NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Apixaban (Eliquis®) for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

Submitted by

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Single technology appraisal (STA)

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Abbreviations

AC	Anticoagulant
ACE	Angiotensin-converting enzyme
AE	Adverse event
AF	Atrial fibrillation
AFSS	Atrial fibrillation severity score
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin-receptor blocker
ASA	Acetylsalicylic acid (aspirin)
AST	Aspartate aminotransferase
BD	Twice daily
BMI	Body mass index
CC	Complications and comorbidities
$CHADS_2$	Cardiac failure, hypertension, age, diabetes, and stoke score
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase
CNS	Central nervous system
CrI	Credibility interval
CRNM	Clinically relevant non-major
CSR	Clinical study report
cTTR	Centre time in therapeutic range
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EMA	European Medicines Agency
ESC	European Society of Cardiology
GI	Gastrointestinal
GFR	Glomerular filtration rate
GPRD	General Practice Research Database
GUSTO	Global use of strategies to open occluded coronary arteries
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
INR	International normalised ratio
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-to-treat

IVRS	Interactive voice response system
LFT	Liver function test
LSPAF	Long standing atrial fibrillation
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LYG	Life years gained
MI	Myocardial infarction
mRS	Modified Rankin Scale
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
NOAC	Novel oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
NVAF	Non-valvular atrial fibrillation
OD	Once daily
OT	On treatment
PE	Pulmonary embolism
PP	Per protocol
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
RRR	Relative risk reduction
SAE	Serious adverse event
SD	Standard deviation
SE	Systemic embolism
SMC	Scottish Medicines Consortium
SOC	System organ class
SPC	Summary of product characteristics
STA	Single technology appraisal
TIA	Transient ischaemic attack
TIMI	Thrombolysis in myocardial infarction
TTO	Time trade off
TTR	Time in therapeutic range
ULN	Upper limit of normal
VAS	Visual analogue scale
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Executive summary

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is characterised by an irregular heartbeat. One of the most serious consequences of this condition is that blood may not be fully expelled from the atrial chambers in the heart, which may lead to the formation of a thrombus (blood clot). Clots may enter the circulation and are likely to cause a stroke or systemic embolism.

Strokes can lead to disability and death. In addition, patients with AF are five times more likely to suffer a stroke than patients without AF; AF-related strokes are generally more severe, more likely to be fatal, and have a greater risk of intracranial haemorrhage than non-AF related strokes. Patients who have already experienced a stroke are at a higher risk of subsequent strokes, and AF itself is an additional risk factor for stroke recurrence.

The prevalence of AF in England and Wales in 2009/2010 was estimated to be between 1.4% and 1.7%. The incidence of AF increases with age, and due to the aging population, is expected to increase further. The cost to the NHS of treating and managing stroke is substantial, estimated in 2004 to be £4.6 billion, and this cost is also projected to increase.

The existing NICE clinical guidelines (2006) recommend that AF patients at low risk of stroke are treated with aspirin, moderate risk patients can be considered for aspirin or warfarin, and those at high risk should receive warfarin unless contraindicated. The recent NICE appraisals of dabigatran and rivaroxaban recommended their use in AF patients who have one or more risk factors for stroke.

Warfarin is currently the standard of care in the UK for patients with AF, and is an effective therapy when well managed. However, in clinical practice, the effectiveness of warfarin may be compromised due to the requirement for routine monitoring to ensure patients are maintained within a narrow therapeutic range (International Normalised Ratio, INR 2-3).

There is an increased risk of bleeding above this INR range, and an increased risk of stroke when this therapeutic range is not reached or maintained. Warfarin also has multiple food and drug interactions. As a result of the difficulties associated with warfarin management, many patients who would be suitable for warfarin are treated with aspirin instead, and hence offered lower protection from the risk of developing a stroke.

Important advantages over warfarin brought about through the introduction of two new oral anticoagulants, dabigatran and rivaroxaban, have been the removal of the need for routine monitoring, together with fewer food/drug interactions. These advantages, however, need to be considered in the context of the effectiveness of these treatments. When comparing the effectiveness of dabigatran versus warfarin, neither of the two doses of dabigatran afforded both superior stroke prevention and a significant reduction in major bleeding. In addition, patients on the higher dose of dabigatran have a significantly higher MI risk, and patients over the age of 80 are required to switch from the more efficacious (higher) dose to the lower dose of dabigatran. Rivaroxaban failed to show superior stroke prevention in the intention to treat population of the ROCKET trial, and had a similar bleeding profile compared with warfarin.

Consequently, a need remains for an oral anticoagulant that has been demonstrated to provide not only superior efficacy but also favourable safety compared with warfarin, without the requirement for regular INR monitoring with fewer food/drug interactions.

Apixaban is a novel anticoagulant which has been studied in two large double-blind randomised controlled trials involving a total of 23,800 patients. ARISTOTLE compares apixaban to warfarin and is the largest of the new oral anticoagulant trials (N=18,201). AVERROES is the only study comparing a new oral anticoagulant with aspirin in patients who are not suitable for (or who are unwilling to take) warfarin.

The ARISTOTLE study demonstrated that, in patients with AF who were suitable for warfarin therapy, apixaban reduced the risk of the primary endpoint of stroke or systemic embolism by 21% compared with warfarin (HR 0.79; 95% CI: 0.66-0.95; p=0.01 for superiority). In addition, apixaban was shown to be superior to warfarin at reducing the rate of death from any cause by 11% (HR 0.89; 95% CI: 0.80–0.99; p=0.047), and of major bleeding by 31% (HR 0.69; 95% CI: 0.60-0.80; p<0.001). Apixaban reduced the rate of clinically important fatal or disabling stroke by 29% (HR 0.71; 95% CI: 0.54–0.94, p=0.003) and major vascular events (HR 0.66; 95% CI: 0.53–0.83, p=0.003). The superior efficacy of apixaban over warfarin was maintained across patients at different levels of stroke risk and across all levels of warfarin control. Apixaban reduced intracranial haemorrhages by 58% compared with warfarin (HR 0.42; 95% CI: 0.30-0.58; p<0.001) and there was no statistically significant difference in GI bleeding. Fewer patients discontinued apixaban compared with warfarin (25.3% versus 27.5% respectively, p=0.001).

In the AVERROES study of patients with AF who were unsuitable for warfarin, apixaban reduced the primary endpoint of risk of stroke or systemic embolism compared with aspirin by 55% (HR 0.45; 95% CI 0.32-0.62; p<0.001). The rate of clinically-important fatal or disabling stroke (HR 0.43; 95% CI: 0.28–0.65, p<0.001) and major vascular events (HR 0.66; 95% CI: 0.53–0.83, p=0.003) was significantly lower with apixaban compared with aspirin. Apixaban reduced the incidence of cardiovascular hospitalisations compared with aspirin (12.6% per year versus 15.9% per year respectively, p<0.001). Of the individual components of bleeding there were no statistically significant differences in major bleeding or clinically-relevant non-major (CRNM) bleeding, although minor bleeding was statistically significant in favour of aspirin. The rate of permanent discontinuation of apixaban was 12% lower than aspirin (HR 0.88, 95% CI: 0.78–0.99, p=0.03).

As no direct head-to-head data are available comparing apixaban with dabigatran and rivaroxaban, an indirect comparison was performed using network meta-analysis (NMA). Indirect comparisons in warfarin-suitable patients showed that apixaban results in significantly fewer MIs than both the dabigatran doses [110mg dose ([redacted]) and 150mg dose (HR [redacted])]. There were no statistically significant differences compared with dabigatran and rivaroxaban in all other efficacy endpoints.

Significantly fewer patients discontinued treatment with apixaban than with rivaroxaban [redacted], dabigatran 110mg [redacted] and dabigatran 150mg [redacted]. Some bleeding outcomes were significantly lower for apixaban compared with rivaroxaban (all bleeding outcomes), dabigatran 150mg/day (major bleeding, other major bleeding, GI bleeding, and any bleeding), and dabigatran 110mg/day (any bleeding), while there were no

statistically significant differences for all other bleeding outcomes. An indirect comparison was conducted in the warfarin-unsuitable population using warfarin-suitable data for rivaroxaban and dabigatran, since no trials of these treatments were available in this population. The results of this indirect comparison were similar to that of the warfarin-suitable population, as the evidence network was the same apart from the addition of the data from the AVERROES study.

The cost-effectiveness of apixaban was assessed using a Markov model similar to that used in previous novel anticoagulant NICE appraisals. Apixaban is similarly priced to the other novel anticoagulants but with similar or greater efficacy. In both warfarin suitable and unsuitable populations, apixaban had slightly higher costs but provided more quality adjusted life years (QALYs) than all other treatments. The base case incremental cost-effectiveness ratios (ICERs) for apixaban compared with warfarin, aspirin, rivaroxaban and dabigatran were all below £20,000 per QALY (ICER vs warfarin: £11,008/QALY; vs aspirin: £2,903/QALY). The cost effectiveness results for apixaban compared with dabigatran and rivaroxaban in the VKA unsuitable population should, however, be interpreted with caution, as neither therapy has data in this specific patient population, and so imputed efficacy estimates from VKA suitable populations are likely to overestimate their QALYs and cost-effectiveness. Apixaban was cost-effective against warfarin across all levels of warfarin control (centre time in therapeutic range) and against all comparators by stroke risk ($CHADS_2$ 1 to 2) at a £30,000 threshold per QALY. One-way sensitivity analyses, scenario analyses and probabilistic sensitivity analyses (apixaban 80% chance of being most cost-effective for VKA suitable patients and 55% for VKA unsuitable at £20,000 per QALY) revealed that the findings were robust to changes in key parameters.

Budget impact analysis estimates the number of patients with non-valvular AF in England and Wales likely to have a $CHADS_2$ score of one or more is 452,462 in 2013-14. Of these 219,897 are estimated to be suitable for warfarin and 232,566 unsuitable. In 2013-14, the total number of patients likely to be treated in both populations with apixaban is estimated to be 2,489 (1,210 and 1,279 in warfarin suitable and unsuitable populations. The total net budget impact of apixaban in both the warfarin suitable and unsuitable populations is estimated at £410 in 2013 and rising to £355,114 in 2017.

Apixaban should be recommended as an option for stroke prevention in AF because:

- It is clinically superior to warfarin in stroke reduction and in reducing bleeding
- It is clinically more effective than aspirin, with a similar bleeding profile
- Compared with warfarin, it does not require the cost and inconvenience of INR monitoring to achieve a narrow therapeutic window; there is therefore less risk of being outside the therapeutic window
- Apixaban does not have the same extent of food and drug interactions as warfarin, which make it difficult for the latter to achieve or maintain the narrow therapeutic window
- Apixaban provides similar efficacy and a significantly better bleeding profile compared with rivaroxaban and dabigatran 150 mg/day without requiring an age-related dose adjustment
- Apixaban is cost-effective compared with all comparators across warfarin suitable and unsuitable populations and has a modest budget impact

Section A – Decision problem

1 Description of technology under assessment

1.1 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: Eliquis®

Approved name: Apixaban

Therapeutic class: Oral anticoagulant (B01A – antithrombotic agent).

1.2 What is the principal mechanism of action of the technology?

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin for its activity and inhibits Factor Xa activity both within and outside the prothrombinase complex. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban both prevents thrombin generation and thrombus development.

1.3 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).

Apixaban does not currently have a UK marketing authorisation for the indication under review. This is expected in December 2012. In May 2011, apixaban received a positive opinion from the European Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

1.4 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).

At the time of writing the EPAR was not available.

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

The prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors.

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
A phase II study in 222 Japanese patients with non-valvular atrial fibrillation (NVAF) has completed (1). This study showed that apixaban 2.5mg and 5mg taken twice daily were well tolerated over 12 weeks. As this was a small study, of short duration, and was

primarily a safety investigation, these data are not considered relevant to this submission. No other trials relevant to this submission are ongoing. The following trials have all completed and are included in this submission:

1. **ARISTOTLE (2):** A phase 3, randomised, double-blind, active-controlled (warfarin INR target range 2-3), parallel-group, multi-centre study to evaluate the safety and efficacy of oral apixaban (5mg BD; 2.5 mg BD in selected patients) in subjects with AF and at least one additional risk factor for stroke. Additional sub-group analyses of patients with renal impairment and those who underwent cardioversion respectively will be presented at the European Society of Cardiology (ESC) Congress, 25-29 August 2012.

2. **AVERROES (3):** A phase 3, randomised, double-blind, active-controlled (aspirin 81–324 mg OD), parallel-group, multi-center study to evaluate the safety and efficacy of oral apixaban (5mg BD; 2.5 mg BD in selected patients) in subjects with AF and at least one additional risk factor for stroke who have failed or are unsuitable for VKA therapy.

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

Apixaban 2.5mg BD is already available in the UK as it is licensed for the prevention of venous thromboembolism. It is anticipated that apixaban 5mg BD will be available for AF patients in the UK following marketing authorisation in December 2012.

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

Apixaban does not yet have regulatory approval for this indication outside the UK. Apixaban has been submitted to the FDA for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF).

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

A submission to the Scottish Medicines Consortium (SMC) is planned for Q3 2012.

1.8 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 1: Unit costs of technology being appraised

Pharmaceutical formulation	2.5mg and 5mg film-coated tablets
Acquisition cost (excluding VAT)	£2.20/day
Method of administration	Oral
Doses	5mg (reduced to 2.5mg in specific patients – see dose adjustments)
Dosing frequency	Twice daily
Average length of a course of treatment	Treatment is continuous
Average cost of a course of treatment	The provisional annual cost is £803 for 5mg twice daily and £803 for 2.5mg twice daily

Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Treatment is continuous
Dose adjustments	Dose reduction for age, body weight and/or serum creatinine. In patients with at least two of the following characteristics; age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 µmol/L), the recommended dose of apixaban is 2.5mg twice daily.

1.9 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.

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

No additional tests or investigations are anticipated.

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

No additional tests or monitoring over and above usual clinical practice are anticipated with apixaban, and it is anticipated that there will be a reduced need for monitoring compared to warfarin.

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

No other therapies are likely to be routinely administered as part of a course of anticoagulation treatment for stroke prevention.

2 Context

2.1 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.

Atrial fibrillation (AF) is the most common cardiac arrhythmia (4) and is characterised by an irregularly irregular heartbeat. AF leads to deterioration in the mechanical function of the atria preventing complete expulsion of blood from the heart. This lack of movement of blood can lead to the formation of a thrombus (blood clot), which can become mobile (emboli), potentially resulting in stroke or systemic embolism (SE).

The prevalence of AF is 1.4% in England (5) and 1.7% in Wales (6) according to data collected as part of the National Health Service (NHS) Quality and Outcomes Framework (QOF) for 2009/2010. Prevalence of AF increases exponentially with age (7); according to UK epidemiological studies AF is uncommon in people aged under 50 years, it then increases to ~1% in individuals 55–64 years, and to 7–13% in individuals 85 years and above (7-11). While AF is known to increase the risk of overall mortality by as much as 60% [Standardised Mortality Ratio (SMR) 1.6 (95% CI: 1.4-1.8) compared to the general population] (12), its most serious manifestation is through the increased risk of stroke.

AF increases the risk of stroke by approximately 5-fold (13), and more than 20% of all strokes are attributed to this arrhythmia (14). Strokes can cause a wide spectrum of clinical sequelae ranging from asymptomatic, minor events to life-changing disabilities, or even death. AF is also associated with an increased risk of SE. Although rare, SE can be devastating, causing severe complications including ischaemic bowel, renal infarction and lower limb ischaemia which itself may lead to amputation (15).

Stroke is the most important consequence of AF, with the greatest impact on morbidity and mortality. The risk of stroke is dependent on a number of factors and ranges from an annual risk of 1% in patients aged over 65 with no risk factors, to over 12% per year in patients with multiple risk factors (4). Such risk factors include age, hypertension, diabetes, heart failure, or history of prior stroke. Furthermore, the risk of recurrent stroke within 5 years of the first stroke is up to 43% (4).

Table 2: Morbidity and mortality (AF-associated stroke)

Morbidity	Mortality
The risk of stroke is increased approximately 5-fold in patients with AF (13)	Strokes due to AF are associated with an increased risk of death (16)
Increased severity and disability associated with AF-related stroke (16)	AF-associated stroke had a 30-day mortality of 30% (18) and a 1-year mortality rate of ~50% (17)
AF-related strokes tend to be severe (17)	

Abbreviations: AF, atrial fibrillation

Strokes associated with AF are generally more severe than strokes in patients who do not have AF (16, 19). The risk of symptomatic intracranial haemorrhage is significantly greater in stroke patients with chronic AF compared to stroke patients without AF (16% vs. 5%; OR 2.95; 95% CI: 1.12-9.30; (20)). Strokes caused by AF are often fatal (16), with Marini et al (2005) showing the 1-year mortality rate of AF-related strokes to be approximately 50% (17). Similarly, the Framingham study suggests a 30-day mortality rate of 30% with AF-

associated stroke (18). Those patients who survive suffer increased levels of disability and longer hospital stays compared with stroke patients without AF (4, 14). For example, AF increases the risk of death, disability and handicap by approximately 50% at 3 months, independently of any other risk factors (16). Surviving stroke is associated with significant levels of psychological distress on the part of both patients and their caregivers (21).

The financial implications to the NHS of treating and managing stroke are substantial. Luengo-Fernandez et al (2006) showed that, in a study of 2004 patients with stroke, the cost to the UK economy was £8 billion (including healthcare productivity and informal care costs) of which £4.6 billion was incurred by the NHS (22). It is also worth noting that the cost of acute stroke in patients with a history of AF is 66% higher than in patients with no history of AF (22). Thus, managing AF-associated strokes is more costly than managing strokes in patients without AF, showing that reducing the incidence of strokes in patients with AF will have wide clinical, economic and societal implications.

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

Apixaban is expected to be indicated for patients with non-valvular atrial fibrillation (NVAF) at risk of stroke or systemic embolism. AF is a clinical area captured by the Quality and Outcomes Framework (QOF) across England and Wales. In the year to March 2011, the prevalence of AF in England was 1.43% and in Wales was 1.74%, resulting in a weighted prevalence of 1.45% across England and Wales (23). Estimates for the five-year trend in the number of patients with AF in England and Wales are presented in the table below, assuming a constant AF incidence of 0.05% (7) and a constant AF-specific mortality rate of 2.7% per year (24).

