial/ (295289)
25. random allocation.sh. (69268)
26. double blind method.sh. (106498)
27. single blind method.sh. (14313)
28. clinical trial/ (454122)
29. clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or multicenter study/ (540347)
30. (clin$ adj25 trial$).ti,ab. (188692)
31. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$ or dummy$)).ti,ab. (110292)
32. placebo$.sh. (28794)
33. placebo$.ti,ab. (127990)
34. random$.ti,ab. (524655)
35. animals/ not (animals/ and humans/) (3398955)
36. or/22-34 (1080720)
37. 36 not 35 (984394)
38. 3 and 21 (3464)
39. 36 and 38 (1058)39 (1058)

Database: EMBASE 1988 -2011 (Week 04)

1 *heart atrium fibrillation/ (21387)
2 ((atrial or auricular) adj fibrillation).tw. (32100)
3 1 or 2 (34499)
4 antivitamin k/ (3675)
5 coumarin derivative/ (5740)
6 warfarin/ (40588)
7 (warfarin$ or coumadin$ or marevan or acenocoumarol or nicoumalone or phenprocoumon or sinthrome or phenindione or fluindione or vitamin k antagonist$ or vka).tw. (16602)
8 or/4-7 (50715)
9 *antithrombocytic agent/ (7618)
10 (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw. (32051)
11 (aspirin? or aspirinine or aspisol or aspro or acetylsalicylic acid$ or acetyl?salicylic acid or acetysal or acylpyrin? or aloxiprimum or colfarit or dispril or dispirin or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).mp. (106054)
12 (indobufen or ibustrin or k 3920).mp. (379)
13 (clopidogrel or iscover or pcr 4099 or plavix or sc 25989c or sc 25990c or sr 25989).mp. (22465)
14 or/9-13 (132111)
15 (idraparinux or org 34006 or org34006 or sanorg 34006 or sanorg34006 or sr 34006 or sr34006).mp. (515)
16 (ximelagatran or xi melagatran or exanta or h 376 95).mp. (1806)
17 (dabigatran or bibr 1048 or pradaxa).mp. (1074)
18 (apixaban or bms 562247 or bms562247).mp. (475)
19 (rivaroxaban or bay 59 7939 or xarelto).mp. (974)
20 or/15-19 (3127)

21 8 or 14 or 20 (168736)
22 clinical trial/ (774028)
23 randomised controlled trial/ (272179)
24 randomization/ (49993)
25 crossover procedure/ (29971)
26 double-blind procedure/ (92784)
27 single-blind procedure/ (13769)
28 placebo/ (140625)
29 random$.tw. (579672)
30 rct.tw. (6275)
31 factorial$.tw. (14365)
32 (crossover$ or cross-over$).tw. (46970)
33 placebo$.tw. (136761)
34 (double$ adj blind$).tw. (96608)
35 (singl$ adj blind$).tw. (9486)
36 assign$.tw. (162890)
37 allocat$.tw. (53403)
38 or/22-37 (1308904)
39 3 and 21 (6208)
40 38 and 39 (2402)
41 conference.so. (323419)
42 40 not 41 (2328)

The Cochrane Central Register of Controlled Trials (CENTRAL)

ID	Search	Hits
#1	MeSH descriptor **Atrial Fibrillation**, this term only	2003
#2	((atrial or auricular) NEAR fibrillation):ti,ab	2953
#3	(#1 OR #2)	3142
#4	MeSH descriptor **Coumarins**, this term only	129
#5	MeSH descriptor **Acenocoumarol**, this term only	100
#6	MeSH descriptor **Warfarin**, this term only	973
#7	(warfarin* or coumadin* or marevan or acenocoumarol or nicoumalone or phenprocoumon or sinthrome or phenindione or fluindione or vitamin k antagonist* or vka):ti,ab	1635
#8	(#4 OR #5 OR #6 OR #7)	1975
#9	MeSH descriptor **Platelet Aggregation Inhibitors**, this term only	2343
#10	(antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg* or (platelet* NEAR inhibit*) or (thrombocyt* NEAR inhibit*)):ti,ab	2910
#11	(aspirin* or aspirinine or aspisol or aspro or acetylsalicylic acid* or acetysal or acylpyrin* or aloxiprimum or colfarit or dispril or dispirin or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin):ti,ab,kw	7517
#12	(indobufen or ibustrin or k 3920):ti,ab,kw	77
#13	(clopidogrel or iscover or pcr 4099 or plavix or sc 25989c or sc 25990c or sr 25989):ti,ab,kw	939
#14	(#9 OR #10 OR #11 OR #12 OR #13)	10081
#15	(idraparinux or org 34006 or org34006 or sanorg 34006 or sanorg34006 or sr 34006 or sr34006):ti,ab,kw	22
#16	(ximelagatran or xi melagatran or exanta or h 376 95):ti,ab,kw	155

#17	(dabigatran or bibr 1048 or pradaxa):ti,ab,kw	46
#18	(apixaban or bms 562247 or bms562247):ti,ab,kw	17
#19	(rivaroxaban or bay 59 7939 or xarelto):ti,ab,kw	70
#20	(#15 OR #16 OR #17 OR #18 OR #19)	307
#21	(#8 OR #14 OR #20)	11756
#22	(#3 AND #21)	497
#23	(#22)	427

Search statement #23 limits the search to Clinical Trials (CENTRAL)

A search of the Bayer in-house database was also undertaken for non-published literature. In addition, the reference lists from any Cochrane reviews and the Hart et al (2007)(138) review were checked for other relevant studies.

The inclusion and exclusion criteria.

Eligibility criteria used in search strategy

	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; 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 (TIA); 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

Only studies reported in full publications were included in the review; studies that were only reported in abstract form were not included. Studies that reported results for sub-group of patients with non-valvular AF were also included.

The data abstraction strategy.

The following data were extracted:

Study characteristics: Author, title, year, country, study design, duration.

Details of participants: number of patients in each treatment arm, age, gender and the following co-morbidity parameters: history of stroke, history of TIA, history of acute myocardial infarction, history of hypertension, history of diabetes, $CHADS_2$ scores, history of heart failure, history of left ventricular ejection fraction (LVEF) ≤ 35%, previous thromboembolic event, history of non-CNS systemic embolism, coronary artery disease, peripheral artery disease.

Details of intervention and comparators: drugs used, duration and intensity

Details of primary and secondary outcomes: all strokes (ischaemic and haemorrhagic), systemic embolism including details of severity and location , ischaemic stroke, intracranial haemorrhage, major extracranial haemorrhage, transient ischaemic attack (TIA), myocardial infarction, all-cause mortality, 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.

Data were extracted independently by two reviewers for accuracy.

Appendix 3: Quality assessment of RCT(s) (section 5.4)

ROCKET AF (1-3)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Computer-generated randomisation schedule prepared by Johnson & Johnson. Randomisation was via a central telephonic Interactive voice-response system (IVRS), with stratification by country, prior use of vitamin K antagonists, and a history of stroke, transient ischaemic attack (TIA) or non-CNS systemic embolism. The IVRS assigned a unique patient number and treatment code and corresponding medication kits for the duration of study.	Yes

ROCKET AF (1-3)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was the concealment of treatment allocation adequate?	Computer-generated randomisation list prepared by Johnson & Johnson. Randomisation was via a central telephonic Interactive voice-response system (IVRS). Unique randomisation number of patient was used on all medication labels (placebo & active treatment). Placebo & active treatments were identical in appearance and given under identical conditions. Investigators were not provided with randomisation codes. [redacted]Rivaroxaban was administered as a once-daily fixed dose that did not require titration. The rivaroxaban dose was adapted at randomisation for those with moderate renal impairment. Warfarin did require titration and modification over time depending on the INR. To maintain the study blind, a double-dummy technique was used to ensure that similar dosing procedures were followed in both treatment groups [redacted] All suspected events (stroke, systemic embolism, MI, death, major bleeding and non-major clinically relevant bleeding events), were adjudicated by independent, blinded, Clinical Events Committee (CEC). Adjudication decisions were the basis for the final analyses.	Yes

ROCKET AF (1-3)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Demographic, baseline and surgical characteristics were similar across treatment groups. See section 5.3.4 Baseline characteristics. Randomisation included stratification by country, prior use of vitamin K antagonists, and a history of stroke, transient ischaemic attack (TIA) or non-CNS systemic embolism. Stratification by country was performed to ensure balance across potential local differences in anticoagulation treatment practices. Stratification by prior VKA use and prior stroke, TIA or non-CNS systemic embolism events was performed since these factors are predictors of future events. The number of patients 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 patients enrolled.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was a double-blind, double-dummy design. [redacted] Placebo tablets matched exactly the appearance of active tablets. To maintain blinding, sham INR results were provided. A point-of-care coagulation testing device displayed a code number that when entered into the Interactive Voice Response System (IVRS) with the patient's study identification number, generates either the subject's real INR or a sham INR depending on the assigned treatment. All suspected outcome events were classified and adjudicated by an independent clinical events committee (CEC) whose members were unaware of the treatment assignments.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	See section 5.3.6 Missing data / Patient discontinuations	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results of all pre-specified outcomes have been reported in full, see section 5.5 Results	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?	ROCKET AF included an ITT analysis. ITT was one of the study populations for which results were analysed and reported	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

Refer to section 9.3, Appendix 3 – as the same search strategy was applied.

Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

Due to size, please see the systematic review report dates 6th May 2011 – conducted by Oxford Outcomes (attached on the covering email to this submission).

Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

No studies of this nature were considered relevant to the decision problem.

Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

N/A

Appendix 8: Search strategy for section 5.9 (Adverse events)

The adverse events and safety data included in this submission are reported from the ROCKET AF trial which was identified during the search for rivaroxaban clinical studies for the prevention of stroke in patients non-valvular atrial fibrillation. See Sections 5.1 and 5.2 for the study identification and selection, and also Section 9.2, Appendix 2 for search strategy.

Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

See section 5.4 and Section 9.3, Appendix 3.

Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

EconLIT

NHS EED.

A literature search was conducted of the following data bases using Ovid SP to identify cost-effectiveness studies relevant to the scope of the decision problem

MEDLINE

EMBASE

Econlit

NHS EED

The date on which the search was conducted.

The search was re-run on the 25th July 2011

The date span of the search.

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 – present
- EMBASE 1988-2011 week 29
- EBM Reviews – NHS Economic Evaluation Database 3rd Quarter 2011
- Econlit 1961-July 2011

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE Search terms

#	Term

1	exp atrial fibrillation
2	((atrial OR atrium OR auricular) AND fibrillat*).mp
3	1 OR 2
4	prophylaxis.mp
5	thromboprophylaxis.mp
6	prevention.mp
7	4 OR 5 OR 6
8	stroke.mp
9	exp stroke
10	8 OR 9
11	7 AND 10
12	anticoagulants.mp
13	anticoagulant AND therapy.mp
14	anticoagulant AND agent.mp
15	rivaroxaban.mp
16	warfarin.mp
17	aspirin.mp
18	coumarin derivative.mp
19	dabigatran.mp
20	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21	exp pharmacoeconomics
22	pharmacoeconomics$.mp
23	exp economics, medical
24	economics, medical.mp
25	economic evaluation.mp

26	cost utility analysis.mp
27	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).mp
28	cost minimization analysis.mp
29	cost effectiveness analysis.mp
30	exp cost benefit analysis
31	21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30
32	3 AND 31 AND 11 AND 20

Embase Search terms

#	Term
1	exp heart atrium fibrillation
2	exp heart atrium arrhythmia
3	exp heart fibrillation
4	((atrial OR atrium OR auricular) AND fibrillat*).mp
5	1 OR 2 OR 3 OR 4
6	prophylaxis.mp
7	thromboprophylaxis.mp
8	prevention.mp
9	6 OR 7 OR 8
10	stroke.mp
11	exp stroke
12	10 OR 11
13	9 AND 12