Table 3: Estimated number of patients with AF in England and Wales, 2013-2017

	Rate	2013	2014	2015	2016	2017
Total population of England and Wales (aged 18+)		44,694,105	45,049,027	45,405,281	45,738,826	46,054,429
AF prevalence	1.45%					
AF mortality	2.7%	17,331	17,466	17,603	17,740	17,879
AF incidence	0.05%	22,347	22,525	22,703	22,869	23,027
Net AF patients		646,892	651,951	657,050	662,180	667,328

Abbreviations: AF, atrial fibrillation

An estimated 80% of AF is non-valvular (25) and 87.4% of patients are at risk of stroke requiring treatment (i.e., with a $CHADS_2$ risk score ≥ 1 (26). Assuming that these proportions remain constant over the next five years, the number of patients with NVAF at risk of stroke, and therefore potentially eligible for apixaban therapy, is presented in Table 4.

Table 4: Estimated number of patients eligible for apixaban in England and Wales, 2013-2017

	Rate	2013	2014	2015	2016	2017
Net AF patients (from Table 3)		646,892	651,951	657,050	662,180	667,328
Patients with NVAF	80%	517,514	521,560	525,640	529,744	533,862

Patients with NVAF and $CHADS_2$ ≥ 1 (ie. eligible for apixaban)	87.4%	452,462	456,000	459,567	463,155	466,756

Abbreviations: AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation

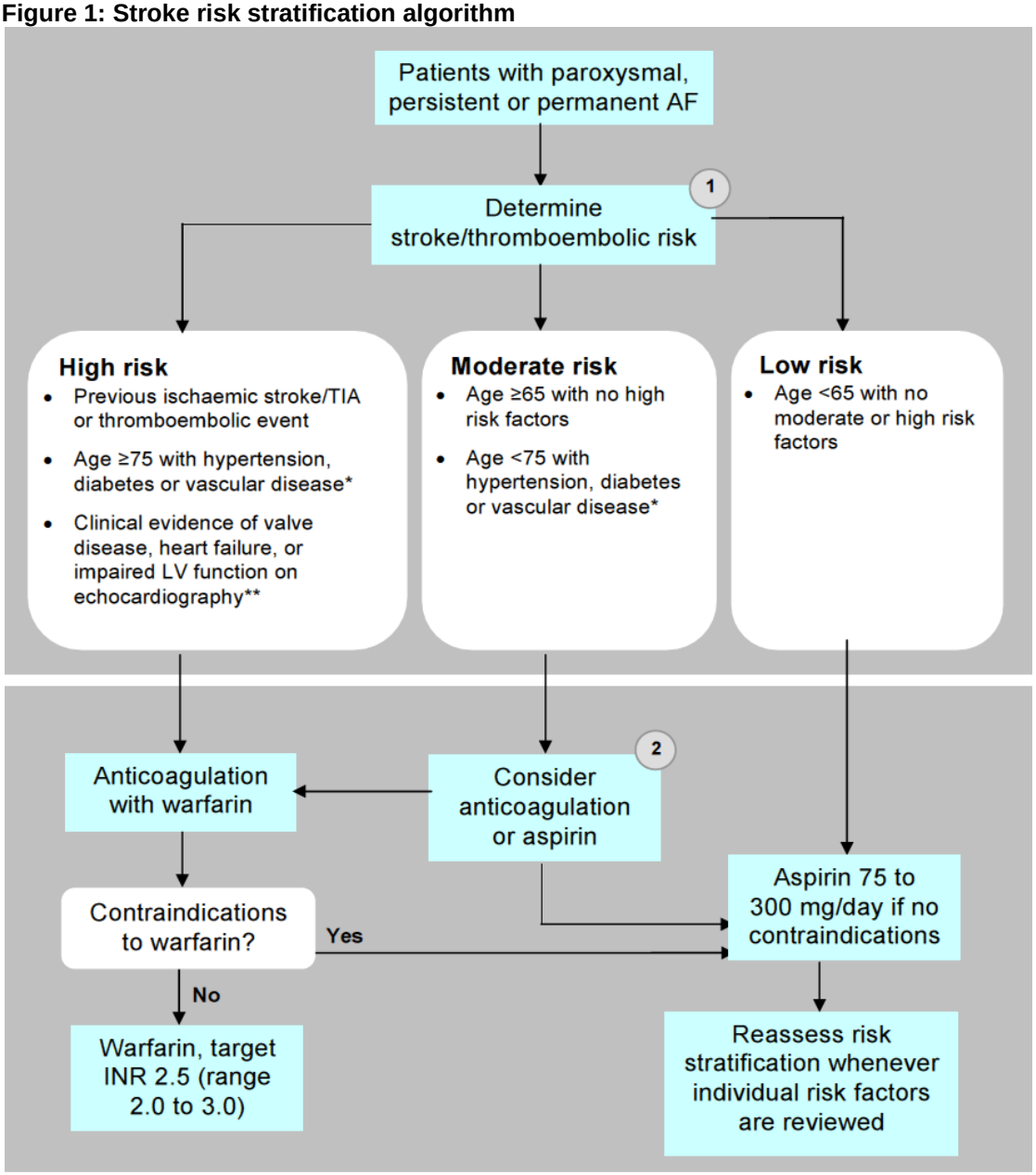
2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE AF clinical guideline (CG36)

In 2006 NICE published a clinical guideline on the diagnosis and management of AF (4). Within the full guideline (27), the anti-thrombotic therapy section included reviews of the evidence for warfarin and aspirin for stroke prevention in AF, which concluded that stroke risk in people with AF can be reduced with anti-thrombotic treatment. The guideline also reviewed the evidence for stroke risk, and Appendix B of the guideline provided a summary of the published stroke risk stratification algorithms. Based on the review of the stroke risk evidence, the NICE guideline adopted an algorithm based on a modified scheme specifically adapted for use in the UK. The stroke risk stratification algorithm presented in Figure 1 below is taken from NICE CG36 which currently recommends that people with AF at high risk of stroke should receive anticoagulation with warfarin (4). In patients with AF at low risk of stroke – such as those under the age of 65 years with no risk factors – or in those patients who are unsuitable for warfarin therapy, treatment with aspirin is recommended (4).

There is currently debate in the UK AF community on the most appropriate stroke risk stratification scheme, with the recently-published European Society of Cardiology (ESC) guidelines recommending use of the CHA_2DS_2-VASc risk score, while NICE is currently reviewing the latest evidence on stroke risk stratification as part of the update to the AF Clinical Guideline (CG36). This could result in changes to the AF antithrombotic treatment pathway in the UK.

Figure 1: 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.

Source: NICE Guidance CG36 (4)

NICE technology appraisals

There have been a number of recent NICE technology appraisals for stroke prevention in AF. The appraisals most relevant to apixaban are of dabigatran (TA249) and rivaroxaban (TA256). Following an appeal, NICE recommended the use of dabigatran for the

prevention of stroke in patients with NVAF on 23 March 2012. Rivaroxaban was also recommended in these patients on 23 May 2012.

2.4 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.

As discussed in 2.3 above, the NICE clinical guidelines outline a mild, moderate and high stroke risk stratification scheme, in which AF patients at low risk of stroke are treated with aspirin, moderate risk patients can be considered for aspirin or warfarin, and high risk patients should receive warfarin unless contraindicated. The recent NICE appraisals of dabigatran and rivaroxaban recommended their use in AF patients with one or more risk factors for stroke, i.e. in patients with moderate to high risk of stroke.

How may apixaban change the existing pathway?

Apixaban is expected to be licensed for patients with non-valvular AF and one or more risk factors for stroke. Patients at moderate or high risk of stroke would be eligible for apixaban, representing an alternative option to warfarin, dabigatran and rivaroxaban. Apixaban is also an option for those patients at moderate risk of stroke who are unsuitable for warfarin. Apixaban provides an evidence-based option across a range of patients at risk of stroke as it has clinical evidence in patients suitable and unsuitable for warfarin therapy.

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

The majority of AF patients in the UK are treated with either warfarin or aspirin (9). Since their approval by NICE, the uptake of dabigatran and rivaroxaban remains low, at well under 0.5% of the total oral anticoagulant prescriptions (28).

Warfarin

Warfarin is the standard of care in the UK and has been shown to be highly effective when well managed in warfarin suitable patients in clinical trials (29). To achieve optimal clinical effectiveness, warfarin requires frequent monitoring and dose adjustments to ensure patients remain within the narrow therapeutic window as defined by the international normalised ratio (INR). INR levels above and below the target range are associated with substantial increases in bleeding and thromboembolic risk respectively (30).

However, the clinical effectiveness of warfarin is likely to be lower in clinical practice than in clinical trials due to local variations in the practice of routine monitoring, and multiple food/drug interactions (31).

Use of warfarin is associated with a significantly increased risk of bleeding in AF patients compared to no warfarin treatment (32). The increased bleeding risk is associated with poor INR control (outside of the range of 2-3), with every unit increase in the INR leading to a significant increase in the odds of a major bleed for both younger (<75 years) and older (>=75 years) AF patients (33). While a therapeutic INR of 2–3 is associated with a significantly lower ischaemic stroke mortality rate in AF patients, INRs over 3 (i.e. over-anticoagulation) are associated with significantly higher mortality due to intracranial

haemorrhage (34). Conversely, the risk of ischaemic stroke increases where there is under-anticoagulation: for example, in a study of warfarin-treated AF patients who had an ischaemic stroke, 74% were found to have sub-therapeutic INRs of <2 at the time of admission to hospital (35).

Another key issue with warfarin treatment is the variability in clinical practice in achieving the therapeutic INR window. In the UK there are several settings in which INR monitoring is delivered, for example: in large, hospital based clinics; smaller primary care based surgeries; intermediary specialist centres; or at home (36-40). In clinical practice warfarin may not be as successful in preventing strokes as the clinical trial data suggest (41). Recent UK studies indicate the proportion of time spent in therapeutic range by AF patients in routine clinical practice varies, with values of 52% (40), 63% (42) and 68% reported (43). A recent General Practice Research Database (GPRD) study found that the risk of stroke varied for warfarin users according to the time spent within therapeutic range, with those spending 70% of time within range having the lowest stroke risk, while those spending <30% and 31–40% time in range having the highest stroke risks (42). Another UK study (44) found that in routine clinical practice only 52% of patients achieved a stable INR (defined as 6 months within the INR range of 2-3). Furthermore these levels of control are likely to be overestimates because poorly-controlled patients do not remain on warfarin, and therefore are not included in medium to long-term INR assessments.

From a patient perspective, successful treatment with warfarin requires following numerous food and alcohol restrictions as well as being aware of likely interactions with other medications (45). In AF patients, the number of medications used concurrently with warfarin is a significant risk factor associated with a major or serious bleed (33, 46), and drug interactions with warfarin can contribute to over-anticoagulation (47). In the UK, warfarin is a leading cause of drug-related hospital admissions (48). Furthermore, some patients become anxious about their INR control, fearing a stroke or a bleed as a result of over or under anticoagulation (49). Such concerns can be onerous to the patient and can impact, not only on their psychological well-being (49), but also on their families. Some patients may therefore be unwilling to commence warfarin treatment, while others may find it difficult to comply with the regimen, and so discontinue treatment.

Currently it is estimated that 46% of all AF patients who should receive warfarin treatment do not (50). In addition, a systematic literature search of UK studies done for the NICE AF guideline cost impact report found that the range of eligible patients not receiving warfarin varied from 20 to 51% (51). Data from an OXVASC study (52) showed that in a population of AF patients (eligible for anticoagulation) with incident ischaemic stroke, 84% had not received warfarin. The authors consider that underuse of anticoagulation is a major barrier to effective stroke prevention.

In summary, a significant proportion of AF patients on warfarin are not well-controlled and therefore at increased risk of stroke, systemic embolism and bleeds. Furthermore, patients eligible for warfarin may find the regimen required for good INR control too onerous to maintain or commence. There remains therefore, a considerable unmet need in the field of stroke prevention in patients with AF despite the availability of warfarin.

Aspirin

NICE CG36 recommends aspirin for low risk patients or as an alternative for patients who are unsuitable for warfarin (NICE CG36), but this guideline is currently being reviewed. In

the most recent NICE menu of QOF indicators (53), anti-platelet therapy is no longer specifically mentioned.

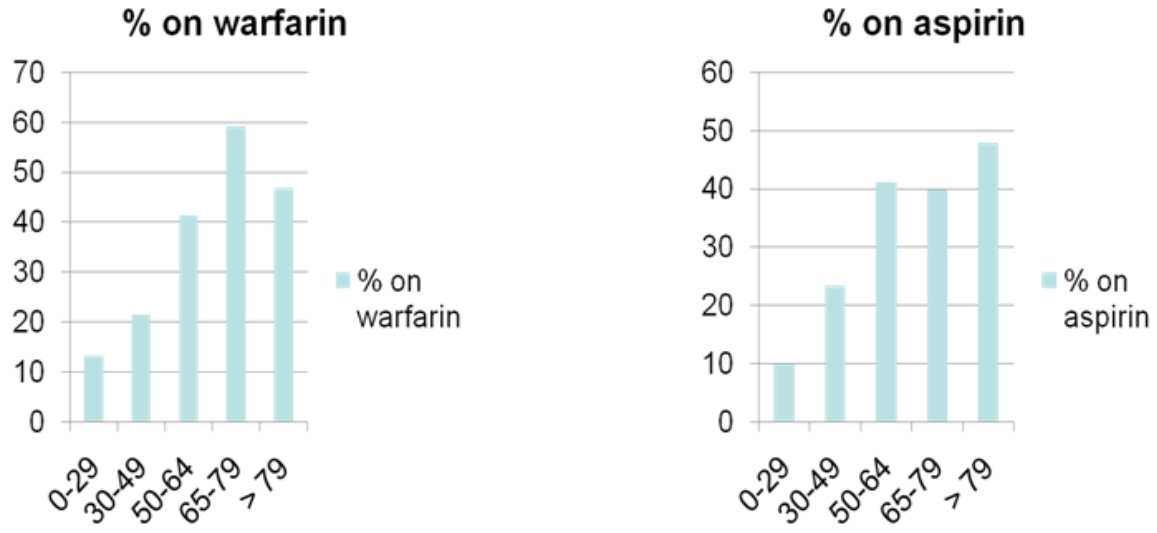
A Cochrane systematic review of eight trials concluded that antiplatelet therapy was associated with a significantly higher incidence of total stroke (4.0% vs. 2.7%, p=0.00069), ischaemic stroke (3.6% vs. 1.9%, p<0.00001) and systemic embolism (0.54% vs. 0.25%, p=0.022) compared to adjusted-dose warfarin and related oral anticoagulants (29). Compared to warfarin, antiplatelets are associated with a lower incidence (0.42% vs. 0.85%, p=0.0078) of intracranial haemorrhage (ICH), but a similar incidence of major extracranial bleeds (2.2% vs. 2.1%, p=0.83) (9) (29). A large real-world study conducted in Denmark (54) confirmed that AF patients taking aspirin had a higher risk of stroke/thromboembolism than patients taking warfarin.

Recent evidence has led the ESC Guidelines to conclude that “aspirin has a limited role in AF and may not be any safer than oral anticoagulation, especially in the elderly” (55). The Danish study found that aspirin had a higher bleeding risk compared to warfarin (54).

Despite its recognised limitations, aspirin is still being initiated in inappropriate patient groups in the UK. A study of 131 primary care practices in England found that approximately 27% of all moderate to high risk AF patients who had never received warfarin were treated with aspirin, and only 5% of those on aspirin had previously been treated with warfarin (9). In a UK GPRD study Gallagher et al (2008) found that despite no major differences in $CHADS_2$ scores, elderly patients were more likely to be initiated on aspirin compared with younger patients (26). More than 75% of patients aged >85 years were initiated on aspirin. This suggests that patients potentially at greatest risk of stroke are being denied effective anticoagulation. The same study found that 50% of all AF patients on aspirin discontinued it after one year, implying that many patients who discontinue may be receiving no protective anti-thrombotic therapy (26). The explanation for the inappropriate initiation of aspirin may be that it is often perceived as a safer option in patients at higher risk of stroke, despite its recognised efficacy limitations (56).

Recent data from 868 GP practices identified by the GRASP-AF tool showed that nearly 110,000 patients had AF, of whom just over 60,000 were high risk patients (57). Figure 2 below shows the distribution of warfarin or aspirin therapy by age group, with many patients over age 65 receiving aspirin instead of warfarin. A significant proportion of these patients are likely to be at high risk and therefore should be receiving warfarin according to the current NICE guideline. Overall, for patients who are suitable for warfarin, there is a significant unmet need as a large proportion are being treated with aspirin and are therefore receiving insufficient stroke prevention.

Figure 2: Treatment with warfarin or aspirin in different age groups



Source: Cowan 2011 (57)

Dabigatran

Dabigatran has recently been approved for stroke prevention in patients with NVAF with one or more risk factors, and was recommended for use by NICE in England and Wales in March 2012. This new oral anticoagulant does not require routine INR monitoring and offers fewer food and drug interactions than warfarin. This indication is supported by the RE-LY study (58) which compared two doses of dabigatran (110mg and 150mg given twice daily) with adjusted dose warfarin in an open-label fashion (prospective, randomised, open-label, blinded endpoint [P.R.O.B.E] design). The data showed that 150mg dabigatran was superior to warfarin for stroke or SE prevention (RR 0.61, 95% CI: 0.53, 0.82; p<0.001) with a comparable major bleeding rate (RR 0.93, 95% CI: 0.81, 1.07; p=0.31). The 110mg dose was non-inferior to warfarin (RR 0.91, 95% CI: 0.74, 1.11; p=0.34) but was associated with a significant reduction in major bleeding (RR 0.80, 95% CI: 0.69, 0.93; p=0.003).

However, both doses of dabigatran were associated with an increase in myocardial infarction. This reached statistical significance for the 150mg dose (38% increase, p=0.048) while there was a similar trend with the 110mg dose (35% increase, p=0.07). Moreover, there was a 50% increase in GI bleeds compared with warfarin (p<0.001) with the 150mg dose. For both doses of dabigatran, there was also a statistically significant higher incidence of dyspepsia (110mg: 11.8%, 150mg: 11.3%) compared with patients on warfarin (5.8%; p<0.001 for both comparisons).

For patients at increased risk of bleeding (for example in patients ≥80 years of age, those aged 75-80 with low stroke and high bleeding risks, or with renal impairment) only the 110mg dose should be used (59, 60). In December 2011 the MHRA issued a drug safety update alerting health-care professionals to the need to base continued dabigatran treatment decisions on annual renal function tests in patients aged 75 and over (61). This was prompted by case reports of fatal haemorrhages with dabigatran, and adds a management component to the use of dabigatran, albeit only in certain sub-groups of patients with AF.