14	anticoagulants.mp
15	anticoagulant AND therapy.mp
16	anticoagulant AND agent.mp
17	rivaroxaban.mp
18	warfarin.mp
19	aspirin.mp
20	coumarin derivative.mp
21	dabigatran.mp
22	14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23	exp pharmacoeconomics
24	pharmacoeconomics$.mp
25	exp health economics
26	health economics.mp
27	exp economic aspect
28	exp economic evaluation
29	economic evaluation.mp
30	exp cost utility analysis
31	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).mp
32	exp cost minimization analysis
33	exp cost effectiveness analysis
34	exp cost benefit analysis

35	23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34
36	5 AND 35 AND 13 AND 22

NHS Economic Evaluation Database Search terms

#	Term
1	exp atrial fibrillation
2	((atrial OR atrium OR auricular) AND fibrillat*).mp
3	1 OR 2
4	prophylaxis.mp
5	thromboprophylaxis.mp
6	prevention.mp
7	4 OR 5 OR 6
8	stroke.mp
9	exp stroke
10	8 OR 9
11	7 AND 10
12	anticoagulants.mp
13	anticoagulant AND therapy.mp
14	anticoagulant AND agent.mp
15	rivaroxaban.mp
16	warfarin.mp

17	aspirin.mp
18	coumarin derivative.mp
19	dabigatran.mp
20	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21	3 AND 11 AND 20

Econlit Search terms

#	Term
1	atrial fibrillation

Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

	Study name: Freeman et al. 2011(81)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being	Yes	

compared clearly described?		
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	No	Only references were provided
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		

22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	N/A	All variables included
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Gage et al. 1995(79)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and	Yes	

justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	No	The aspirin dose was not stated
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	Study mainly reports DRGs
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	

20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Lightowlers & McGuire 1998(82)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	However it is not clear what life years gained free from stroke means in the context of the analysis
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported	N/A	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	Information was provided but some details are unclear
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes	No	

presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Shah et al 2011(83)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	No	Only references were provided
13. Were the details of the subjects from whom valuations were obtained given?	No	This was stated for one study but not for many others
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were	Yes	

appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

	Study name: Sorenson et al 2011(80)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	The introduction mainly focused on the clinical aspects of the disease area
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and	Yes	

results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	The reference is given but details of the study are not in the text
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Inflation was referenced but not detailed for reported costs
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	No	Life time horizon is stated but the number of years is not
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity	Yes	

analysis described?		
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

NHS Economic Evaluation Database (NHS EED)

EconLIT.

Using the OVID SP platform, the following databases were used:

EMBASE (1988- 2011)

MEDLINE, including Medline® In-Process (1950 – 2011)

The Cochrane Library (including: the Cochrane database of systematic reviews [CDSR], Database of abstracts of reviews of effects [DARE], the Cochrane central register of controlled trials, the Health Technology Assessment [HTA] database, and the NHS Economic Evaluation Database [NHS EED] accessed via Wiley Interscience

HEED

EconLit

The date on which the search was conducted.

The original search was run on 17 May 2010. The update search was run on 11 May 2011.

The date span of the search.

Initial searches were performed (for the period 1980 to 2010), and these searches were then updated to the period ending May 2011. No papers after this date were considered.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The searches used relevant medical subject headings and free-text terms.

#	Utility Search for AF events
1	*heart atrium fibrillation/ or *heart atrium arrhythmia/ or *heart fibrillation/
2	((atrial or atrium or auricular) adj fibrillat$).ti,ab.
3	1 or 2
4	stroke/
5	brain ischaemia/ or brain infarction/
6	cerebrovascular accident/
7	(stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$1 or neurologic$ deficit$).ti,ab.
8	((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior

circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm or obstruction or disorder$)).ti,ab.

9 4 or 5 or 6 or 7 or 8

10 thromboembolism/ or thrombosis/ or embolism/

11 systemic embolism.ti,ab.

12 embol$.ti,ab.

13 thromb$.ti,ab.

14 occlusion.ti,ab.

15 10 or 11 or 12 or 13 or 14

16 heart infarction/

17 heart muscle ischaemia/

18 ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or heart or acute) adj infarct$3).ti,ab.

19 ((ischemi$1 or ischaemi$1) adj (myocardium or myocardial or heart)).ti,ab.

20 ((acute or occlusion$1 or disease$1) adj coronary).ti,ab.

21 16 or 17 or 18 or 19 or 20

22 bleeding/

23 (h?emorrhag$ or bleed$).ti,ab.

24 22 or 23

25 "quality of life"/

26 quality adjusted life year/

27 health status/

28 short form 36/

29 short form 6D/

30 time trade off/

31 (quality of life or qol).ti,ab.

32 (quality adjusted life year$ or qaly$).ti,ab.

33 (Utilit$ or disutilit$).ti,ab.

34 (eq5d or eq 5d or eq-5d or euroqol or euroqol5d or euroqol-5d).ti,ab.

35 (Time trade off or time trade-off or TTO).ti,ab.

36 (short form 36 or shortform 36 or SF-36 or SF36 or SF 36).ti,ab.

37 (short form 6d or shortform 6d or sf-6d or sf6d or sf 6d).ti,ab.

38 (standard gamble$ or SG).ti,ab.

39 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40 3 and 39

41 9 and 40

42 15 and 40

43 21 and 40

44 24 and 40

45 40 or 41 or 42 or 43 or 44

46 limit 45 to (human and english language)

#	Utility Search Terms for AF Treatment
1	*heart atrium fibrillation/ or *heart atrium arrhythmia/ or *heart fibrillation/
2	((atrial or atrium or auricular) adj fibrillat$).ti,ab.
3	1 or 2
4	"quality of life"/
5	quality adjusted life year/
6	health status/
7	short form 36/
8	short form 6D/
9	time trade off/
10	(quality of life or qol).ti,ab.
11	(quality adjusted life year$ or qaly$).ti,ab.
12	(Utilit$ or disutilit$).ti,ab.
13	(eq5d or eq 5d or eq-5d or euroqol or euroqol5d or euroqol-5d).ti,ab.
14	(Time trade off or time trade-off or TTO).ti,ab.
15	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).ti,ab.
16	(short form 6d or shortform 6d or sf-6d or sf6d or sf 6d).ti,ab.
17	(standard gamble$ or SG).ti,ab.

18 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 warfarin/

20 Warfarin.ti,ab.

21 phenprocoumon/

22 phenprocoumon.ti,ab.

23 acenocoumarol/

24 acenocoumarol.ti,ab.

25 anticoagulant agent/

26 (anticoagulant$ or anti-coagulant$).ti,ab.

27 antivitamin k/ or coumarin anticoagulant/

28 (vitamin K antagonist$ or VKA$ or coumarin$).ti,ab.

29 clopidogrel/

30 clopidogrel.ti,ab.

31 acetylsalicylic acid/

32 (Aspirin or (acetylsalicylic adj acid)).ti,ab.

33 (clopidogrel and (Aspirin or (acetylsalicylic adj acid))).ti,ab.

34 rivaroxaban/

35 rivaroxaban.ti,ab.

36 dabigatran/

37 dabigatran.ti,ab.

38 apixaban/

39 apixaban.ti,ab.

40 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41 3 and 18 and 40

42 limit 41 to (human and english language)

Details of any additional searches (for example, searches of company databases [include a description of each database]).

Further references identified through reviewing the papers included (snowballing) were also reviewed and included if they met the inclusion/exclusion criteria. In addition, a hand search was conducted to identify potentially relevant publications.

The inclusion and exclusion criteria.

Below are the inclusion/exclusion criteria in accordance with the PICOS statement that were used for the papers included in this parameter.

Utility values for atrial fibrillation, stroke, post-stroke, embolism, myocardial infarction and bleeding events (i.e., for all events in the model); and utility weights associated with warfarin, phenprocoumon, acenocoumarol, clopidogrel, aspirin, clopidogrel plus aspirin, rivaroxaban, dabigatran and apixaban.		
	Exclusion	***Inclusion***
Population	Children **OR** Mixed patient populations for which the results of AF patients are not separable	Atrial Fibrillation
Intervention	Reporting utility's instruments without conversion to utility measure **OR** Diagnostic, surgical, interventional procedures compared to other diagnostic, surgical, interventional procedures (i.e. ablations, pacing, etc.) **OR** Drug therapies not on 'inclusion' list	utility weights associated w/ warfarin **OR** utility weights associated w/ phenprocoumon **OR** utility weights associated w/ acenocoumarol **OR** utility weights associated w/ clopidogrel **OR** utility weights associated w/ aspirin **OR** utility weights associated w/ warfarin **OR** utility weights associated w/ clopidogrel plus aspirin **OR** utility weights associated w/ rivaroxaban **OR** utility weights associated w/ dabigatran **OR** utility weights associated w/ apixaban **OR** utilities value for atrial fibrillation **OR** utilities value for stroke **OR** utilities value for post-stroke **OR** utilities value for embolism **OR** utilities value for bleeds **OR** utilities value for myocardial infarction
Comparator	-	-
Outcomes	-	Utility measurements
Study design	Letters **OR** comments	All others **including** economic evaluations (papers discussing models as tables within paper may report utility values used)

The data abstraction strategy.

References identified by the systematic literature search were screened for appropriateness by title and abstract by two reviewers. Studies were selected that reported one of the outcomes specified. Selected studies were ordered and assessed in full by the team using agreed inclusion/exclusion criteria.

Direct measures of utility values were extracted.

Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

NHS EED

EconLIT.

Electronic databases searched

- Medline (Ovid 1950 to date)
- EMBASE (Ovid 1974 to date)
- Cochrane Library 2011 Issue 1 including:
  - Health Technology Assessment Database (HTA)
  - NHS Economic Evaluation Database (NHS EED)
  - Cochrane Groups
- EconLIT (for AEA members)

The date on which the searches were conducted.

The searches were undertaken on 17th & 18th February 2011.

The date span of the search.

All databases were searched from their date of inception to the date of the search, with the exception of the searches using the 'Anticoagulation' filter which included

publications from 1st January 2006 only. This is to allow for the searches that would have already taken place during development of NICE CG36 on Atrial Fibrillation(1).

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

In developing the search strategies the following recent NICE clinical guidelines were consulted as they included literature searches within areas of interest i.e. atrial fibrillation, anticoagulation thromboprophylaxis, administration and monitoring, and stroke management:

- Atrial Fibrillation in primary and secondary care(1)
- NICE CG68 guideline on Stroke(146) and
- The recent guideline on Venous thromboembolism(124)

Search and keyword strategies were developed from available search strings, additional free-text terms and subject filters. Also bibliographies of resulting full-text papers and reviews were checked to ensure all relevant data was captured.

For EMBASE and Medline:

	Number of hits	
	EMBASE	**Medline**
Economic Search **AND** Atrial Fibrillation search	4491	3075
AND [Limit to: Human and English Language]		
Stroke search **OR**	971	724
Systemic embolism search **OR**	49	29
Myocardial infarction search **OR**	860	354
Rehabilitation or Exercise (after stroke) search **OR**	215	98
'Bleeding' search terms **OR**	798	363
Anticoagulation search [limit to: 2006-17/02/11]	869	755

Cochrane database search strategy:

#1 (atrial fibrillation) 3367
#2 MeSH descriptor **Atrial Fibrillation** explode all trees 2003
#3 (#1 OR #2) 239

EconLIT search strategy:

#1 atrial fibrillation

Economic search strategies (EMBASE & Medline)