GPRD shows that almost 29% of AF patients initiated on warfarin are aged 80 years and above (42). This means that a significant proportion of patients will receive the 110mg dose of dabigatran, which has only been shown to be non-inferior to warfarin. Furthermore, many younger patients eligible for the 150mg dose are likely to be moved to the 110mg dose within a short period of time due to increased bleeding risk concerns, limiting the benefits they may accrue with the 150mg dose.

The RE-LY cTTR subgroup analysis showed that the greatest benefit of dabigatran for reducing stroke, systemic embolism, pulmonary embolism, myocardial infarction and cardiovascular mortality versus warfarin was in the group with poor INR control (62). This would imply that patients who are well controlled on warfarin would derive relatively limited benefit from switching to dabigatran (59, 62).

Therefore, despite the removal of the need for routine INR monitoring and fewer food and drug interactions with this new oral anticoagulant, there still remains an unmet need for a medicine that can provide, within a single dose, both superior efficacy coupled with better safety compared to warfarin.

Rivaroxaban

Rivaroxaban has recently been approved for stroke prevention in patients with NVAF with one or more risk factors, and was recommended for use in England and Wales by NICE in May 2012. As with dabigatran, this treatment does not require INR monitoring and has fewer food and drug interactions than warfarin. This indication is supported by the ROCKET-AF study (63). This study compared rivaroxaban 20mg once a day with adjusted dose warfarin in patients at high-risk of stroke (mean $CHADS_2$ score 3.5). The mean TTR reported in the warfarin arm was 55%, lower than in other contemporaneous studies (62-68%) (63, 64). The differences in $CHADS_2$ scores and TTR make it difficult to compare this trial with other oral anticoagulant trials.

The results showed that rivaroxaban was non-inferior to warfarin ($p<0.001$) and failed to show superiority in the intention-to-treat analysis (HR 0.88, 95% CI: 0.75, 1.03; $p=0.12$) on the primary efficacy outcome of stroke plus systemic embolism. ROCKET-AF also showed that rivaroxaban had similar overall bleeding rates compared to warfarin on the primary safety endpoint of major bleeding plus clinically relevant non-major bleeding (HR 1.03, 95% CI: 0.96, 1.11; $p=0.44$). While intracranial haemorrhage was significantly reduced (33% decrease $p=0.02$) a significant increase in GI bleeds was observed (46% increase $p<0.001$) compared to warfarin. There was a statistically significant imbalance in baseline myocardial infarction history, with rivaroxaban patients having fewer baseline events (16.6%) compared to warfarin patients (18%, $p<0.05$), which may have influenced the observed treatment effect of a lower, but non-significant incidence of MI for rivaroxaban (HR 0.81, 95% CI 0.63, 1.06; $p=0.121$).

Since rivaroxaban has similar efficacy and safety compared to warfarin, there remains an unmet need for an agent that can provide both superior efficacy with a better safety profile than warfarin.

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

The final scope of the NICE appraisal of apixaban specifies the relevant comparator treatments as:

- Warfarin (in people for whom warfarin is suitable)
- Dabigatran
- Rivaroxaban

Warfarin is the oral anticoagulant most commonly used in practice in the UK and is therefore considered the main comparator for apixaban. Although the draft NICE scope for apixaban included aspirin as a comparator, the final scope supporting documents state that, since there is now more than one alternative anticoagulant available for people unsuitable for warfarin, aspirin would rarely be used in people requiring anticoagulation and should not be included as a comparator (pp5-6). However, as outlined in Sections 2.3 and 2.5 above, aspirin is currently recommended for patients unsuitable for warfarin or those at low risk of strokes, and is also still widely used in clinical practice in England and Wales. Aspirin remains therefore, a relevant comparator in this submission. Dabigatran and rivaroxaban are two newly licensed anticoagulants both of which have only very recently been recommended by NICE. Although these are not yet widely used they are also considered relevant comparators.

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

There is currently no antidote to apixaban. Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., the transfusion of fresh frozen plasma should be considered.

Oral administration of activated charcoal after apixaban administration reduced apixaban exposure and may be considered in the management of apixaban overdose (SmPC, Appendix 1).

If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

In a recent study of *in vitro* human healthy donor blood, the effects of apixaban were attenuated or even reversed by existing coagulation factors, with PCC (prothrombin complex concentrate) and rFVIIa (recombinant factor VIIa) showing more efficacy depending on the haemostatic parameter (65). Further research (ongoing) will be needed to convert these preliminary data into potential clinical recommendations.

2.8 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.

Initially it is anticipated that apixaban will be initiated in secondary care with follow-up in primary care. Apixaban can be directly initiated by the cardiologist obviating the need within secondary care to refer the patient to a warfarin clinic to be initiated. Apixaban does

not require any other resource associated with administration, monitoring or testing – this is in contrast to warfarin which consumes large amounts of resource for regular monitoring (blood sampling, testing and dose adjustments). By removing the need for INR monitoring, apixaban could therefore reduce the cost implications to the NHS. In the NICE dabigatran and rivaroxaban appraisals, NICE concluded that the best estimate of the mean annual INR monitoring cost saving per patient is £242. This was a reasonable and conservative estimate, since considerable numbers of warfarin patients have difficulties managing their INR control, which could result in up to 30 INR visits per year (59, 66). As clinicians become more familiar with apixaban in the longer term, there is the potential that in the future apixaban could be initiated and managed within primary care.

Initiation of warfarin requires patients to receive direct counselling about the drug and the importance of its monitoring. Patients are supplied with a warfarin booklet to help them with this. Because apixaban has a shorter half life than warfarin, compliance becomes more important and, as with any long-term therapy, patients will require a certain amount of education and counselling. However, this is not expected to be at the level required for warfarin, thereby leading to a beneficial saving of health care professional time.

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

Apixaban does not require additional infrastructure to be put in place. Furthermore, because apixaban does not require routine monitoring of INR levels, over time the availability of apixaban will allow the NHS to consider changing the significant infrastructure required to treat and monitor patients receiving warfarin treatment for AF, potentially simplifying the infrastructure and reducing costs.

3 Equity and equality

3.1 Identification of equity and equalities issues

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

No specific equity or equality issues were raised in NICE CG36.

3.1.2 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.

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

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Warfarin is, and has been for many decades, the standard of care for managing stroke risk in patients with AF in the UK. However, the clinical effectiveness of warfarin is likely to be lower in clinical practice than in clinical trials due to i) the requirement for routine monitoring and dose adjustments to maintain patients within its narrow therapeutic range, and ii) multiple food/drug interactions. A significant proportion of AF patients using warfarin are not well-controlled and therefore at increased risk of stroke, systemic embolism and bleeding.

In patients with AF, apixaban significantly reduces the incidence of stroke or systemic embolism, bleeding, and mortality compared to warfarin. It does not require routine monitoring of INR levels and associated dose adjustments, nor does it have any major food/drug interactions, advantages which have the potential to deliver significant health-related benefits both to patients and the NHS over the current standard of care. Over time, the availability of apixaban will allow the NHS to consider changing the significant infrastructure required to treat and monitor patients being treated with warfarin for AF.

Aspirin is still widely used in the management of AF, despite its limited clinical effectiveness and safety. Apixaban is the only new anticoagulant with RCT data compared to aspirin, which demonstrated that apixaban more than halved the risk of stroke and SE: indeed, this study was terminated early due to the reduction in stroke risk achieved with apixaban compared to aspirin, with no statistically significant difference in the risk of major bleeding. The use of apixaban in the considerable number of patients currently treated with aspirin therefore has the potential to deliver very substantial health benefits to patients and related benefits to the NHS in England and Wales.

Dabigatran and rivaroxaban have recently been approved for stroke prevention in patients with NVAF with one or more risk factors, and have been recommended for use in England and Wales by NICE in March and May 2012 respectively. These new oral anticoagulants do not require routine INR monitoring and offer fewer food and drug interactions than warfarin. Dabigatran 150 mg was superior to warfarin at stroke or SE prevention with a comparable major bleeding rate, while the 110 mg dose was non-inferior to warfarin with a significant reduction in major bleeding. However, both doses were associated with an increase in myocardial infarction, which reached statistical significance in the 150mg dose. There was also a statistically significant increase in GI bleeds compared with warfarin with the 150mg dose. For patients at increased risk of bleeding (for example in patients ≥80 years of age, those aged 75-80 with low stroke and high bleeding risks, or with renal impairment) only the 110mg dose is recommended for use. Rivaroxaban was found to be non-inferior to warfarin and failed to show superiority in the intention-to-treat analysis on the primary efficacy outcome of stroke plus systemic embolism. Rivaroxaban also had similar overall bleeding rates on the primary safety endpoint of major bleeding plus clinically relevant non-major bleeding, with a significant increase in GI bleeds compared to warfarin. In light of the efficacy and safety results for these two new treatments, there

remains an unmet need for an agent that can provide, both superior efficacy coupled with a better safety profile compared to warfarin.

Apixaban significantly reduces the incidence of stroke and systemic embolism, major bleeding, and all-cause mortality compared to warfarin. Based on the network meta-analyses (NMAs) reported in this submission, apixaban provides similar efficacy (stroke prevention) to dabigatran and rivaroxaban, and significant reductions in the incidence of MI compared to both doses of dabigatran. Apixaban also significantly reduces the incidence of all bleeding (compared with both doses of dabigatran and rivaroxaban), major bleeding, other major bleeding and GI bleeding (compared with dabigatran 150mg and rivaroxaban) and the rate of discontinuations compared to both dabigatran doses and rivaroxaban.

In summary, apixaban provides a similar level of stroke protection to dabigatran and rivaroxaban, but with significantly lower rates of bleeding and treatment discontinuations, thereby affording the NHS and AF patients a new standard of stroke prevention care.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

There are very considerable long-term consequences of major bleeding, including higher mortality, and a subsequent increase in cardiac events and MI. Since apixaban has been shown in ARISTOTLE and the NMAs to have significantly lower major bleeding rates compared with warfarin, dabigatran 150 mg, and rivaroxaban in patients with AF, there is expected to be consequent mortality and morbidity protection associated with its use in this population. Dabigatran 150 mg and rivaroxaban in their respective trials versus warfarin, did not significantly reduce the rates of major bleeding. Apixaban should therefore be considered an innovation in the management of patients with AF. These longer term consequences could not be considered in the economic model due to lack of available data. As a result the costs per QALY for apixaban are likely to be conservative estimates.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

AF specific data is not available.

5 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with non-valvular AF who are at risk of stroke or systemic embolism	As per the final scope	
Intervention	Apixaban	As per the final scope	
Comparator(s)	Warfarin (in people for whom warfarin is suitable) Dabigatran etexilate Rivaroxaban	As per the final scope plus aspirin for people for whom warfarin is suitable	As outlined in sections 2.3 and 2.5 above, aspirin is currently recommended for patients unsuitable for warfarin or those at low risk of strokes, and is also still widely used in clinical practice in England and Wales. Aspirin remains therefore, a relevant comparator in this submission.
Outcomes	Stroke non-CNS systemic embolism Myocardial infarction Mortality Transient ischaemic attacks Adverse effects of treatment including haemorrhage Health-related quality of life	As per the final scope with the exception of transient ischaemic attacks	Transient ischaemic attacks were not recorded in the ARISTOTLE trial
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 being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per the final scope	

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Subgroups to be considered	If evidence allows, consideration will be given to subgroups defined by: • INR time in therapeutic range (TTR) on warfarin • Patients with different level of stroke/ thrombo-embolic risks. Guidance will only be issued in accordance with the marketing authorisation.	As per final scope	
Special considerations, including issues related to equity or equality	None	As per final scope	

Abbreviations: AF, atrial fibrillation; CNS, central nervous system; INR, International normalised ratio; TTR, time in therapeutic range

Section B – Clinical and cost effectiveness

6 Clinical evidence

Clinical Summary

Apixaban has been studied in two large double-blind randomised controlled trials involving a total of 23,800 patients. ARISTOTLE compares apixaban with warfarin and is the largest of the new oral anticoagulant trials (N=18,201). AVERROES is the only study comparing a new oral anticoagulant with aspirin in patients who are not suitable for (or are unwilling to take) warfarin. No head-to-head data are available for apixaban versus dabigatran and rivaroxaban, so an indirect comparison was performed using network meta-analysis (NMA).

The ARISTOTLE study demonstrated that, in patients with AF who were suitable for warfarin therapy, apixaban reduced the risk of the primary endpoint of stroke or systemic embolism by 21% compared with warfarin (HR 0.79; 95% CI: 0.66–0.95; p=0.01 for superiority). In addition:

- Apixaban was superior to warfarin at reducing the rate of death from any cause by 11% (HR 0.89; 95% CI: 0.80–0.99; p=0.047), and major bleeding by 31% (HR 0.69; 95% CI: 0.60–0.80; p<0.001).
- Apixaban significantly reduced the rate of major vascular events (HR 0.66; 95% CI: 0.53–0.83, p=0.003) and clinically important fatal or disabling stroke by 29% (HR 0.71; 95% CI: 0.54–0.94, p=0.003) compared to warfarin.
- The superior efficacy of apixaban over warfarin was maintained across patients at different levels of stroke risk and across all levels of warfarin control.
- Apixaban reduced intracranial haemorrhages by 58% compared with warfarin (HR 0.42; 95% CI: 0.30–0.58; p<0.001) and there were no statistically significant differences between the groups in major GI bleeding.
- Fewer patients discontinued apixaban compared with warfarin (25.3% versus 27.5% respectively, p=0.001).

In the AVERROES study of patients with AF who were unsuitable for warfarin, apixaban reduced the primary endpoint of risk of stroke or systemic embolism compared with aspirin by 55% (HR 0.45; 95% CI 0.32–0.62; p<0.001).

In addition:

- Apixaban significantly reduced the rate of clinically-important fatal or disabling stroke (HR 0.43; 95% CI: 0.28–0.65, p<0.001) and major vascular events (HR 0.66; 95% CI: 0.53–0.83, p=0.003) compared with aspirin.
- Apixaban reduced the incidence of cardiovascular hospitalisations compared with aspirin (12.6% per year versus 15.9% per year respectively, p<0.001).
- Of the individual components of bleeding there were no statistically significant differences in major bleeding or clinically-relevant non-major (CRNM) bleeding, although minor bleeding was statistically significant in favour of aspirin.
- The rate of permanent discontinuation of apixaban was 12% lower than aspirin (HR 0.88, 95% CI: 0.78–0.99, p=0.03).

Indirect comparisons in warfarin-suitable patients showed apixaban treatment results in

significantly fewer MIs than both the dabigatran doses [110mg dose (HR [redacted]) and 150mg dose (HR [redacted]].

- There were no significant differences compared with dabigatran and rivaroxaban in all other efficacy endpoints.
- Significantly fewer patients discontinued treatment with apixaban than rivaroxaban ([redacted]), dabigatran 110mg ([redacted]), and dabigatran 150mg ([redacted]).
- Some bleeding outcomes were significantly lower for apixaban (compared with rivaroxaban: all bleeding outcomes; dabigatran 150mg/day: major bleeding, other major bleeding, GI bleeding, and any bleeding; dabigatran 110mg/day: any bleeding), while there were no statistically significant differences for all other bleeding outcomes.

An indirect comparison was conducted in the warfarin-unsuitable population using warfarin-suitable data for rivaroxaban and dabigatran, since no trials of these treatments were available in this population. The results of this indirect comparison were similar to that of the warfarin-suitable population, as the evidence network was the same apart from the addition of the data from the AVERROES study.

6.1 Identification of studies

Two systematic reviews were conducted to identify from the published literature:

1) RCT evidence on the efficacy and safety of apixaban and relevant comparators for stroke prevention in patients with atrial fibrillation (AF) at moderate to high risk for stroke

2) Non-RCT evidence on the efficacy and safety of apixaban for stroke prevention in patients with atrial fibrillation (AF) at moderate to high risk for stroke

The searches were supplemented by hand searching; the bibliographies of relevant articles, clinical trial databases and conference proceedings.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for atrial fibrillation, pharmacological intervention(s) of interest, and clinical trial design.

The search strategy for RCT evidence is provided in Section 10.2 (Appendix 2) and for non-RCT evidence in Section 10.6 (Appendix 6).

6.2 Study selection

6.2.1 Eligibility criteria

Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a “reason code” to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion.

Inclusion and exclusion selection criteria for the RCT search are shown in Table 5 and for the non-RCT search in Table 6.

Table 5: Eligibility criteria applied to search results of RCT evidence systematic review (SR)

	Description	Justification
Inclusion criteria		
Population	Adults with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism	Consistent with final scope
Interventions	• Vitamin K antagonist (VKA) including adjusted-dose warfarin • Aspirin [Acetylsalicylic acid (ASA)] (in VKA unsuitable patients only) • Rivaroxaban • Dabigatran • Apixaban	Consistent with final scope *Although not in the final scope, aspirin is still widely used in clinical practice in England and Wales and therefore is a relevant comparator in this submission
Outcomes	• Stroke • Systemic embolism • Myocardial infarction (fatal and non-fatal) • Composite outcomes (e.g. all strokes, myocardial infarction or vascular death) • Major/minor bleeding • Intracranial bleeding • Gastrointestinal bleeding • Mortality • Re-admission rates	Consistent with final scope with the exception that studies were not filtered for TIA as this was not in the original draft scope,and health-related quality of life (which was captured in the economic systematic review)
Study design	Prospective randomised controlled trials	Non-RCT studies were identified through a separate search
Language restrictions	No restriction	
Exclusion criteria		
Population	Subjects <18 years of age, patients with valvular/rheumatic AF	
Interventions	Studies not investigating apixaban or relevant comparator	
Study design	Non-RCT	Non-RCT studies were identified through a separate search
Language restrictions	No restriction	

Abbreviations: AF, atrial fibrillation; CNS, central nervous system; RCT, randomised controlled trial; TIA, transient ischaemic attack

Table 6: Eligibility criteria used in search strategy for non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Adults with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism	Consistent with final scope

	Description	Justification
Interventions	• Apixaban • No restriction on comparator	Consistent with final scope
Outcomes	• Stroke • Systemic embolism • Myocardial infarction (fatal and non-fatal) • Composite outcomes (e.g. all strokes, myocardial infarction or vascular death) • Major/minor bleeding • Intracranial bleeding • Gastrointestinal bleeding • Mortality • Re-admission rates	Consistent with final scope with the exception that studies were not filtered for TIA as this was not in the original draft scope,and health-related quality of life (which was captured in the economic systematic review)
Study design	Non-RCTs including: • Prospective cohorts • Case-control/case-referent studies • Retrospective cohorts • Database studies • Cross-sectional studies	RCTs were identified through a separate search
Exclusion criteria		
Population	Subjects <18 years of age, patients with acute AF	
Interventions	Studies not investigating apixaban	
Study design	RCTs	RCTs were identified through a separate search
Language restrictions	Non-English publications	

6.2.2 Flow diagram of included and excluded studies

The schematic for the systematic review of RCT evidence is shown in Figure 35 (in Appendix 2, section 10.2).The systematic review was conducted between 20th April and 5th May 2011. Following assessment and exclusion of studies based on title, abstract and full text, 45 publications (representing 40 RCTs) satisfied the selection criteria.