EMBASE			Medline		
No.	**Search term**	**Hits**	**No.**	**Search term**	**Hits**
1	exp HEALTH ECONOMICS/ OR exp ECONOMICS/	596451	1	exp ECONOMICS/ OR ECONOMICS, HOSPITAL/ OR ECONOMICS, MEDICAL/ OR ECONOMICS, NURSING/ OR ECONOMICS, PHARMACEUTICAL/	430649
2	"COST"/ OR "COST BENEFIT ANALYSIS"/ OR "COST CONTROL"/ OR "COST EFFECTIVENESS ANALYSIS"/ OR "COST MINIMIZATION ANALYSIS"/ OR "COST OF ILLNESS"/ OR "DRUG COST"/ OR "HEALTH CARE COST"/ OR "HOSPITAL COST"/ OR "HOSPITALIZATION COST"/ OR "NURSING COST"/	299770	2	exp "COSTS AND COST ANALYSIS"/	153484
3	exp ECONOMIC ASPECT/ OR exp FEE/ OR exp "COST"/	882665	3	exp "FEES AND CHARGES"/	24932
4	exp MEDICAL FEE/ OR exp FEE/	29377	4	exp BUDGETS/	10778
5	exp FINANCE/ OR exp HOSPITAL FINANCE/	10051	5	exp HEALTH RESOURCES/	17362
6	exp RESOURCE ALLOCATION/ OR exp RESOURCE MANAGEMENT/	22761	6	exp MODELS, ECONOMIC/ OR exp MODELS, THEORETICAL/ OR exp MODELS, ORGANIZATIONAL/	979278
7	exp FUNDING/	9131	7	exp "COST OF ILLNESS"/	13507
8	exp MATHEMATICAL MODEL/	149373	8	economic AND model$.tw.	15486
9	exp BUDGET/	15192	9	(economic$ OR pharmacoeconomic$ OR pharmaco-economic$).ti,ab	116450
10	economic AND model*.tw.	20253	10	cost$.tw.	269777
11	(economic* OR pharmacoeconomic* OR pharmacoeconomic*).ti,ab	135437	11	budget$.tw.	15311
12	cost*.tw.	320282	12	price$ OR pricing$.tw.	19404
13	budget*.tw.	17783	13	financial OR finance OR finances OR financed.tw.	61328
14	price* OR pricing*.tw.	23361	14	fee OR fees.tw.	15931
15	financial OR finance OR finances OR financed.tw.	136973	15	value adj2 money OR monetary.tw.	3886
16	fee OR fees.tw.	31770	16	RESOURC$.TW.	123232
17	value adj2 money OR monetary.tw.	4393	17	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	1724387

Atrial Fibrillation search strategies (EMBASE & Medline)

EMBASE			Medline		
No.	**Search term**	**Hits**	**No.**	**Search term**	**Hits**
23	exp HEART ATRIUM FIBRILLATION/	46832	18	exp ATRIAL FIBRILLATION/	26110
24	exp HEART ATRIUM ARRHYTHMIA/	69178	19	((atrial OR atrium OR auricular) AND fibrillat*).ti,ab	29729
25	exp HEART FIBRILLATION/	65903	20	18 OR 19	36321
26	((atrial OR atrium OR auricular) AND fibrillat*).ti,ab	36903			
27	23 OR 24 OR 25 OR 26	92357			

Stroke search strategies (EMBASE & Medline)

EMBASE			Medline		
No.	**Search term**	**Hits**	**No.**	**Search term**	**Hits**
29	exp STROKE/	94074	22	exp STROKE/	61860
30	exp CEREBROVASCULAR ACCIDENT/	36408	23	exp BRAIN ISCHAEMIA/	68803
31	exp BRAIN INFARCTION/	37673	24	exp BRAIN INFARCTION/ OR exp CEREBRAL INFARCTION/ OR exp CEREBROVASCULAR DISORDERS/	228605
32	exp BRAIN STEM INFARCTION/	794	25	((brain OR cerebr* OR cerebell* OR cortical OR vertebrobasilar OR hemispher* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR MCA OR anterior circulation OR posterior circulation OR basal ganglia) AND (ischemi* OR ischaemi* OR infart* OR thromb* OR emboli* OR occlus* OR hypox* OR vasospasm OR obstruction OR disorder*)).ti,ab	4565
33	exp CEREBELLUM INFARCTION/	764	26	stroke.ti,ab	106627
34	(stroke OR poststroke OR cerebrovasc* OR brain AND vasc* OR cerebral AND vasc* OR cva* OR apoplex* OR (ischaemi* OR ischemi*) AND attack* OR tia OR neurologic* AND deficit*).ti,ab	29509	27	poststroke OR cerebrovasc* OR (cerebral AND vasc*) OR cva OR apoplex* OR (ischemi* AND attack) OR (ischemi* AND attack) OR tia OR (neurologic AND deficit).ti,ab	141732
35	((brain* OR cerebr* OR cerebell* OR cortical OR vertebrobasilar OR hemispher* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR MCA OR anterior circulation OR posterior circulation OR basal ganglia) AND (ischemi* OR ischaemi* OR infarct* OR thrombo* OR emboli* OR occlus* OR hypox* OR vasospasm OR obstruction OR disorder*)).ti,ab	6009	28	22 OR 23 OR 24 OR 25 OR 26 OR 27	331681
36	29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35	181110			

Systemic embolism or myocardial infarction search strategies (EMBASE & Medline)

EMBASE			Medline		
No.	**Search term**	**Hits**	**No.**	**Search term**	**Hits**
38	(systemic AND emboli*).ti,ab	5338	30	(systemic AND emboli*).ti,ab	4509
40	exp HEART INFARCTION/	198634	32	exp MYOCARDIAL INFARCTION/	129051
41	(myocardial AND (ischemi* OR ischaemi*)).ti,ab	63411	33	(myocardia* AND (ischemi* OR ischaemi* OR infarct*)).ti,ab	155129
42	(myocardial AND infarction*).ti,ab	133064	34	exp MYOCARDIAL ISCHAEMIA/	312260
43	exp HEART MUSCLE ISCHAEMIA/	58741	35	32 or 33 or 34	345610
44	40 or 41 OR 42 OR 43	279244			

Rehabilitation or exercise (after stroke) search strategies (EMBASE & Medline)

EMBASE			Medline		
No.	**Search term**	**Hits**	**No.**	**Search term**	**Hits**
46	(rehab* OR exercise* OR physiotherapy OR (physical AND therap*)).ti,ab	330953	37	(rehab* OR exercise* OR physiotherapy OR (physical AND therap*)).ti,ab	274255
57	exp SPEECH REHABILITATION/ OR exp REHABILITATION PATIENT/ OR exp REHABILITATION NURSING/ OR exp REHABILITATION MEDICINE/ OR exp REHABILITATION CENTER/ OR exp REHABILITATION/ OR exp REHABILITATION CARE/ OR exp HOME REHABILITATION/ OR exp HEART REHABILITATION/ OR exp COMMUNITY BASED REHABILITATION/ OR exp COGNITIVE REHABILITATION/ OR exp AUDITORY REHABILITATION/ OR exp PSYCHOSOCIAL REHABILITATION/ OR exp PULMONARY REHABILITATION/ OR exp VOCATIONAL REHABILITATION/	172061	38	exp MOUTH REHABILITATION/ OR exp REHABILITATION/ OR exp REHABILITATION CENTERS/ OR exp REHABILITATION NURSING/ OR exp "REHABILITATION OF HEARING IMPAIRED"/ OR exp REHABILITATION, VOCATIONAL/	132534
48	exp EXERCISE/	150424	39	exp EXERCISE/	53704
49	46 or 47 or 48	504453	40	37 OR 38 OR 39	382718

'Bleeding' search strategies (EMBASE & Medline)

EMBASE			Medline		
No.	**Search term**	**Hits**	**No.**	**Search term**	**Hits**
51	exp BLEEDING/	408465	42	exp HAEMORRHAGE/ OR exp SUBARACHNOID HAEMORRHAGE/ OR exp CEREBRAL HAEMORRHAGE/ OR exp GASTROINTESTINAL HAEMORRHAGE/ OR exp BRAIN ISCHAEMIA/	285886
52	exp BRAIN HAEMORRHAGE/	61212	43	(hemorrhag* OR haemorrhag* OR bleed*).ti,ab	245484
53	(hemorrhag* OR haemorrhag* OR bleed*).ti,ab	280351	44	intracrania*.ti,ab	63028
54	intracranial.ti,ab	70238	45	42 or 43 or 44	462970
55	51 OR 52 OR 53 OR 54	559093			

Anticoagulation search strategies (EMBASE & Medline)*

EMBASE					
No.	**Search term**	**Hits**	**No.**	**Search term**	**Hits**
57	anticoagula*.tw.	60182	47	prophylaxis OR prevent*.tw.	793115
58	exp FIBRINOLYTIC AGENT/	83471	48	thromboprophyla*.tw	1875
59	exp ANTITHROMBOCYTIC AGENT/	203471	49	exp ANTICOAGULANTS/	163890
60	exp ANTITHROMBIN/	5602	50	exp FIBRINOLYTIC AGENTS/	134610
61	anti AND coagula* OR antithromb* OR anti AND thrombi* OR antiemboli* OR anti AND emboli* OR thrombin AND inhibit*.tw.	21305	51	exp PLATELET AGGREGATION INHIBITORS/	80183
62	thromboprophyla*.ti,ab	2413	52	exp ANTITHROMBINS/	11836
63	(prophyla* OR prevent*).ti,ab	943172	53	(anticoagula* OR anti AND coagula* OR antithrombi* OR anti AND thrombi* OR antiemboli* OR anti AND emboli* OR thrombin AND inhibit*).ti,ab	17331
64	exp ANTICOAGULANT AGENT/	372084	54	dabigatran OR pradaxa OR rivaroxaban OR xarelto OR rendix OR lepirudin OR refludan.tw.	951
65	exp ANTICOAGULATION/	20360	55	exp HEPARIN/	51559
66	calciparine OR monoparin OR calcium AND multiparin OR bemiparin OR zibor OR dalteparin OR fragmin OR clexane OR lovenox OR tinzaparin OR innohep OR antixarin OR cy222 OR embolex OR monoembolex OR suleparoide OR ardeparin OR certoparin OR parnaparin OR reviparin OR tedelparin.tw.	7988	56	heparin* OR LMW* OR dalteparin OR enoxaparin OR nadroparin OR heparinoid*.tw.	82541
67	dabigatran OR rivaroxaban OR rendix OR xarelto OR	136594	57	calciparine OR monoparin OR calcium AND multiparin OR bemiparin	1079

	pradaxa OR lepirudin OR refludan OR heparin* OR LMW* OR dalteparin OR enoxaparin* OR nadroparin OR heparinoid* OR UFH.tw.			OR zibor OR fragmin OR clexane OR lovenox OR tinzaparin OR innohep OR antixarin OR cy222 OR embolex OR monoembolex OR suleparoide OR ardeparin OR certoparin OR parnaparin OR reviparin OR tedelparin.tw.	
68	coumarin* OR warfarin* OR VKA OR fondaparinux OR idraparinux OR arixtra OR apixaban.tw.	63046	58	coumarin* OR warfarin*.tw.	24481
69	acenocoumarol OR brodifacoum OR bromadiolone OR cloricromen OR coumafos OR coumadin OR coumatetralyl OR coumetarol OR dicoumarol OR difenacoum OR ethyl-biscoumacetate OR flocoumafen OR galbanic OR nicoumalone OR phenindione OR phenprocoumon OR phepromaron OR tioclomarol OR sinthrone.tw.	13459	59	fondaparinux OR idraparinux OR arixtra OR apixaban.tw.	1085
70	pentasaccharide*.ti,ab	1821	60	acenocoumarol OR brodifacoum OR bromadiolone OR cloricromen OR coumafos OR coumadin OR coumatetralyl OR coumetarol OR dicoumarol OR difenacoum OR ethyl-biscoumacetate OR folocoumafen OR galbanic-acid OR nicoumalone OR phenindione OR phenprocoumon OR phepromaron OR tioclomarol OR sinthrone.tw.	4332
71	exp ACETYLSALICYLIC ACID/	121963	61	pentasaccharide*.tw.	1647
72	(aspirin OR acetylsalicylic AND acid OR antiplatelet OR anti AND platelet).ti,ab	20624	62	aspirin.tw.	30883
73	57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	1377295	63	acetylsalicyclic AND acid OR antiplatelet OR anti AND platelet.tw.	17346
			64	exp ASPIRIN/	33712
			65	47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 or 62 or 63 or 64	1083604

**The Anticoagulation filter used was based on that detailed in the NICE CG92, to ensure all various brand / generic names were included.*

Details of any additional searches (for example, searches of company databases [include a description of each database]).