An update of the systematic review, using the same search strategy, was conducted on 28th February 2012 (with a date restriction of 2011 to present). The update identified a further 11 records.

In total 56 records representing 41 RCTs were identified, of which two investigated the intervention of interest (apixaban):

- AVERROES (3)
- ARISTOTLE (2)

The remaining 39 RCTs reported on comparator interventions, including one dabigatran RCT and one rivaroxaban RCT which were eligible for indirect comparison/network meta-analysis. Further information is provided in Section 6.7.

The schematic for the systematic review of non-RCT evidence is shown in Figure 36 (in Appendix 6, section 10.6). The systematic review was conducted between 20th April and 5th May 2011. Following assessment and exclusion of studies based on title, abstract and full text no records for non-RCTs were identified. An update of the systematic review, using the same search strategy, was conducted on 28th February 2012 (with a date restriction of 2011 to present). No records were identified.

6.2.3 Data sources of identified studies

In total the systematic review and subsequent update identified two apixaban RCTs in the population of interest. Data for apixaban within this submission are reported from the following sources:

ARISTOTLE	• Clinical study report for ARISTOTLE – (CV185030) (67) • Publication – Granger et al, 2011 (2) and associated online supplement
AVERROES	• Clinical study report for AVERROES (CV185048) (68) • Publication – Connolly et al, 2011 (3) and associated online supplement

6.2.4 Complete list of relevant RCTs

The systematic reviews of clinical evidence identified 2 RCTs of apixaban in the population of interest to this submission (Table 7). Active comparator treatments were used in both studies.

Table 7: List of relevant RCTs

Trial	Phase	Intervention	Comparator	Population	Primary study ref.
ARISTOTLE	III	Apixaban 5 mg BD (2.5 mg BD in selected patients)	Warfarin INR target range 2.0–3.0	Subjects with AF and at least one additional risk factor for stroke	Granger et al, 2011 (2) CSR (67)
AVERROES	III	Apixaban 5 mg BD (2.5 mg BD in selected patients)	Aspirin 81–324 mg OD	Subjects with AF and at least one additional risk factor for stroke who have failed or are unsuitable for VKA therapy	Connolly et al, 2011 (3) CSR (68)

Abbreviations: AF, atrial fibrillation; BD, twice daily; INR, international normalised ratio, OD, once daily; VKA, vitamin K antagonist

6.2.5 Studies comparing the intervention directly with the appropriate comparator(s) stated in the decision problem

Both studies compared the intervention with appropriate comparators as stated in the decision problem:

- ARISTOTLE compared apixaban with warfarin
- AVERROES compared apixaban with aspirin

6.2.6 Studies excluded from further discussion

No identified studies were excluded from further discussion.

6.2.7 List of relevant non-RCTs

No non-RCTs relevant to this submission were identified.

6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

The methodology of the two RCTs (ARISTOTLE and AVERROES) is summarised in Table 8.

Table 8: Comparative summary of methodology of the RCTs

	ARISTOTLE	AVERROES
Study objective	The primary objective was to determine if apixaban was non-inferior to warfarin (INR target range 2.0–3.0) for the combined endpoint of stroke and SE, in subjects with AF and at least one additional risk factor for stroke	The primary objective was to determine if apixaban 5 mg BD was superior to aspirin (81–324 mg OD) for preventing the composite outcome of stroke or SE in patients with AF and at least one additional risk factor for stroke who have failed or are unsuitable for VKA therapy
Location	Multicentre in 39 countries, including 19 European (41 UK sites)	Multicentre in 36 countries including 17 European (18 UK sites)
Design	Phase III, active-controlled, randomised, double-blind, double-dummy, parallel group	Phase III, active-controlled, randomised, double-blind, double-dummy, parallel group
Duration of study	The treatment period lasted until the attainment of approximately 448 primary efficacy events	The double-blind treatment period of the study was to be completed after at least 226 subjects had a primary efficacy endpoint
Method of randomisation	Subjects were randomised 1:1 to apixaban or warfarin via IVRS. Randomisation was stratified by clinical site and prior warfarin status (naïve and experienced)	Subjects were randomised 1:1 to apixaban or aspirin via IVRS
Method of blinding (care provider, patient and outcome assessor)	Study medications were prepared in a double dummy design using placebo matching the active treatments. Subjects, investigators, administrative/adjudication committees, and the Sponsor's staff conducting the study were blind to treatment assignments.	Study medications were prepared in a double dummy design using placebo matching the active treatments. Subjects, investigators, administrative/adjudication committees, and the Sponsor's staff conducting the study were blind to treatment assignments
Intervention(s) and	• Apixaban 5 mg BD (or 2.5 mg BD for selected patients with an increased	• Apixaban 5 mg BD (or 2.5 mg BD for selected patients with an increased

	ARISTOTLE	AVERROES
comparator(s)	risk of bleeding†) + warfarin placebo tablet(s) • Warfarin 2 mg tablets (1 daily dose of up to 6 mg and 1 daily warfarin placebo) adjusted to give an INR of 2.0–3.0 + apixaban placebo Subjects who were receiving a VKA before randomisation were instructed to discontinue the drug 3 days before randomisation, and the study drug was initiated when the INR was <2.0. Dosing for warfarin/warfarin-placebo was based on INR monitoring using a blinded, encrypted, point-of-care INR device. An algorithm was provided to guide the adjustment of the warfarin dose	risk of bleeding†) + aspirin placebo tablet(s) • Aspirin 81–342 mg (between 1 and 4 81 mg tablets) + apixaban placebo. Aspirin dose was at the discretion of the investigator
Permitted and disallowed concomitant medications	Potent inhibitors of CYP3A4, aspirin >165 mg/day, other antithrombotic agents, and glycoprotein IIb/IIIa inhibitors were prohibited whilst taking study drug. If treatment with these agents became necessary during the study, the study drug was to be temporarily interrupted	Potent inhibitors of CYP3A4, and other antithrombotic agents were prohibited. Investigators were strongly encouraged to discontinue any non-study aspirin. Subjects taking a thienopyridine at baseline were not eligible for inclusion, although they could be prescribed during the study if an indication emerged
Primary efficacy outcome	The time to first occurrence of confirmed stroke (ischaemic or haemorrhagic) or SE during the treatment period	The time to first occurrence of stroke (ischaemic or haemorrhagic) or SE during the treatment period
Secondary efficacy outcomes	Time to first occurrence of confirmed: stroke; SE; all-cause death; composite of stroke, SE, major bleeding; composite of stroke, SE, all-cause death; composite of stroke, SE, all-cause death, major bleeding; composite of stroke, SE, MI, all-cause death; composite of stroke, SE and major bleeding in warfarin-naïve subjects	Days from randomisation to first occurrence of stroke, SE, MI or vascular death Days from randomisation to first occurrence of all-cause death
Primary safety outcome	Time from first dose of study drug to first occurrence of confirmed ISTH major bleeding	Occurrence of major bleeding

Abbreviations: AF, atrial fibrillation; BD, twice daily; INR, International normalised ratio; ISTH, International Society on Thrombosis and Haemostasis; IVRS, interactive voice response system; MI, myocardial infarction; OD, once daily; SE, systemic embolism; VKA, vitamin K antagonist

†Subjects with ≥ 2 of the following criteria: aged 80 years or older; a body weight of ≤ 60 kg, or a serum creatinine level of ≥ 1.5 mg/dL

6.3.2 Participants

The inclusion and exclusion criteria for ARISTOTLE and AVERROES are summarised in Table 9.

Table 9: Eligibility criteria of the RCTs

Trial	Inclusion criteria	Exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
ARISTOTLE	Males or females ≥ 18 year of age, with AF or atrial flutter not due to a reversible cause documented by ECG at time of enrolment, or AF/flutter documented on 2 separate occasions ≥ 2 weeks apart in the 12 months prior to enrolment, and presenting with ≥ 1 additional risk factor for stroke. Risk factors for stroke: • Age ≥ 75 years • Prior stroke, transient ischaemic attack or SE • Either symptomatic congestive heart failure within 3 months or left ventricular dysfunction with a left ventricular ejection fraction ≤ 40% by echocardiography, radionuclide study or contrast angiography • Diabetes mellitus • Heart failure (NYHA class 2 or higher at time of enrolment) • Hypertension requiring pharmacological treatment	• AF due to reversible causes • Moderate or severe mitral stenosis • Conditions other than atrial fibrillation that required anticoagulation • Stroke within the previous 7 days • A need for aspirin at a dose of >165 mg/day or for both aspirin and clopidogrel • Severe renal insufficiency (serum creatinine level of >2.5 mg/dL or calculated creatinine clearance of <25 mL/min
AVERROES	Male or females ≥ 50 years of age, with documented permanent, paroxysmal or persistent AF, presenting with ≥ 1 risk factor for stroke, and not currently receiving VKA therapy. Risk factors for stroke: • Prior stroke or transient ischaemic attack • Age ≥ 75 years • Arterial hypertension on treatment • Diabetes mellitus • Heart failure (NYHA class 2 or higher at time of enrolment) • Left ventricular ejection fraction of 35% or less • Documented peripheral arterial disease	• Presence of conditions other than AF for which the patient required long-term anticoagulation • Valvular disease requiring surgery • A serious bleed in the previous 6 months or a high risk of bleeding • Current alcohol or drug abuse or psychosocial issues • Life expectancy of less than 1 year • Severe renal insufficiency (a serum creatinine level of >2.5 mg/dL or a calculated creatinine clearance of <25 mL/min) • Alanine aminotransferase or aspartate aminotransferase level >2x ULN or a total bilirubin >1.5x ULN • Allergy to aspirin

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; MI, myocardial infarction; NYHA, New York Heart Association; SE, systemic embolism; ULN, upper limit of normal; VKA, vitamin K antagonist

6.3.3 Baseline characteristics

ARISTOTLE

Patient baseline characteristics for ARISTOTLE are summarised in Table 10. The two treatment groups were well balanced with respect to both baseline demographic and disease characteristics.

Table 10: Characteristics of participants in ARISTOTLE across randomised groups

	Apixaban (N = 9120)	Warfarin (N = 9081)
Age (years) Mean±SD	 69.1±9.61	 69.0±9.74
Gender, n (%) Male	 5886 (64.5)	 5899 (65.0)
Region, n (%) North America Latin America Europe Asian Pacific	 2249 (24.7) 1743 (19.1) 3672 (40.3) 1456 (16.0)	 2225 (24.5) 1725 (19.0) 3671 (40.4) 1460 (16.1)
Median systolic blood pressure (mm Hg)	130	130
Median weight (kg)	82	82
Prior myocardial infarction, n (%)	1319 (14.5)	1266 (13.9)
Prior clinically relevant or spontaneous bleeding, n (%)	1525 (16.7)	1515 (16.7)
Type of atrial fibrillation, n (%) Paroxysmal Persistent/ permanent	 1374 (15.1) 7744 (84.9)	 1412 (15.5) 7668 (84.4)
Prior use of VKA for >30 consecutive days, n (%)	5208 (57.1)	5193 (57.2)
Qualifying risk factors, n (%) Age ≥ 75 years Prior stroke, TIA, or systemic embolism Heart failure or reduced LVEF Diabetes Hypertension requiring treatment	 2850 (31.2) 1748 (19.2) 3235 (35.5) 2284 (25.0) 7962 (87.3)	 2828 (31.1) 1790 (19.7) 3216 (35.4) 2263 (24.9) 7954 (87.6)
$CHADS_2$ score† at enrolment, n (%) ≤ 1 2 ≥ 3 Mean±SD	 3100 (34.0) 3262 (35.8) 2758 (30.2) 2.1±1.1	 3083 (34.0) 3254 (35.8) 2744 (30.2) 2.1±1.1
Medications at time of randomisation, n (%) ACE inhibitor/ARB Amiodarone Beta-blocker Aspirin Clopidogrel Digoxin Calcium blocker Statin NSAID Gastric antacid	 6464 (70.9) 1009 (11.1) 5797(63.6) 2859 (31.3) 170 (1.9) 2916 (32.0) 2744 (30.1) 4104 (45.0) 752 (8.2) 1683 (18.5)	 6368 (70.1) 1042 (11.5) 5685 (62.6) 2773 (30.5) 168 (1.9) 2912 (32.1) 2823 (31.1) 4095 (45.1) 768 (8.5) 1667 (18.4)
Renal function, creatinine clearance, n (%) Normal (>80 mL/min) Mild impairment (>50 to 80 mL/min) Moderate impairment (>30 to 50 mL/min) Severe impairment (≤ 30 mL/min) Not reported	 3761 (41.2) 3817 (41.9) 1365 (15.0) 137 (1.5) 40 (0.4)	 3757 (41.4) 3770 (41.5) 1382 (15.2) 133 (1.5) 39 (0.4)
Study doses of 2.5 mg BD apixaban (or placebo)	428 (4.7)	403 (4.4)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; TIA, transient ischaemic attack; VKA, vitamin K antagonist

†$CHADS_2$ score is an index of the risk of stroke in patients with atrial fibrillation. Scores range from 1 to 6, with higher scores indicating a greater risk of stroke. Congestive heart failure, hypertension, age ≥ 75 years, and diabetes are each assigned 1 point, and previous stroke or transient ischaemic attack is assigned 2 points. The score is calculated by summing all the points for a given patient

AVERROES

Patient baseline characteristics for AVERROES are summarised in Table 11. The treatment groups were well balanced for the baseline characteristics and physical measurements with no clinically relevant differences for randomised subjects.

A total of 2216 (40%) randomised patients had previously received but discontinued VKA therapy. The reasons for unsuitability of VKA therapy are summarised in Table 12.

Table 11: Characteristics of participants in AVERROES across randomised groups

	Apixaban (N=2808)	**Aspirin (N=2791)**
Age (years), mean±SD	69.7±9.44	70.0±9.71
Gender male, n (%)	1660 (59.1)	1617 (57.9)
Region n (%)		
North America	408 (15)	396 (14)
Latin America	589 (21)	596 (21)
Western Europe	625 (22)	633 (23)
Eastern Europe	639 (23)	611 (22)
Asia and South Africa	547 (19)	555 (20)
Mean BMI (kg/m^2)	28.4	28.2
Systolic blood pressure (mm Hg), mean ±SD	132±16	132±16
Baseline electrocardiographic findings n (%)		
Atrial fibrillation	1923 (68)	1894 (68)
Atrial flutter	19 (1)	20 (1)
Sinus rhythm	707 (25)	730 (26)
Paced or other rhythm	147 (5)	139 (5)
Left ventricular hypertrophy	490 (17)	498 (18)
Classification of atrial fibrillation n (%)		
Paroxysmal	760 (27)	752 (27)
Persistent	587 (21)	590 (21)
Permanent	1460 (52)	1448 (52)
Use of VKA within 30 days before screening n (%)	401 (14)	426 (15)
Use of aspirin within 30 days before screening n (%)	2137 (76)	2081 (75)
Risk factors for stroke n (%)		
Prior stroke or transient ischaemic attack	390 (14)	374 (13)
Hypertension, receiving treatment	2408 (86)	2429 (87)
Heart failure	1118 (40)	1053 (38)
NYHA class 1 or 2	932 (33)	878 (31)
NYHA class 3 or 4	186 (7)	175 (6)
Left ventricular ejection fraction ≤ 35%	144 (5)	144 (5)
Peripheral artery disease	66 (2)	87 (3)
Diabetes, receiving treatment	537 (19)	559 (20)
Mitral stenosis	64 (2)	50 (2)
$CHADS_2$ score at enrolment, n (%)		
0 or 1	1004 (36)	1022 (37)
2	1045 (37)	954 (34)
≥ 3	758 (27)	812 (29)
Mean score	2.0±1.1	2.1±1.1
Medication use at baseline n (%)		
ACE inhibitor or ARB	1790 (64)	1786 (64)
Verapamil or diltiazem	251 (9)	248 (9)
Beta-blocker	1563 (56)	1534 (55)
Digoxin	821 (29)	754 (27)
Amiodarone	298 (11)	328 (12)
Statin	883 (31)	879 (31)

Study dose of aspirin or aspirin-placebo 81 mg 162 mg 243 mg 324 mg Data not available	 1816 (65) 718 (26) 73 (3) 193 (7) 7 (<1)	 1786 (64) 750 (27) 60 (2) 184 (7) 11 (<1)
Study dose of 2.5 mg BD apixaban (or placebo)	179 (6)	182 (7)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BD, twice daily; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; TIA, transient ischaemic attack; VKA, vitamin K antagonist

Table 12: Reasons for unsuitability of VKA therapy†

Reason for unsuitability n (%)	Apixaban (N=2808)	Aspirin (N=2791)	Previous use of VKA (N=2216)	No previous use of VKA (N=3383)
Assessment that INR could not be maintained in the therapeutic range	465 (17)	468 (17)	932 (42)	–
AE not related to bleeding during VKA therapy	86 (3)	94 (3)	180 (8)	–
Serious bleeding event during VKA therapy	92 (3)	82 (3)	173 (8)	–
Assessment that INR could not or was unlikely to be measured at requested intervals	1196 (43)	1191 (43)	827 (37)	1560 (46)
Expected difficulty in contacting patient for urgent change in dose of VKA	322 (11)	331 (12)	167 (8)	486 (14)
Uncertainty about patient's ability to adhere to instructions regarding VKA therapy	437 (16)	405 (15)	262 (12)	580 (17)
Concurrent medications that could alter activity of VKA	50 (2)	53 (2)	33 (1)	70 (2)
Concurrent medications whose metabolism could be affected by VKA	35 (1)	46 (2)	19 (1)	62 (2)
Assessment that patient would be unable or unlikely to adhere to restrictions	134 (5)	141 (5)	127 (6)	148 (4)
Hepatic disease	13 (<1)	9 (<1)	4 (<1)	18 (1)
Mild cognitive impairment	85 (3)	86 (3)	56 (3)	115 (3)
Heart failure or cardiomyopathy	179 (6)	188 (7)	95 (4)	272 (8)
Other factors that could be associated with increased risk of VKA use	96 (3)	123 (4)	121 (5)	98 (3)
$CHADS_2$ score of 1 and VKA therapy not recommended by physician	590 (21)	605 (22)	458 (21)	737 (22)
Other characteristics indicating risk of stroke too low to warrant treatment with VKA	55 (2)	40 (1)	32 (1)	63 (2)
Patient's refusal to take VKA	1053 (38)	1039 (37)	819 (37)	1273 (38)
Other reasons	184 (7)	189 (7)	249 (11)	124 (4)
$CHADS_2$ score of 1 as only reason for unsuitability of VKA therapy	313 (11)	336 (12)	216 (10)	433 (13)
Patient's refusal to take VKA as only reason for unsuitability	421 (15)	394 (14)	199 (9)	616 (18)
Multiple reasons for unsuitability of VKA therapy	1444 (51)	1440 (52)	1436 (65)	1448 (43)

†The reason for unsuitability was missing for one patient in the apixaban group

6.3.4 Outcomes

The outcomes investigated in ARISTOTLE and AVERROES, and their relevance to the decision problem are presented in Table 13.