The following websites were also searched for resource and cost data in Atrial Fibrillation / Stroke / Anticoagulation services:

- National Institute for Health & Clinical Excellence (NICE) (www.nice.org.uk)
- NHS Improvement (www.improvement.nhs.uk)
- Department of Health (www.dh.gov.uk)
- National Institute for Health Research (NIHR) Health Technology Assessment programme (www.hta.ac.uk)

The terms used to search the above NICE / Department of Health / NHS websites were 'atrial fibrillation', 'stroke' and 'anticoagulation'. References were included in the review for data extraction if they were directly applicable i.e. explicitly contained cost or resource data derived from studies involving atrial fibrillation patients and more general references containing cost / resource data on anticoagulation services or stroke in unspecified or mixed-indication populations were selected in the event of data gaps.

The bibliographies of all selected papers and some disease background reviews were also checked to identify any additional relevant studies.

The inclusion and exclusion criteria.

TYPES OF STUDIES

No restrictions on the type of study were included in the searches. Any studies reporting on resource or economic and cost aspects of the use of anticoagulation in the prevention of stroke in atrial fibrillation were included[7].

TYPES OF PARTICIPANTS

- Patients of 18 years or older
- Diagnosis of atrial fibrillation

TYPES OF OUTCOME MEASURE

- Detailed resource and resource costs from all reported perspectives associated with atrial fibrillation and:

- Stroke prevention
- Anticoagulation services (incl primary care, clinics, self-monitoring)

dealing with

- Major & minor bleeding – intracranial and extracranial
- Systemic embolism
- Myocardial infarction
- Stroke management

PUBLICATION

- Only English language papers were included.
- Studies reported in abstract form only with no further information available online or via Bayer were excluded.

The data abstraction strategy.

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant were obtained where possible. The relevance of each study was assessed according to the inclusion / exclusion criteria set out above. Studies that did not meet all the criteria were excluded and their bibliographic details listed with reasons for exclusion.

Where data on resources and resource costs were presented in sufficient detail e.g. resource, frequency of resource, and / or accompanying unit costs, this was extracted directly into tables. Cost-effectiveness data was not extracted or appraised because this had already been performed and reported separately.

Literature search results

The systematic literature searches resulted in a total of 3,613 titles which were reviewed for relevance. A total of 3,497 studies were excluded and 116 reviewed based on the complete publication. One hundred and three of these references were subsequently rejected for not meeting the study inclusion criteria and 13 were left that described some or all resource use and costs involved in stroke prophylaxis in atrial fibrillation or stroke or anticoagulation in a more general population (see Figure 41). Of these, the search of NICE and NHS / Department of Health websites (detailed in section 9.13.5) had located 8 relevant citations:

- costing reports / analyses associated with NICE guidelines on Atrial Fibrillation(17), Stroke(132) and Thromboprophylaxis in hospitalised patients(124)
- A systematic review and modelling study of the different models of managing long-term oral anticoagulation therapy (clinical and cost-effectiveness)(128)
- Kings College & LSE report for National Audit Office – Economic burden of stroke(147). NB this online report did not give details of resource / unit costs but has now been updated and published in the Age and Ageing journal as Saka et al (2009)(123). The 2009 publication does include resource details and costs which can be extracted.
- Progress in improving stroke care: modelling paper. Report on the findings from our modelling of stroke care provision(131)
- *Atrial fibrillation cost benefit analysis*, Marion Kerr, Department of Health (2008)(127).
- NICE Commissioning guide for Oral Anticoagulation (OAC) Services - Commissioning and benchmarking tool (2010)(119)