Table 13: Primary and secondary outcomes of the RCTs

Trial	Primary outcome(s)	Secondary outcome(s)	Outcome measures	Reliability/validity/ current use in clinical practice

ARISTOTLE	**Efficacy**
	Days from randomisation to first occurrence of stroke (ischaemic or haemorrhagic) or SE
	
	Safety
	Days from first dose of study drug to first occurrence of confirmed ISTH major bleeding
		Efficacy
		Days from randomisation to first occurrence of:
		• Stroke, SE or major bleeding
		• Stroke, SE, or major bleeding in warfarin naïve subjects
		• Stroke, SE, or all-cause death
		• Stroke, SE, major bleeding, or all-cause death
		• Stroke, SE, major bleeding, MI or all-cause death
		• Ischaemic or of unspecified type stroke, or all-cause death
		• Haemorrhagic stroke, or all-cause death
		• SE or all-cause death
		• MI or all-cause death
		• All-cause death
		
		Safety
		Days from first dose of study drug to first occurrence of:
		• Composite of confirmed ISTH major bleeding and CRNM bleeding
			Stroke was defined as a focal neurologic deficit, from a non-traumatic cause, lasting at least 24 hours and was categorised as ischaemic (with or without haemorrhagic transformation), haemorrhagic, or of uncertain type (in patients who did not undergo brain imaging or in whom an autopsy was not performed).
			
			Systemic embolism was judged to occur where there was a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), which was supported by evidence of embolism from surgical specimens, autopsy, angiography, vascular imaging, or other objective testing.
			
			Bleeding was defined according to ISTH guidelines;
			• Major bleeding:
			  ○ Clinically overt bleeding accompanied by a decrease in haemoglobin of ≥ 2 g/dL and/or transfusion of ≥ 2 units of packed red blood cells
			  ○ Bleeding that occurred in a critical site
			  ○ Bleeding that was fatal
			• CRNM bleeding – clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to either:
			  ○ Hospital admission
			  ○ Physician guided medical or surgical treatment
				The primary and secondary efficacy and safety endpoints were adjudicated on the basis of pre-specified criteria by a Clinical Events Committee, who were not aware of study-group assignments

Trial	Primary outcome(s)	Secondary outcome(s)	Outcome measures	Reliability/validity/ current use in clinical practice
		• All bleeding endpoints reported by investigator	○ A change in antithrombotic therapy • All acute clinically overt bleeding events not meeting criteria for major bleeding or clinically relevant non-major bleeding were classified as minor bleeding • Bleeding events were also classified by the TIMI and GUSTO criteria (ARISTOTLE only)	
AVERROES	**Efficacy** The time to first occurrence of stroke (ischaemic or haemorrhagic) or SE during the treatment period **Safety** Time from first dose of study drug to first occurrence of confirmed ISTH major bleeding	**Efficacy** Days from randomisation to first occurrence of stroke, SE, MI or vascular death Days from randomisation to first occurrence of all-cause death **Safety** Days from first dose of study drug to first occurrence of • Major or CRNM bleeding • Any bleeding		

Abbreviations: CRNM, clinically relevant non-major; GUSTO, Global use of strategies to open occluded coronary arteries; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; SE, systemic embolism; TIMI, Thrombolysis in myocardial infarction

6.3.5 Statistical analysis and definition of study groups

Table 14: Summary of statistical analyses in RCTs

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ARISTOTLE	The primary objective was to determine if apixaban was non-inferior to warfarin (INR target range 2.0 - 3.0) for the combined endpoint of stroke and SE, in subjects with AF and at least one additional risk factor for stroke. Secondary objectives were to determine if apixaban was superior to warfarin for; • the combined endpoint of stroke and SE • major bleeding (ISTH criteria) • all-cause death	A hierarchical testing strategy was followed to control the type 1 error in the study to ≤ 5%. • NI for the primary efficacy endpoint was assessed first • If NI for the primary efficacy endpoint (using an NI margin of 1.38) was demonstrated then superiority was tested at the one-sided α=0.025 • If superiority for the primary efficacy endpoint was demonstrated, then superiority for ISTH major bleeding was tested at the one-sided α=0.025 • If superiority for major bleeding was demonstrated, then superiority for all-cause death was tested at the one-sided α=0.025 The primary and key secondary analyses were performed with the use of the Cox proportional hazards model, with previous warfarin status and geographic region (North America, South America, Europe, or Asian Pacific) used as strata in the model.	With 448 subjects with confirmed primary outcome events, the study would have at least 90% power to meet regulatory definitions of non-inferiority (upper bound of the 2-sided 95% CI for the RR <1.38 and upper bound of the 2-sided 99% CI for RR <1.44). With an average 2.1 years follow-up, and assuming a stroke rate of 1.20 per hundred patient-years, approximately 18,000 randomised subjects allocated in a 1:1 ratio to the apixaban or warfarin group would be needed to achieve the desired power. An incidence of 1% loss to follow up was assumed.	The primary and secondary efficacy analyses included all patients who underwent randomisation (intention-to-treat population) and included all events from the time of randomisation until the pre-defined cut-off date for efficacy outcomes. The analyses of bleeding events included all patients who received at least one dose of a study drug and included all events from the time the first dose of a study drug was received until 2 days after the last dose was received. Subjects who did not experience an efficacy endpoint event were censored at the earlier of: • their death date (when death is not part of the endpoint) • last contact date (for subjects who withdrew consent to be followed up or were lost to follow-up) • the efficacy cut-off date Subjects who did not experience a bleeding endpoint were censored at the earlier of: • 2 days after discontinuation of study drug • death date • last-contact date (for subjects who withdrew consent to be followed up or were lost to follow-up) at the end of the study

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
AVERROES	The primary objective of the study was to determine if apixaban was superior to aspirin for preventing the composite outcome of stroke or SE	Formal interim analyses were planned when 50% and 75% of the primary efficacy events had accrued. Stopping rules were based on an analysis of the primary outcome for which modified Haybittle–Peto boundaries of 4 SD (log hazard ratio) were used in the first half of the study and 3 SD in the second half. If either of these thresholds was crossed, a confirmatory analysis was to be performed 3 months later, and if that analysis also crossed the specified boundary, the data and safety monitoring board could recommend that the trial be terminated. A hierarchical testing strategy was followed to control the overall type 1 error in the study • Superiority of apixaban relative to aspirin for the primary efficacy endpoint was tested first • If superiority for the primary efficacy endpoint was demonstrated, then superiority of apixaban relative to aspirin was tested for the secondary efficacy endpoint • If superiority for the secondary endpoint was demonstrated, then superiority of apixaban relative to aspirin was tested for the endpoint for all-cause death. Cox proportional-hazards modelling and log-rank testing were used for efficacy and safety analyses.	With 226 primary outcome events, the study would have at least 90% power to detect a 35% relative risk reduction (RRR) of apixaban versus aspirin at the one-sided α= 0.025. With an average 1.6 years of follow-up and assuming a stroke rate of 3.3 per hundred subject-years in aspirin-treated subjects, at least 5600 randomised subjects allocated in a 1:1 ratio to the apixaban or aspirin group were needed to achieve the desired power. An incidence of 1% loss to follow up was assumed.	All primary efficacy analyses were based on the intention-to-treat (ITT) principle. Subjects without an efficacy endpoint were censored at the earlier of: • their vascular death date (when vascular death is not part of the endpoint) • nonvascular death date (when non-vascular death is not part of the endpoint) • last contact date • efficacy cut-off date Safety analyses were conducted on the treated-subjects dataset. Subjects who did not experience a bleeding endpoint were censored at the earlier of: • end of the Double-blind Treatment Period • death date • last-contact date at the end of the double-blind phase of the study

Abbreviations: INR, international normalised ratio; ISTH, International Society on Thrombosis and Haemostasis; SE, systemic embolism

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

In ARISTOTLE and AVERROES pre-planned subgroup analyses for the primary efficacy and safety endpoints were performed for the subgroups of clinical interest described in Table 15.

Table 15: Subgroups assessed for primary efficacy and safety endpoints

Characteristic	Subpopulations in ARISTOTLE	Subpopulations in AVERROES
Prior warfarin/VKA status	Experienced; Naïve	–
VKA unsuitable	–	Demonstrated; Expected
Reason VKA unsuitable	–	Subject refused treatment with VKA (only reason); $CHADS_2$ score =1 and physician does not recommend VKA (only reason); All others
Apixaban dose	2.5 mg BD or matching placebo; 5 mg BD or matching placebo	2.5 mg BD or matching placebo; 5 mg BD or matching placebo
Aspirin dose	–	81 mg; 162 mg; 243 mg; 324 mg
Geographic region	North America; Latin America; Europe; Asia/Pacific; US†, Eastern EU†,‡, Western EU†,‡	North America; Latin America; Europe; Asia/Pacific
Age	<65 years; ≥ 65 to <75 years; ≥ 75 years	<65 years; ≥ 65 to <75 years; ≥ 75 years
Gender	Male; Female	Male; Female
Female age group	≤ 50 years; >50 years	–
Race	White; Black or African American; Asian; Other	White; Black or African American; Asian; Other
Ethnicity	Hispanic/Latino; Not Hispanic/Latino	Hispanic/Latino; Not Hispanic/Latino
Weight	≤ 60 kg; >60 kg	≤ 60 kg; >60 kg
Body mass index	≤ 28 kg/m^2; >28 to 33 kg/m^2; >33 kg/m^2	≤ 28 kg/m^2; >28 to 33 kg/m^2; >33 kg/m^2
Level of renal impairment	Severe or moderate: ≤ 50 mL/min; Mild >50 to 80 mL/min; Normal >80 mL/min	Severe or moderate: ≤ 50 mL/min; Mild >50 to 80 mL/min; Normal >80 mL/min
Number of risk factors	≤ 1; ≥ 2	≤ 1; ≥ 2
$CHADS_2$ score	≤ 1; 2; ≥ 3	≤ 1; 2; ≥ 3
Prior stroke or TIA	Yes; No	Yes; No
Age ≥ 75 years	Yes; No	Yes; No
Diabetes mellitus	Yes; No	Yes; No
Hypertension requiring pharmacological treatment	Yes; No	Yes; No
Heart failure	Yes; No	Yes; No
Aspirin at randomisation	Yes; No	–
Clopidogrel at randomisation†	Yes; No	–
Type of AF†	Permanent or persistent; paroxysmal	–

†Post-hoc analysis; ‡Eastern Europe: Czech Republic, Hungary, Poland, Romania, Russia, Ukraine; Western EU: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK. Abbreviations: AF, atrial fibrillation; BD, twice daily; TIA, transient ischaemic attack; VKA, vitamin K antagonist

Each of the subgroups were analysed using a Cox proportional hazards model (stratified by prior warfarin/VKA status in ARISTOTLE) with terms for treatment group. The estimated RR and two-sided 95% CI were calculated to assess the treatment effect

within each of the subgroups. The p-value for the test of the treatment by grouping variable interaction was calculated based on a Cox proportional hazards model (stratified by prior warfarin/VKA status in ARISTOTLE) with terms for treatment group, the groups variable and treatment by grouping variable interaction.

For ARISTOTLE an additional pre-specified subgroup analysis for the primary efficacy and safety endpoints was performed for subgroups based on INR control using quartiles of time in therapeutic range (TTR) (69). Individual TTR during the trial was calculated for each warfarin treated patient by the commonly used Rosendaal method (70). The centre's TTR (cTTR) was calculated as the median of individual TTRs during the whole study among its warfarin patients and was assigned as a proxy for the centre's quality of INR control for all its patients (assigned to either warfarin or apixaban, to allow preservation of randomisation). The interquartile cut-off limits for the cTTR were identified to keep the patient numbers within each quartile approximately balanced.

Outcomes were compared across the four groups defined by the quartiles of the cTTR. Tests for interactions between the cTTR and randomised treatment effects were evaluated by multivariable Cox regression analyses using the patients' assigned cTTR value as a continuous variable. Interactions were adjusted for baseline variables potentially influencing both TTR and outcome: age, sex, body weight, $CHADS_2$ score, prior stroke, diabetes mellitus, hypertension, heart failure, baseline medications and warfarin naïve/experienced status.

Participant flow

CONSORT flow charts showing the numbers of patients enrolled to enter ARISTOTLE and AVERROES, and numbers randomly allocated to each treatment are presented in Figure 3 and Figure 4, respectively.

In ARISTOTLE, fewer subjects discontinued the study drug permanently in the apixaban group (25.3%) than in the warfarin group (27.5%) (p=0.001). Similarly, in AVERROES fewer subjects discontinued the study drug permanently in the apixaban group (19.9%) than in the aspirin group (23.3%). In both studies the most common reasons for discontinuation in both treatment arms were the subject's request to discontinue study treatment and AEs.

Figure 3: Participant flow – ARISTOTLE

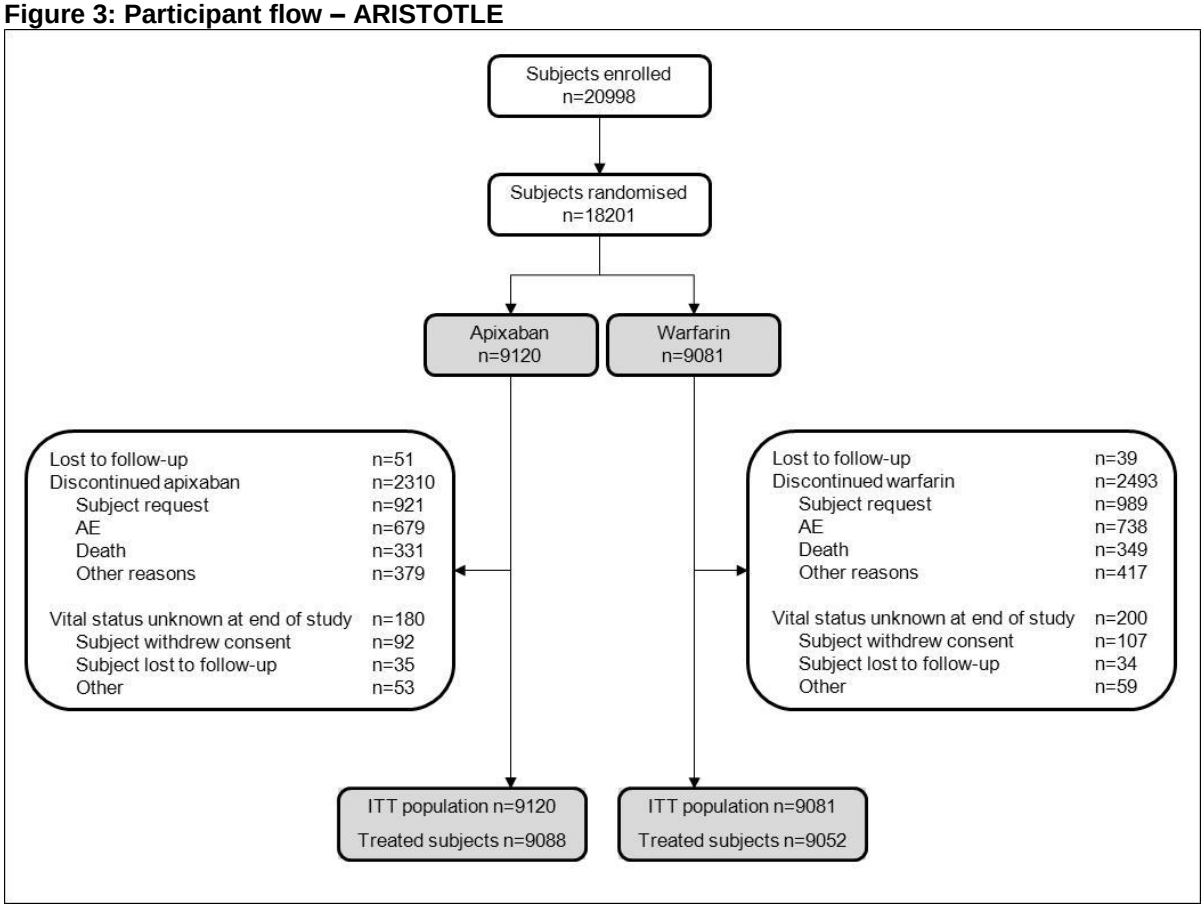
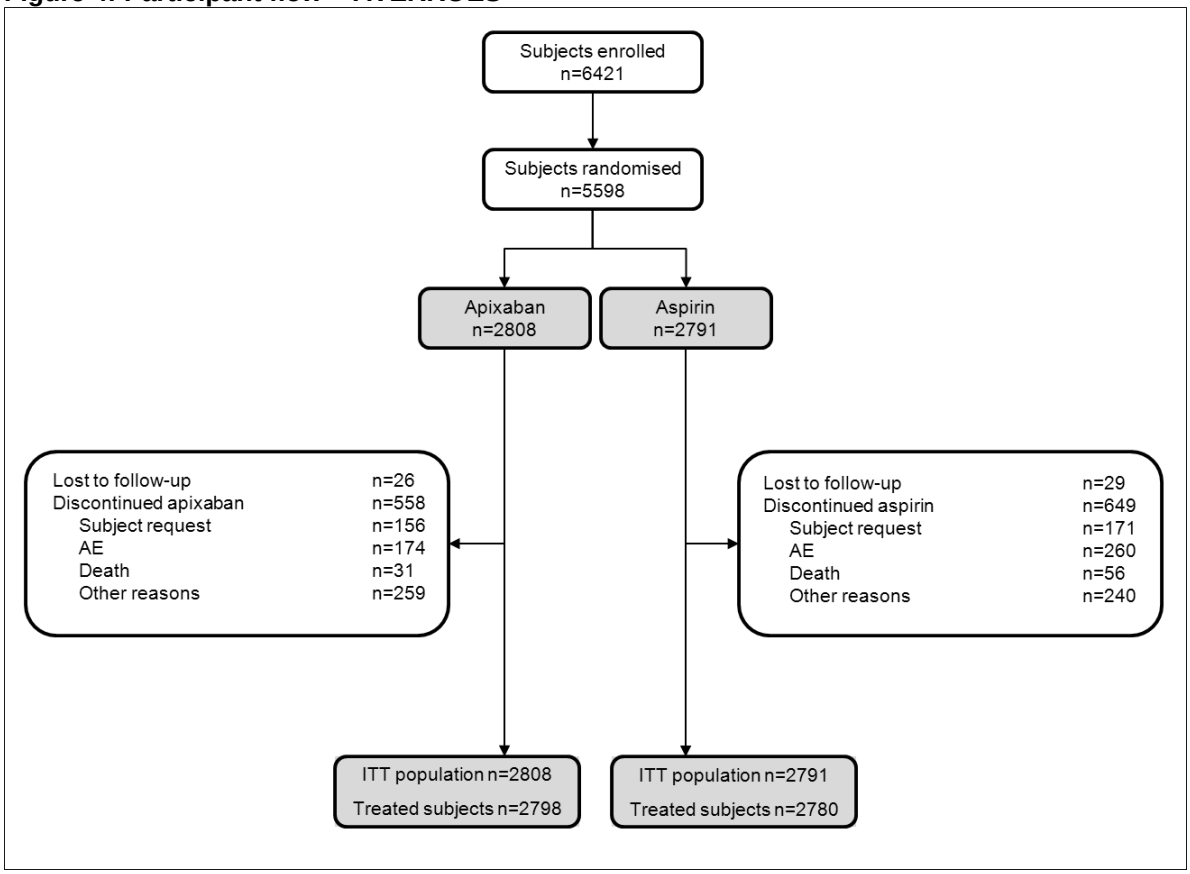


Figure 4: Participant flow – AVERROES



6.4 Critical appraisal of relevant RCTs

Critical appraisals of ARISTOTLE and AVERROES are presented in Table 16. A complete quality assessment for each RCT is provided in Section 10.3.

Table 16: Quality assessment results for RCTs

Trial no. (acronym)	ARISTOTLE	AVERROES
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	Yes fewer subjects discontinued study drug permanently in the apixaban group (25.3%) than in the warfarin group (27.5%) (p=0.001).	Yes fewer subjects discontinued study drug permanently in the apixaban group (19.9%) than in the aspirin group (23.3%).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	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	Yes

6.5 Results of the relevant RCTs

6.5.1 ARISTOTLE

Summary

- In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism (HR 0.79; 95% CI: 0.66–0.95; p=0.01).
- The rate of clinically important fatal or disabling stroke was significantly lower with apixaban than warfarin (HR 0.71; 95% CI: 0.54–0.94)
- Apixaban was superior to warfarin for the prevention of death due to any cause (HR 0.89; 95% CI: 0.80–0.99; p=0.047)
- Fewer patients discontinued the study drug in the apixaban group than the warfarin group (25.3% versus 27.5% respectively, p=0.001)
- The efficacy of apixaban versus warfarin was maintained:
  - Across patients at different levels of stroke risk
  - Regardless of levels of warfarin control (TTR)
  - In patients who required a dose reduction (2.5 mg BD)
- The rate of MI was numerically lower in the apixaban group than in the warfarin group (HR 0.88; 95% CI: 0.66–1.17; p=0.37)

Study drugs

The mean duration of exposure to double-blind study drug was approximately 1.8 years in each treatment group. The mean duration of exposure was similar when treatment groups were summarised by prior warfarin /VKA status.

Maintenance of an acceptable target INR for warfarin-treated subjects was a key component of this study design. The time that INR was in the therapeutic target range of 2.0–3.0 (TTR) was summarised for subjects randomised to warfarin. For subjects randomised to apixaban, both the real and the sham INR (reported to preserve the blind) were summarised. After exclusion of INR values during the first 7 days following randomisation and during study-drug interruptions, patients in the warfarin group had an INR in therapeutic range for a median of 66.0% of the time and a mean of 62.2% of the time.

Discontinuations

It is important that patients with AF receive appropriate anticoagulation therapy to minimise the risk of stroke. Fewer patients in the apixaban group than in the warfarin group discontinued study drug before the end of the trial: 25.3% in the apixaban group vs 27.5% in the warfarin group (p=0.001). This shows that at the end of the study patients were more likely to remain on treatment in the apixaban group, and were therefore more likely to be receiving the benefit of anticoagulation.

Primary Efficacy Results

Apixaban was superior to warfarin for reduction of stroke (haemorrhagic or ischaemic) and SE (hazard ratio (HR), 0.79; 95% CI: 0.66–0.95; p=0.01). The primary outcome of stroke or SE occurred in 212 patients in the apixaban group (1.27% per year) and in 265 patients in the warfarin group (1.60% per year) (Table 17 and Figure 5).

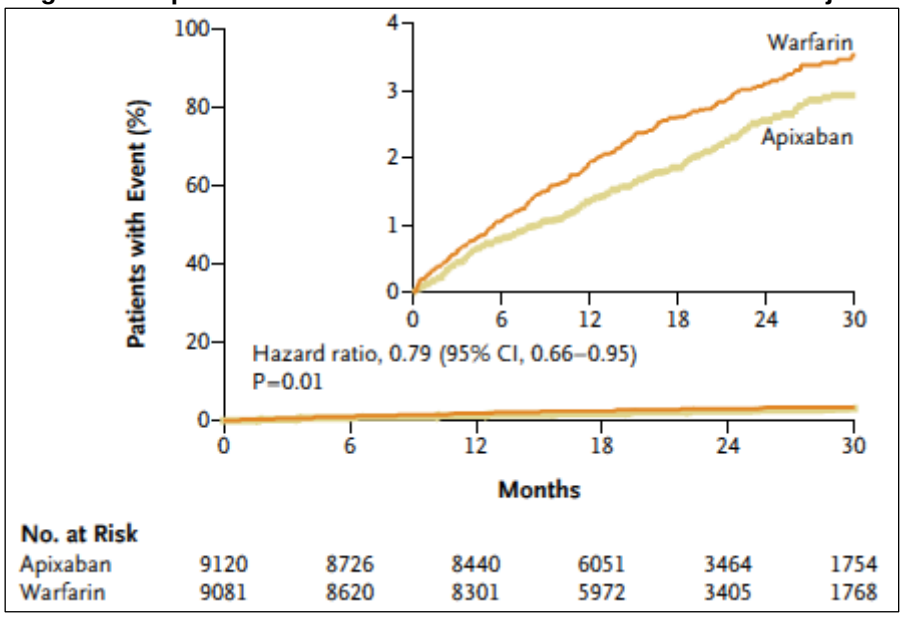
The incidence of each individual efficacy endpoint including haemorrhagic stroke, ischaemic or unspecified stroke, and SE was lower for apixaban than warfarin (Table 17). The rate of haemorrhagic stroke was 49% lower in the apixaban group than in the warfarin group (p<0.001), and the rate of ischaemic or uncertain type of stroke was 8% lower (Table 17).

Table 17: Summary of primary efficacy outcome – randomised subjects

	Apixaban N=9120		Warfarin N=9081		Hazard ratio (95% CI)	p-value
	Pts with event no.	Event rate %/yr	Pts with event no.	Event rate %/yr		
Primary outcome: stroke or SE	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischaemic or uncertain type	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Haemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
SE	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70

Abbreviations: pts, patients; SE, systemic embolism; yr, year; CI, confidence interval

Figure 5: Kaplan-Meier curve for stroke or SE – randomised subjects



Fatal or disabling stroke (Rankin score 3–6) occurred in 84 patients in the apixaban group (0.50% per year) and in 117 patients in the warfarin group (0.71% per year) (HR, 0.71; 95% CI: 0.54–0.94). Fatal stroke occurred in 42 patients in the apixaban group and 67 patients in the warfarin group.

Secondary Efficacy Results

According to the sequential testing strategy, since superiority of apixaban compared with warfarin was demonstrated for both the primary efficacy endpoint, and ISTH major bleeding (see Section 6.9.1), superiority for all-cause death was tested. Apixaban was superior to warfarin for prevention of all-cause death (HR, 0.89; 95% CI: 0.80–0.99; p=0.047) (Table 18).

This was also supported by numerically lower rates of death from cardiovascular and non-cardiovascular causes for apixaban. In the apixaban group the rate of death from cardiovascular causes (including death from haemorrhagic stroke) was 1.80% per year compared with 2.02% per year in the warfarin group (HR, 0.89; 95% CI: 0.76–1.04), and the rate of death from non-cardiovascular causes (including fatal bleeding other than that from haemorrhagic stroke) was 1.14% per year in the apixaban group compared with 1.22% per year in the warfarin group (HR, 0.93; 95% CI: 0.77– 1.13). The rate of myocardial infarction (MI) was lower in the apixaban group than in the warfarin group, but the difference was not significant (Table 18).

Table 18: Summary of secondary efficacy outcomes – randomised subjects

	Apixaban N=9120		Warfarin N=9081		Hazard ratio (95% CI)	p-value
	Pts with event no.	Event rate %/yr	Pts with event no.	Event rate %/yr		
Key secondary outcome						
Death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, SE, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
MI	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, SE, MI, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
PE or DVT	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; pts, patients; SE, systemic embolism; yr, year; CI, confidence interval

Subgroup analyses

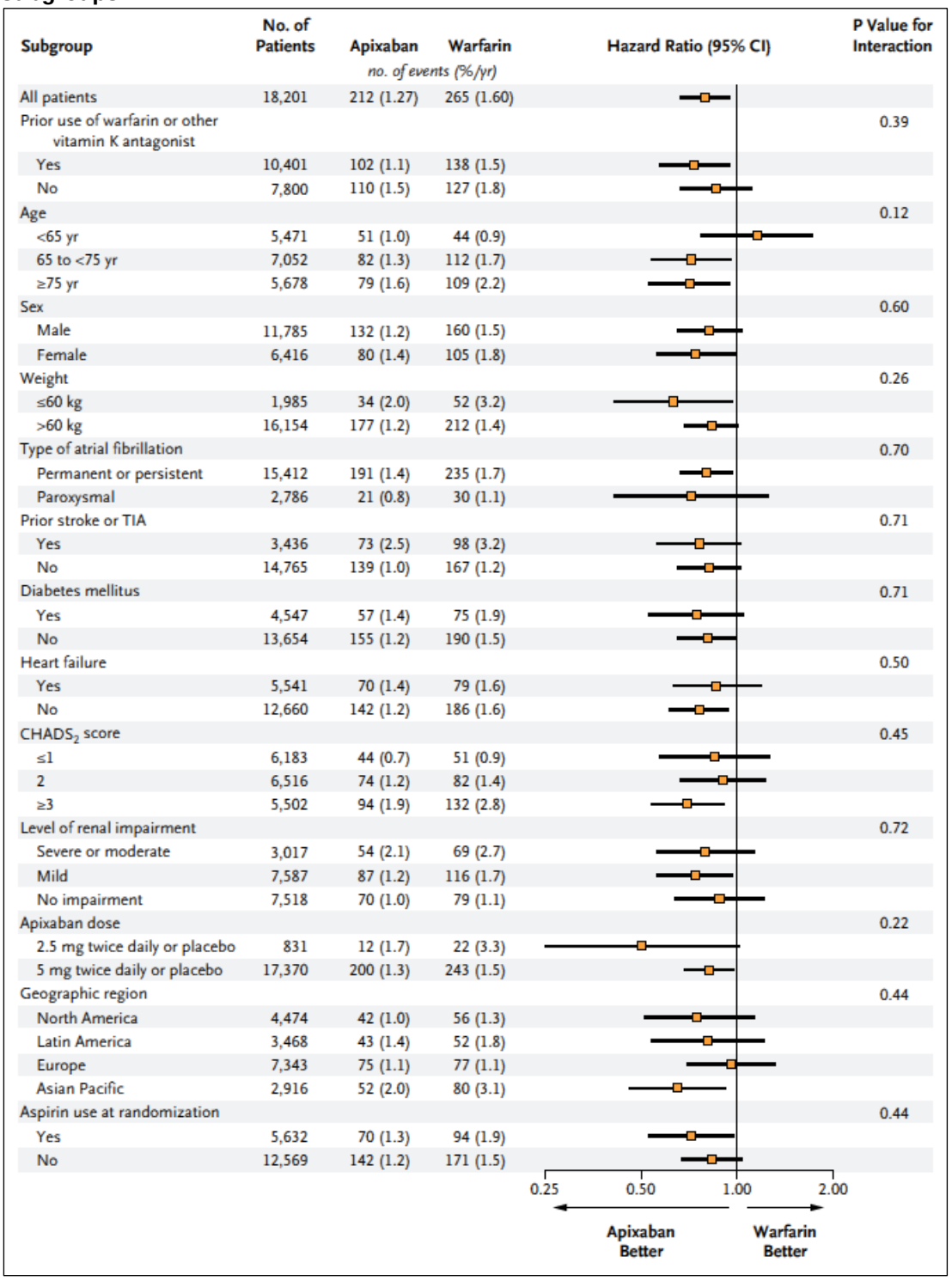
Subgroup analyses addressed whether the efficacy profile of apixaban was markedly different within distinct subgroups compared with that observed in the overall study. Analyses for the primary efficacy endpoint were performed for subgroups of clinical interest.

The reduction of stroke and SE with apixaban was consistent across the majority of the 21 pre-specified subgroups (Figure 6). Apixaban showed a robust effect in reducing stroke/SE compared with warfarin in subjects at high risk for stroke/SE, including the elderly (age ≥ 75 years), subjects with $CHADS_2$ ≥ 3, and subjects with severe or moderate renal impairment. Although the study was not powered to demonstrate superiority within subgroups, the estimated HR was <1 within all but one subgroup of clinical interest, suggesting that the risk of stroke/SE was lower in the apixaban group than in the warfarin group. The only subgroup with an estimated HR ≥ 1 was age group <65 years (HR=1.16) but the associated CI included 1 (95% CI: 0.77–1.73) and a p-value of >0.10 for interaction.

Statistical tests for interaction were not significant (p>0.10) for all of the 21 pre-specified subgroups.

The protocol specified that the dose of apixaban/placebo assigned at randomisation was to be 2.5 mg BD instead of 5 mg BD for subjects who were deemed to be at higher risk for bleeding (i.e. had at least 2 of 3 criteria: age ≥ 80 years, weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL). The 2.5 mg apixaban dose was assigned to 4.6% of randomised subjects. The efficacy of apixaban was not impacted by using a reduced dose in these subjects. In fact, although the 2.5 mg BD subgroup was small, apixaban showed a robust effect in reducing stroke/SE compared to warfarin both within the 2.5 mg BD and the 5 mg BD subgroups.

Figure 6: Relative risks of stroke and systemic embolism according to major pre-specified subgroups



Pre-specified subgroups not included in the figure were subgroups according to race, ethnic group, BMI, number of risk factors, age >75 years, and use or non-use of clopidogrel at the time of randomisation, as well as subgroups of women according to age group. Abbreviations: TIA, transient ischaemic attack

cTTR sub-group analysis

The reduction of stroke and SE with apixaban was consistent across the TTR subgroups (Table 19).

Table 19: Relative risks of stroke or SE with apixaban compared with warfarin, according to TTR subgroup

	Apixaban		Warfarin		
cTTR (%)	**Events**	**Rate/100 person years**	**Events**	**Rate/100 person years**	**HR (95% CI)**
< 58.0	70	1.75	88	2.28	0.77 (0.56–1.06)
58.0–65.7	54	1.30	68	1.61	0.80 (0.56–1.15)
65.7–72.2	51	1.21	65	1.55	0.79 (0.54–1.13)
>72.2	36	0.83	44	1.02	0.81 (0.52–1.26)

Source: Wallentin, 2011 (69)

These results suggest that the benefits of apixaban over warfarin in preventing stroke or SE are consistent regardless of the centre's quality of INR control.

6.5.2 AVERROES

Summary

- Apixaban, compared with aspirin, more than halved the rate of stroke and SE in patients with AF who were unsuitable for VKA therapy (HR 0.45; 95% CI: 0.32–0.62, p<0.001)
- The rate of clinically important fatal or disabling stroke was significantly lower with apixaban than aspirin (HR 0.43; 95% CI: 0.28–0.65, p<0.001)

- Apixaban showed a clinically important reduction in major vascular events (composite of stroke, SE, MI, or vascular death) relative to aspirin (HR 0.66; 95% CI: 0.53–0.83, p=0.003)
- Apixaban reduced the incidence of cardiovascular hospitalisations relative to aspirin (12.6% per year versus 15.9% per year, p<0.001)
- The rate of discontinuation of study drug was 12% lower in the apixaban group than in the aspirin group (HR 0.88, 95%CI: 0.78–0.99, p=0.03)

Early termination of study

The results of the first planned interim analysis of efficacy were reviewed by the data and safety monitoring committee (DMC) on February 19, 2010. At this time 104 events had occurred and a treatment benefit in favour of apixaban for the primary outcome that exceeded four standard deviations was observed. Results of a confirmatory analysis were reviewed on May 28, 2010, at which time the p-value was 0.000002 and the DMC made a recommendation that the study be terminated due to the superior efficacy of apixaban. Events that occurred up to May 28, 2010 were included in the primary analyses – the mean duration of follow-up was 1.1 years.

Discontinuations

It is important that patients with AF receive appropriate anticoagulation therapy to minimise the risk of stroke. Fewer patients in the apixaban group than in the aspirin group discontinued the study drug before the end of the trial: 17.9% in the apixaban group versus 20.5% in the aspirin group (HR 0.88; 95%CI: 0.78-0.99, p=0.03). This shows that, at the end of the study, patients were more likely to remain on treatment in the apixaban group, and were therefore more likely to be receiving the benefit of anticoagulation.

Primary Efficacy Results

Apixaban was superior to aspirin (p<0.001) for the prevention of stroke or SE in subjects with AF and at least one additional risk factor for stroke and who had failed or were expected to be unsuitable for VKA treatment (Table 20 and Figure 7). The event rates were 1.6% and 3.7% per year for apixaban and aspirin, respectively (HR with apixaban, 0.45; 95% CI: 0.32–0.62; p<0.001). Apixaban significantly reduced both stroke and SE rates relative to aspirin (Table 20). The rates of ischaemic stroke were 1.1% per year for apixaban and 3.0% per year for aspirin (HR with apixaban, 0.37; 95% CI: 0.25–0.55; p<0.001).