Figure 41. Results of literature search screening

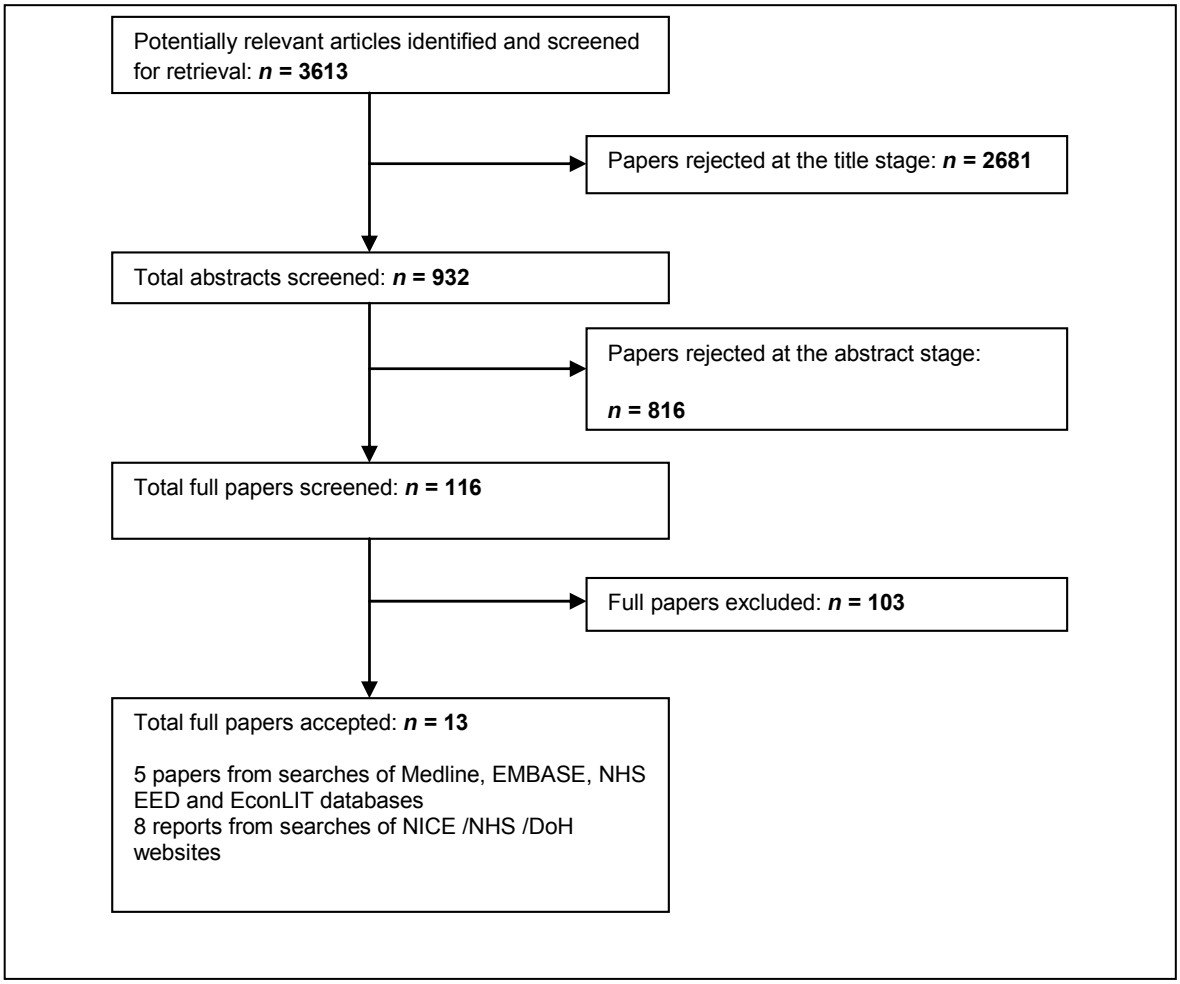

Potentially relevant articles identified and screened for retrieval: n = 3613
Papers rejected at the title stage: n = 2681
Total abstracts screened: n = 932
Papers rejected at the abstract stage:
n = 816
Total full papers screened: n = 116
Full papers excluded: n = 103
Total full papers accepted: n = 13
5 papers from searches of Medline, EMBASE, NHS EED and EconLIT databases
8 reports from searches of NICE /NHS /DoH websites

Table 113. Summary of characteristics of selected studies – studies involving atrial fibrillation patients only

Reference	Country of study	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up
Abdelhafiz & Wheeldon 2003(125)	UK	1999-2000	Yes. Real world data. Anticoagulation clinic, some GP / nurses took samples & forwarded to anticoagulation service	Incremental costs (incl. incremental effectiveness, number needed to treat with warfarin to prevent 1 stroke per year). Patient & NHS perspective. NHS ref costs 1999-2000	402 (Non valvular Atrial Fibrillation)	Mean 19 (8.1) months
Freeman et al 2011(81)	US perspective, based on an International study	2008	For Resource Identification only	Cost-effectiveness analysis 2008 US dollars Excl indirect costs	n/a For Resource Identification only Atrial Fibrillation base case	Costs projected over 35 years
Jowett et al 2008(126)	UK, Australia, France, Portugal, Spain, Sweden (UK data reported here)	Sept 2001 to June 2002	Yes, UK participants involved. UK results reported separately. Trial data. Anticoagulation clinic	Cost and resource analysis of attending anticoagulation clinic (Patient / Societal perspective)	101 UK patients with atrial fibrillation	Max 2 questionnaires (completed during INR monitoring visit)
Kerr (2008)(127)	UK	Based on incidence figures for 2006	Yes, although used Copenhagen and Framingham study % to estimate mortality rates for in hospital, within 30 days and within 1 year of stroke.	Burden of illness study	Estimated English cohort	1 year

Table 114. Summary of characteristics of selected studies – studies involving patients with mixed indications

Reference	Country of study	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up
Connock et al 2007(128)	UK, non-UK studies considered in literature search	Lit search up to September 2005 NHS ref costs 2005	Yes, UK-specific data reported separately & UK derived costs / weightings used	Systematic Review (NICE). Clinical and cost effectiveness of self-monitoring vs. anticoagulation clinics including economic model. NHS perspective. NHS ref costs 2005	n/a Any patient requiring anticoagulation. Anticoagulation control unit costs and weightings for acute complication events primarily derived from SMART trial which involved patients with atrial fibrillation (majority indication - % unspecified)	-

Reference	Country of study	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up
McCahon et al 2007(129)	UK	1ST July 2003 to 30 June 2004	Yes, UK participants, real world. Anticoagulant clinic vs. patient self-monitoring	Resource and cost analysis BNF, NHS ref costs PSSRU 2003	38 self-monitoring, 40 controls (anticoagulant clinic). Mixed indications including atrial fibrillation (54%)	12 month
Parry et al 2001(130)	UK	Spring 1999	Yes based on UK practice, participants, resource & costs	Cost and resource analysis of attending anticoagulation clinic (Patient / Societal perspective) 1998 prices	Any patient attending Anticoagulation clinic	Single visit data per patient only
NICE CG36 (AF) 2006 incl costing report(1;17)	UK, non-UK studies considered in literature search	Lit search up to Dec 2005	Yes, UK-specific date reported separately where available. Costs based on NHS.	Clinical and cost effectiveness. NHS perspective. NHS ref costs 2004/2005	Anticoagulation costs not specific to atrial fibrillation patients	-
NICE CG68 2008 costing report (Acute Stroke)(132; 146)	UK, non-UK studies considered in literature search	Lit search up to 31st October 2007	Yes, UK-specific date reported separately where available. Costs based on NHS.	Clinical and cost effectiveness. NHS perspective. NHS ref costs 2006/2007	All stroke patients – regardless of a diagnosis of AF	-
NICE CG92 (thrombopro phylaxis) 2010(124)	UK, non-UK studies considered in literature search	Lit search up to 10th December 2008	Yes, UK-specific date reported separately where available. Costs based on NHS.	Clinical and cost effectiveness. NHS perspective. NHS ref costs 2006/2007	Patients admitted to hospital requiring thrombo-prophylaxis	-
Saka et al 2009(123)	UK	2006/2007 Updated analysis of Kings College and London School of Economics cost of illness study(2005)(26).	Yes, UK registry and costings used. Resource based on actual UK practice	Cost of illness study Direct costs – PSSRU 2006, BNF 2004, Payment by results tariff, 2005-2006	Stroke patients	12 months
National Audit Office(131)	UK		Yes resource and unit costs based upon UK practice	Economic model measuring improvements of stroke care in terms of costs and outcomes. PSSRU 2008, NHS Ref costs 2007-2008	Stroke management	Stroke care pathway modeled over 10 year perspective
NICE Anticoagulat ion Service Commission ing and Benchmarki ng tool(119)	UK	2009 / 2010	Yes, NICE commissioning guide therefore costs used in NHS service provision planning and implementation	NHS costs 2009 / 2010	All patients requiring anticoagulation	-