Fatal or disabling stroke occurred in 31 patients in the apixaban group (1.0% per year) and in 72 patients in the aspirin group (2.3% per year) (HR, 0.43; 95% CI: 0.28–0.65).

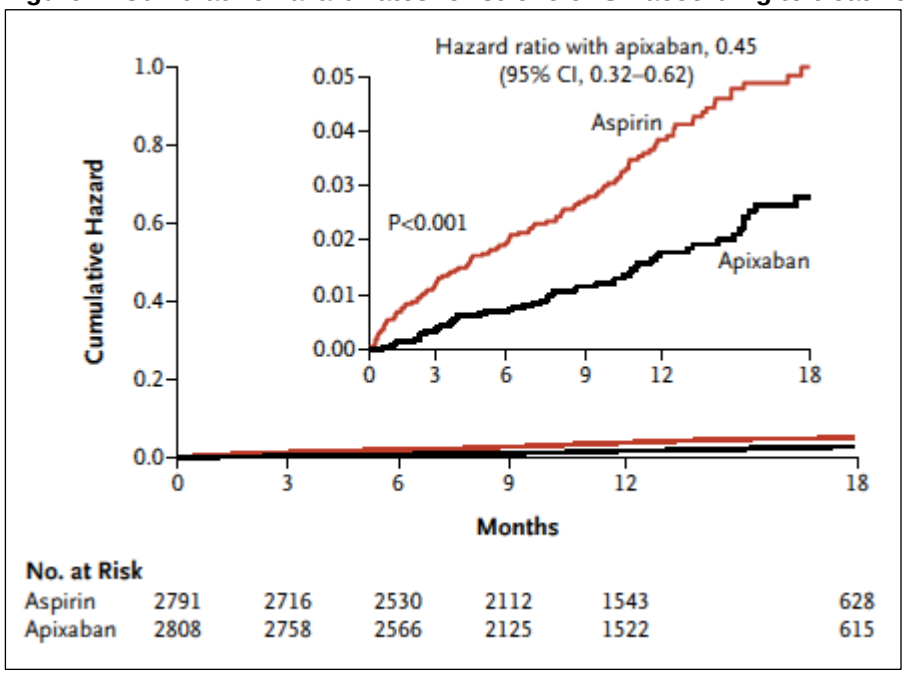
Table 20: Summary of primary efficacy outcome – randomised subjects

	Apixaban N=2,808		Aspirin N=2,791		Hazard ratio (95% CI)	p-value
	Pts with event no.	Event rate† %/yr	Pts with event no.	Event rate† %/yr		
Primary outcome: stroke or SE	51	1.6	113	3.7	0.45 (0.32–0.62)	<0.001
Stroke	49	1.6	105	3.4	0.46 (0.33–0.65)	<0.001
Ischaemic	35	1.1	93	3.0	0.37 (0.25–0.55)	<0.001
Haemorrhagic	6	0.2	9	0.3	0.67 (0.24–1.88)	0.45
Unspecified	9	0.3	4	0.1	2.24 (0.69–7.27)	0.18
Disabling or fatal	31	1.0	72	2.3	0.43 (0.28–0.65)	<0.001
Systemic embolism	2	0.1	13	0.4	0.15 (0.03–0.68)	0.01

Abbreviations: Pts, patients; SE, systemic embolism; yr, year; CI, confidence interval

†The percent per year is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have more than one event

Figure 7: Cumulative hazard rates for stroke or SE according to treatment group



Secondary Efficacy Results

Apixaban showed a clinically important reduction in major vascular events (composite of stroke, SE, MI, or vascular death) relative to aspirin (HR, 0.66; 95% CI: 0.53–0.83, p=0.003) (Table 21). Apixaban reduced the incidence of all-cause death compared with aspirin although this effect was not statistically significant.

Apixaban reduced the incidence of cardiovascular hospitalisations relative to aspirin (HR, 0.79; 95% CI: 0.69–0.91, p<0.001).

Table 21: Summary of secondary efficacy outcomes – randomised subjects

	Apixaban N=2808		Aspirin N=2791		Hazard ratio (95% CI)	p-value
	Pts with event	Event rate†	Pts with event	Event rate†		
	no.	%/yr	no.	%/yr		
Stroke, SE, or death	143	4.6	223	7.2	0.64 (0.51–0.78)	<0.001
Stroke, SE, MI or death from vascular cause	132	4.2	197	6.4	0.66 (0.53–0.83)	<0.001
Stroke, SE, MI, death from vascular cause, or major bleeding event	163	5.3	220	7.2	0.74 (0.60–0.90)	0.003
MI	24	0.8	28	0.9	0.86 (0.50–1.48)	0.59
Death from any cause	111	3.5	140	4.4	0.79 (0.62–1.02)	0.07
Death from vascular cause	84	2.7	96	3.1	0.87 (0.65–1.17)	0.37
Hospitalisation for CV cause	367	12.6	455	15.9	0.79 (0.69–0.91)	<0.001

Abbreviations: CV, cardiovascular; MI, myocardial infarction; Pts, patients; SE, systemic embolism; yr, year; CI, confidence interval

†The percent per year is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have more than one event

Subgroup analyses

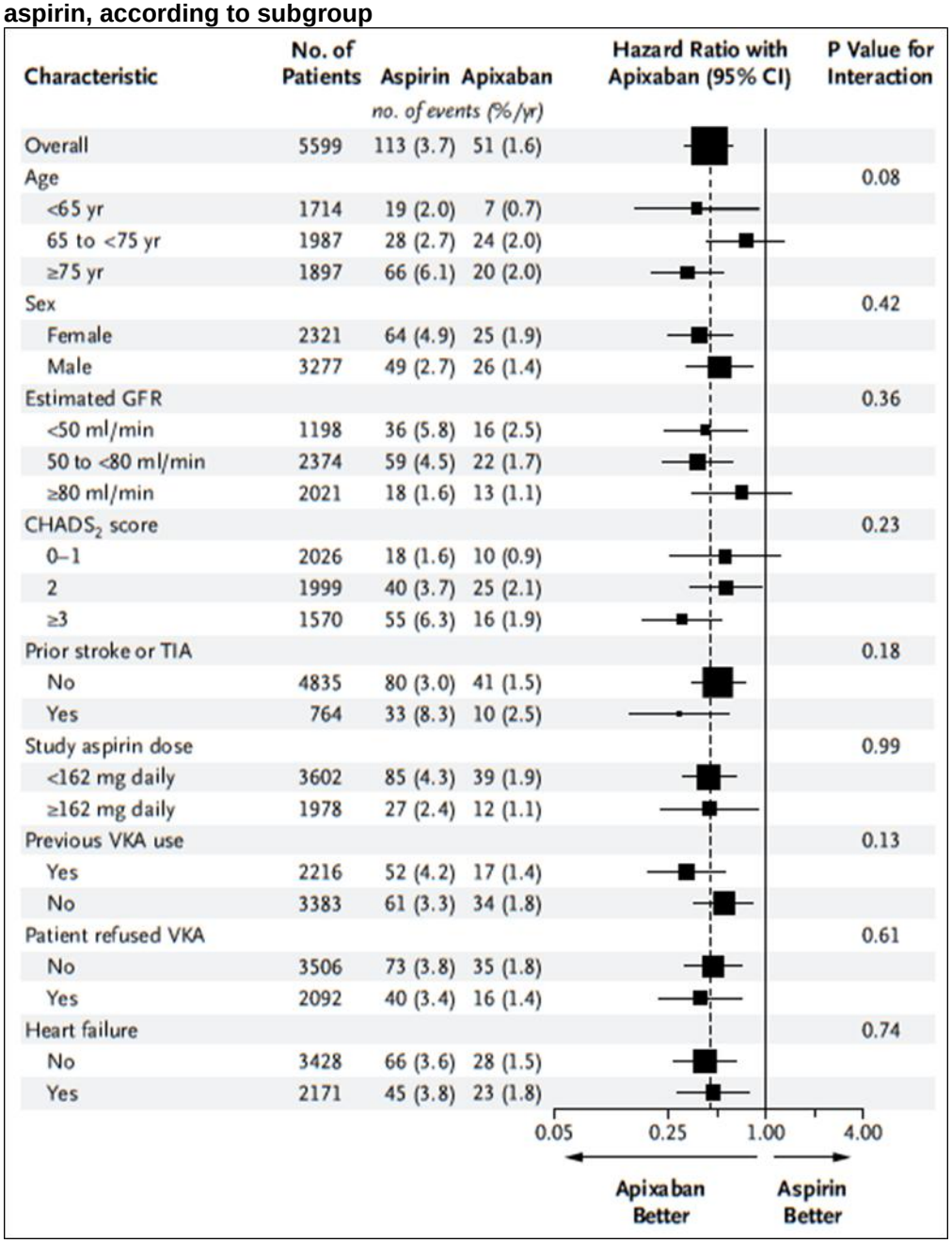
Subgroup analyses addressed whether the efficacy profile of apixaban was markedly different within distinct subgroups compared to that observed in the overall study. Analyses for the primary efficacy endpoint were performed for subgroups of clinical interest. Overall, the results within each subgroup were consistent with the primary efficacy results for the study (Figure 8). The benefit of apixaban was consistent in subgroups according to $CHADS_2$ score and according to prior use/non-use of VKAs. Among patients who were at high risk because of a previous stroke or TIA (n=764), there was a reduction in the rate of stroke or SE with apixaban (2.5% per year) as compared with aspirin (8.3% per year). Although the study was not designed to ensure adequate power for subgroup analyses, the upper bounds of the 95% CIs for the HR were <1 (when estimable) for most of the subgroup categories.

There were no significant interactions between the treatment effects and various characteristics of the patients.

The protocol specified that the dose of apixaban/placebo assigned at randomisation was to be 2.5 mg BD rather than 5 mg BD for subjects who had at least 2 of 3 criteria (age ≥ 80 years, weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL) since these subjects were deemed to be at a higher risk for bleeding. This reduced dose was assigned to 6.4% of subjects. The efficacy of apixaban was not negatively impacted by using a reduced dose in these subjects. In fact, although the 2.5 mg BD subgroup was small and the study was not powered to demonstrate superiority within subgroups, apixaban showed a robust effect in reducing stroke/SE compared with aspirin both within the 2.5 mg BD and the 5 mg BD subgroups with HRs of 0.26 (95% CI: 0.07–0.93) and 0.47 (95% CI: 0.33–0.66),

respectively. Furthermore, the observed event rates for stroke/SE for subjects randomised to apixaban were similar (1.63%/year in the 2.5 mg BD subgroup and 1.62 %/year in the 5 mg BD subgroup).

Figure 8: Relative risks of stroke or SE with apixaban compared with aspirin, according to subgroup



The squares and horizontal lines indicate hazard ratios and corresponding 95% CI; the sizes of the squares are proportional to the sizes of the subgroups. Dashed vertical lines represent the point estimates of the overall hazard ratio.

Abbreviations: GFR, glomerular filtration rate; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist; yr, year

6.6 Meta-analysis

6.6.1 Meta-analysis methods and results

A meta-analysis was inappropriate because there are only two apixaban trials in the indication under review and they have different comparators. Since there is only a single phase 3 trial for dabigatran and rivaroxaban respectively in the indication under review, a meta-analysis was not possible for these comparator treatments.

6.6.2 Qualitative overview if meta-analysis inappropriate

N/A

6.6.3 Trials excluded from analysis

N/A

6.7 Indirect and mixed treatment comparisons

Summary

- In the absence of head to head RCT evidence network meta-analyses were conducted to determine the relative efficacy and safety of apixaban versus dabigatran and rivaroxaban
- However, the other NOACS did not have data in the warfarin unsuitable population so data from the warfarin-suitable trials (RE-LY and ROCKET) were used in the NMAs

In the warfarin suitable and unsuitable populations the three NOACs have similar efficacy:

- Apixaban was associated with a statistically significant reduction in myocardial infarction compared with dabigatran 150 mg and dabigatran 110 mg
- There were no statistically significant differences between the three NOACs for the other efficacy outcomes

In the warfarin suitable and unsuitable populations, apixaban has lower bleeding and discontinuation rates compared with both dabigatran 150 mg and rivaroxaban

- Apixaban has a statistically significant lower incidence of all bleeding outcomes compared with rivaroxaban (ICH, major bleeding, other major bleeding, GI bleeding, CRNM bleeding, and any bleeding)
- Apixaban has a statistically significant lower incidence of major bleeding, other major bleeding, GI bleeding, and any bleeding compared with dabigatran 150 mg
- Apixaban has a statistically significant lower incidence of any bleeding compared with dabigatran 110 mg
- Apixaban had a statistically significant lower incidence of discontinuation than both dabigatran and rivaroxaban

6.7.1 Identification of studies

Please see Section 6.1 for the methods used to identify RCT evidence on the efficacy and safety of apixaban and relevant comparators for stroke prevention in patients with atrial fibrillation (AF) at moderate to high risk for stroke. Eligibility criteria and a flow diagram of included and excluded studies can be found in Section 6.2.

6.7.2 Study selection, and methodology, quality assessment and results of relevant RCTs

In line with the NICE scope for apixaban in adults with non-valvular AF at risk of stroke or systemic embolism, network meta-analyses (NMAs) were conducted to determine the relative efficacy and safety of apixaban and the other NOACs dabigatran etexilate and rivaroxaban. Four of the 41 RCTs identified by the systematic review included a NOAC versus active comparator and were eligible for inclusion in the NMAs. A summary of the trials used to inform the NMAs is provided in Table 22. A quality assessment of these four RCTs is provided in Section 10.5 (Appendix 5).

As shown in Table 22 there are a number of differences across the included studies in trial design, patients enrolled and populations analysed:

- The ARISTOTLE, ROCKET-AF and AVERROES trials were double-blind, double-dummy studies – in contrast in the RE-LY study the assignments to dabigatran or warfarin were not concealed.
- Subjects were enrolled in the ARISTOTLE, AVERROES and RE-LY studies if they had a $CHADS_2$ score of ≥ 1, whereas ROCKET-AF enrolled a higher risk population ($CHADS_2$ ≥ 2). At baseline the mean $CHADS_2$ score for the ROCKET-AF study was 3.58 compared with 2.1 for both RE-LY and ARISTOTLE.
- The mean percentage of time in which the INR was in the therapeutic range of 2.0–3.0 for warfarin was 64% in the RE-LY trial, 62% in the ARISTOTLE trial, and 55% in the ROCKET-AF trial.
- The AVERROES and RE-LY study publications based all efficacy and safety analyses on the ITT principle. In the ARISTOTLE study publication, efficacy analyses were conducted on the ITT population and safety analyses on the on-treatment (OT) population. Analyses of efficacy in the ROCKET-AF trial publication were conducted on a per protocol (PP) population to demonstrate non-inferiority, with superiority and safety analyses run on the OT population.

These differences highlight the challenges associated with cross-trial indirect comparisons in this indication.

Table 22: Summary of the trials used to conduct the NMAs

Trial name (primary ref)	Treatment	Dose	Trial design	Patient population	Mean age	% Male	Length follow-up	Mean % TTR	Efficacy and safety populations as reported in the primary publication
ARISTOTLE (2)	Apixaban	5 mg BD*	Randomised, double-blind, double-dummy	Subjects with AF and a $CHADS_2$ score ≥ 1	69.1	64.4	1.8 years	–	Efficacy: ITT – all randomised patients Safety: OT – all patients who received ≥ 1 dose of study drug
	Dose-adjusted warfarin	INR 2.0–3.0			64.5	65.0		62%	
RE-LY (58)‡	Dabigatran 110 mg	100 mg BD	Randomised, two doses of dabigatran administered in a blinded fashion, open-label use of warfarin	Subjects with AF and a $CHADS_2$ score ≥ 1	71.4	64.3	2 years	–	Efficacy: ITT Safety: ITT
	Dabigatran 150 mg	150 mg BD			71.5	63.2		–	
	Dose-adjusted warfarin	INR 2.0–3.0			71.6	63.3		64%	
ROCKET–AF (63)	Rivaroxaban	20 mg OD	Randomised, double-blind, double-dummy	Subjects with non-valvular AF and a $CHADS_2$ score ≥ 2	71.2	60.3	1.9 years	–	Efficacy: PP – all patients who received ≥ 1 dose of study drug, did not have a major protocol violation. OT population was used to test for superiority in the event non-inferiority was achieved on the PP population. ITT population analysed for the primary outcome only Safety: OT – all patients who received ≥ 1 dose of study drug regardless of adherence to protocol
	Dose-adjusted warfarin	INR 2.0–3.0			71.2	60.3		55%	

Trial name (primary ref)	Treatment	Dose	Trial design	Patient population	Mean age	% Male	Length follow-up	Mean % TTR	Efficacy and safety populations as reported in the primary publication
AVERROES (3)	Apixaban	5 mg BD*	Randomised, double-blind, double-dummy	Subjects with AF and a $CHADS_2$ score ≥ 1 who have failed/are unsuitable for VKA therapy	69.7	59.1	1.1 years†	–	Efficacy – ITT Safety – ITT
	Aspirin	81–324 mg/d			70.0	57.9		–	

Abbreviations: BD, twice daily; INR, International normalised ratio; OD, once daily; TTR, time in therapeutic range; †The AVERROES trial was terminated early by the Data Safety Monitoring Board as the treatment benefit in favour of apixaban for the primary outcome exceeding 4 standard deviations; ‡A later publication of the RE-LY trial was identified by the systematic review which reported additional primary efficacy and safety outcome events recorded during routine clinical site closure visits after the database was locked (Connolly et al 2010) ((71)). Data from the 2010 publication were used in sensitivity analyses. *2.5 mg BD was used in small sub-populations.

6.7.3 Summary of trials used to inform the comparison

In order to compare apixaban with the appropriate comparators for the submission, two NMAs were conducted: 1) in patients who are suitable for warfarin treatment (NMA 1) and, 2) in patients for whom warfarin would not be considered, or who are unsuitable for warfarin (NMA 2).

Although not in the final NICE scope, aspirin is still recommended for use by the NICE AF guideline (CG36) in patients at low to moderate risk of stroke or SE and in those with moderate to high risk who are unsuitable for warfarin. Furthermore, aspirin is still widely used in clinical practice in England and Wales (see Section 2.5 above) and is therefore a relevant comparator in this submission. However, AVERROES is the only study that enrolled patients unsuitable for warfarin treatment and compared a NOAC with aspirin. Since there are no trials of dabigatran or rivaroxaban in the warfarin unsuitable population, NMA 2 was conducted using data from the RE-LY and ROCKET studies to obtain a connected evidence network. Due to these data limitations, NMA 2 represents a mix of warfarin suitable and unsuitable populations, rather than a pure warfarin unsuitable population.

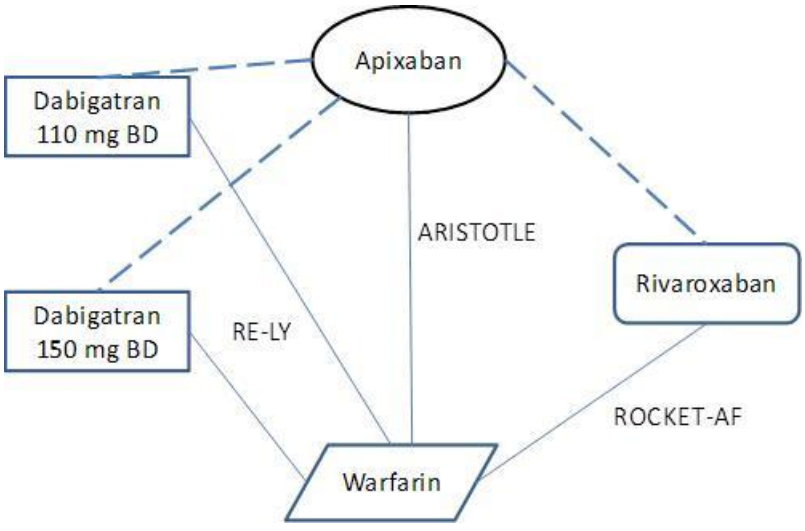
NMA 1: Warfarin-suitable analysis

Three RCTs were included in NMA 1:

- ARISTOTLE (2): apixaban 5 mg BD vs warfarin INR 2.0–3.0
- ROCKET-AF (63): rivaroxaban, 20 mg OD vs warfarin INR 2.0–3.0
- RE-LY (58): dabigatran 110 mg BD vs dabigatran 150 mg BD vs warfarin INR 2.0–3.0

Comparisons between all treatments were made based on the predefined network shown in Figure 9.

Figure 9: Network diagram for warfarin-suitable population (NMA 1)



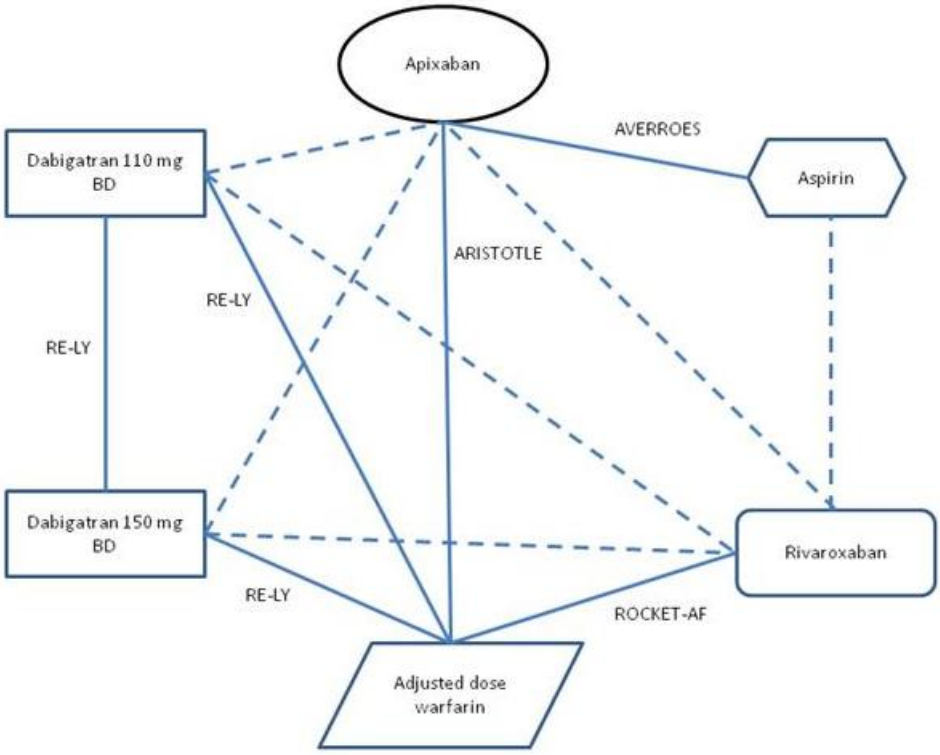
NMA 2: Warfarin unsuitable analysis

Four RCTs were included in the analysis:

- AVERROES (3): apixaban 5 mg BD vs aspirin 81 to 324 mg/day
- ROCKET-AF (63): rivaroxaban 20 mg OD vs warfarin INR 2.0–3.0
- RE-LY (58): dabigatran 110 mg BD vs dabigatran 150 mg BD vs warfarin INR 2.0–3.0
- ARISTOTLE (2): apixaban 5 mg BD vs warfarin INR 2.0–3.0 – (required for this network in order to connect AVERROES to RE-LY and ROCKET (via warfarin))

Comparisons between all treatments were made based on the predefined network shown in Figure 10.

Figure 10: Network diagram for patients unsuitable for warfarin (NMA 2)



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

The efficacy and safety outcomes shown in column 1 of Table 23 were analysed in both NMA 1 and NMA 2. Data were extracted from the primary publications where available. However, as stated in Section 6.7.2 there were some differences across the trials regarding the efficacy and safety populations that were analysed and reported in the primary publications. Therefore, for consistency across trials, additional data not available in the primary publications were sought from other sources. Table 23 below shows the outcomes for which additional data were identified (represented by ✓) and the source of this data (in the footnote).

Table 23: NMA 1 and NMA 2 outcomes and additional data sources

	Additional data			
	AVERROES safety OT population†	**ROCKET additional ITT data‡**	**ROCKET any bleed data§**	**RE-LY 2010 updated ITT data¶**
Efficacy outcomes				
Stroke and systemic embolism (SE)				✓
Any stroke	✓	✓		✓
SE		✓		
Haemorrhagic stroke		✓		
Ischaemic stroke		✓		
Myocardial infarction (MI)		✓		✓
All-cause mortality		✓		
Fatal stroke				
Disabling stroke				
Non-disabling stroke				
Discontinuations		✓ ††		
Bleeding outcomes				
Intracranial haemorrhage (ICH)	✓			✓
Major bleeding	✓			✓
Gastrointestinal (GI) bleeding	✓			✓
Other major bleed‡‡	✓			✓
CRNM bleeding	✓			
Any bleeding	✓		✓	✓

✓ Shows data identified for that outcome; †Safety analyses of the OT population (all subjects who received at least one dose of double-blind study drug) for AVERROES, from the clinical study report (68); ‡From a slide set obtained from the FDA website (72), and rivaroxaban SPC (73); §Calculated by adding adjudicated minimal bleeding event rates reported in the FDA briefing document for rivaroxaban (74) to other bleeding event rates;¶RE-LY update publication (Connolly et al 2010) reported additional primary efficacy outcome events recorded during routine clinical site closure visits after the database was locked (71). ††ITT data reported in online appendix of publication; ‡‡Calculated by subtracting ICH from major bleed

Health-related quality of life outcomes were not measured in the trials, with the exception of RE-LY (58), therefore an NMA for this outcome was unfeasible.

The analysis of event rates considered the total number of events that occurred during the patients' exposure to the risk (total events across all patients divided by total patient-

years exposed). This allowed for cases where the patient may have experienced the event more than once and for differences in trial follow-up. If event rates were not reported in the publication they were estimated from the number of patients experiencing the outcome (this calculation is explained in Appendix 14, section 10.14).

Base case analyses

The following data were used for the base case analyses:

- RE-LY 2009 data from the primary study publication (NMA 1 and NMA 2) – this was deemed the most appropriate dataset since the RE-LY 2010 update is a research letter and represents a post-hoc analysis that occurred after the trial database was locked
- ROCKET ITT efficacy data (NMA 1 and NMA 2) – the ITT event-rate data identified for haemorrhagic stroke, ischaemic stoke, non-CNS embolism, MI and all-cause mortality was used as this has been accepted by the EMEA as the most appropriate efficacy analysis (75). ITT event-rate data were not available for fatal stroke, disabling stroke and non-disabling stroke and OT data were used for these outcomes
- OT data for AVERROES safety outcomes (NMA 2) – the OT dataset is usually used for safety analyses as it excludes randomised subjects never exposed to study drug, and so from a safety perspective is more conservative as the number of observed adverse events is compared with a smaller denominator, i.e. the total number of subjects randomised who received at least one dose of study drug

The data used in the base case analysis for each outcome are presented in Table 110 (in Appendix 14, section 10.14) – the dataset used for each analysis is clearly shown.

Data assumptions

For several outcomes, assumptions were made in order to calculate the relevant event-rate data. These are detailed below:

- Any bleed: This outcome was not reported in the ROCKET-AF publication (63). However data for minimal bleed were reported in an FDA report. The event rates for minimal bleed were added to those for the primary safety outcome (major or clinically relevant non-major bleeding). One caveat with this approach is that double-counting cannot be excluded since some patients will have had a minimal bleed in addition to the primary safety outcome
- Disabling stroke: To obtain data for the RE-LY, AVERROES and ARISTOTLE studies, the incidence of ‘fatal stroke’ was subtracted from the incidence of ‘fatal or disabling stroke’.
- Non-disabling stroke: To obtain data for both the AVERROES and ARISTOTLE studies, the incidence of ‘disabling or fatal stroke’ was subtracted from the incidence of ‘total stroke’. Since these trials investigate first stroke events, the likelihood of double counting is very small
- Other major bleed: This was calculated by subtracting the incidence of ICH from the incidence of major bleed.

Sensitivity analyses

For completeness and transparency, the following sensitivity analyses were considered for each outcome (where data were available):

1) Substitution of the RE-LY 2009 efficacy data (from the primary publication) with the updated RE-LY 2010 efficacy data (NMA 1 and NMA 2)
2) Substitution of the ROCKET efficacy ITT data (from the slide set and SPC) with ROCKET efficacy OT data (from the primary publication) (NMA 1 and NMA 2)

The data used in the sensitivity analyses are presented in Table 111 (in Appendix 14, section 10.14).

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

Fixed and random effects models were fitted to the data for NMA 1 and NMA 2. The "goodness of fit" of each model was tested by calculating the residual deviance and the Deviance Information Criterion (DIC) which is a Bayesian method for model comparison calculated by WinBUGS (76). If the average residual deviance[a] is close to one then the model is considered to fit the data well. In the current analysis, the DIC values were similar for both the fixed- and random-effects models for each outcome and so there was little difference in the model fit to the data.

Random effect models assume that the true treatment effect varies between studies due to heterogeneity. However, section 9.6.5.1 of the Cochrane Systematic Review Handbook (77) recommends that calculations investigating heterogeneity should be based on at least ten studies, while section 9.5.4 notes that where there are too few studies the random effects model will produce poor estimates of the variation in between-study treatment effects. Given that the largest network (NMA2) in the submission only contains 4 RCTs, only the fixed effects model is considered to provide relevant estimates of treatment effects and uncertainty in this submission.

WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian network meta-analysis. A Poisson likelihood with a log link was used to calculate the hazard ratio for all treatments compared with other treatments (78). In the models, it is assumed that treatment effects are drawn from a (log) normal distribution and these parameters are assigned uninformative priors.

No model adjustment for sparse data/rare events was necessary in these NMAs.

Point estimates and 95% credible intervals[b] for hazard ratios (HR) using Markov Chain Monte Carlo (MCMC) methods were modelled. Vague or flat priors, such as N(0, 100)

[a]Total residual deviance divided by the number of trial arms in the analysis
[b]Credible intervals are the Bayesian equivalent of frequentist confidence intervals

were assigned for basic parameters throughout (78). To ensure convergence was reached, trace plots were assessed (79).

After running the WinBUGS models for 100,000 iterations to ensure the model had converged, the HR (for event rates) for each of the next 20,000 simulations was estimated and the point estimate of the calculated data was taken to be the median of the 20,000 simulations and the 95% credible intervals[b] for the calculated data were taken from between the 2.5th and 97.5th percentiles from the distribution of the calculated data. The WinBugs code for the fixed effects model is located in Appendix 14 in Section 10.14.

6.7.6 Please present the results of the analysis.

NMA 1 – warfarin suitable population

Results of the base case analysis for apixaban versus comparators are presented in Table 24. Results of the sensitivity analyses are presented in Table 112 and Table 113 in Appendix 14. Results for rivaroxaban and dabigatran versus comparators are presented in Table 116, Table 117, and Table 118 in Appendix 14.

When considering the base case results for the group of warfarin-eligible patients from the fixed-effects model for each outcome, the following conclusions can be made with regards to apixaban versus the other NOACs:

Efficacy outcomes

- Apixaban had a statistically significant lower incidence of MI compared with both doses of dabigatran:
    - Apixaban versus dabigatran 110mg (HR [redacted])
    - Apixaban versus dabigatran 150mg (HR [redacted])
- There were no other statistically significant differences between apixaban and the other NOAC treatments for the efficacy outcomes

Safety outcomes

- Apixaban had a statistically significant lower incidence of all bleeding outcomes compared with rivaroxaban:
    - Intracranial Haemorrhage (HR [redacted])
    - Major bleeding (HR [redacted])
    - GI bleeding (HR [redacted])
    - Other major bleeding (HR [redacted])
    - CRNM bleeding (HR [redacted])
    - Any bleeding (HR [redacted])
- Apixaban had a statistically significant lower incidence of the following bleeding outcomes compared with dabigatran 150 mg:
    - Major bleeding (HR [redacted])
    - GI bleeding (HR [redacted])

    - Other major bleeding (HR [redacted])
    - Any bleeding (HR [redacted])
- Apixaban had a statistically significant lower incidence of the following bleeding outcomes compared with dabigatran 110 mg:
    - Any bleeding (HR [redacted])
- Apixaban had a statistically significant lower incidence of study discontinuations compared with all other NOAC treatments:
    - Apixaban versus rivaroxaban (HR [redacted])
    - Apixaban versus dabigatran 110mg (HR [redacted])
    - Apixaban versus dabigatran 150mg (HR [redacted])
- There were no other statistically significant differences between apixaban and the other NOAC treatments on the safety outcomes.

Table 24: NMA 1 (warfarin suitable population) base case analysis

	Hazard ratio [95% CrI]			
	Apixaban vs dabigatran 150 mg	**Apixaban vs dabigatran 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR[†]	NR[†]	[redacted]	[redacted]
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]			
	Apixaban vs dabigatran 150 mg	**Apixaban vs dabigatran 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]

Results shown in bold are significantly different; †Data for this outcome not reported for the RE-LY trial; Abbreviations: CrI, credibility interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; MI, myocardial infarction; SE, systemic embolism

NMA 2 – warfarin unsuitable population

Base case analysis

Results of the base case analysis for apixaban versus comparators are presented in Table 25. Results of the sensitivity analyses are presented in Table 114 and Table 115 in Appendix 14. Results for rivaroxaban and dabigatran versus comparators are presented in Table 119, Table 120, and Table 121 in Appendix 14.

When considering the base case results for the group of warfarin-unsuitable patients from the fixed effects model for each outcome, the following conclusions can be made with regards to apixaban versus the other NOACs:

Efficacy outcomes

- Apixaban had a statistically significant lower incidence of MI compared with both doses of dabigatran:
  - Apixaban versus dabigatran 110mg (HR [redacted])
  - Apixaban versus dabigatran 150mg (HR [redacted])
- There were no other statistically significant differences between apixaban and the other NOAC treatments for the efficacy outcomes.

Safety outcomes

- Apixaban had a statistically significant lower incidence of all bleeding outcomes compared with rivaroxaban:
  - Intracranial Haemorrhage (HR [redacted])
  - Major bleeding (HR [redacted])
  - GI bleeding (HR [redacted])
  - Other major bleeding (HR [redacted])
  - CRNM bleeding (HR [redacted])
  - Any bleeding (HR [redacted])
- Apixaban had a statistically significant lower incidence of the following bleeding outcomes compared with dabigatran 150 mg:
  - Major bleeding (HR [redacted])
  - GI bleeding (HR [redacted])
  - Other major bleeding (HR [redacted])
  - Any bleeding (HR [redacted])

- Apixaban had a statistically significant lower incidence of the following bleeding outcomes compared with dabigatran 110 mg:
    - Any bleeding (HR [redacted])
- Apixaban had a statistically significant lower incidence of study discontinuations compared to all other NOAC treatments:
    - Apixaban versus rivaroxaban (HR [redacted])
    - Apixaban versus dabigatran 110mg (HR [redacted])
    - Apixaban versus dabigatran 150mg (HR [redacted])
- There were no other statistically significant differences between apixaban and the other NOAC treatments for the safety outcomes.

Table 25: NMA 2 (warfarin suitable and unsuitable population) base case analysis

	Hazard ratio [95% CrI]				
	Apixaban vs dabigatran 150 mg	**Apixaban vs dabigatran 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**	**Apixaban vs aspirin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR[†]	NR[†]	[redacted]	[redacted]	[redacted]
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]				
	Apixaban vs dabigatran 150 mg	**Apixaban vs dabigatran 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**	**Apixaban vs aspirin**
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results shown in bold are significantly different; †Data for this outcome not reported for the RE-LY trial; Abbreviations: CrI, credibility interval; CRNM, clinically relevant non-major; ICH, intracranial haemorrhage; GI, gastrointestinal; MI, myocardial infarction; SE, systemic embolism

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

Ideally, it is recognised that it would be useful to consider the impact of covariates (for example, number of risk factors for stroke) in the analysis. However, since there were so few studies that could be included (and for most treatments there was only one study per treatment), it was not considered appropriate to do this. Section 9.6.5.1 of the Cochrane Systematic Review Handbook (77) states that "typical advice" for producing "useful findings" from calculations investigating heterogeneity would be based on at least ten studies. In addition, many authors have commented on the difficulties of covariate analysis with few studies. For example, Higgins 2004 (80) report that fixed effect analysis with covariate can "produce seriously misleading results in the presence of heterogeneity" and that "standard meta-regression methods suffer from substantially inflated false-positive rates ... when there are few studies".

Although exploration of heterogeneity using covariate analysis was not appropriate, NMAs were carried out to explore consistency of treatment effects across stroke risk severity ($CHADS_2$ score) and centre-level time in therapeutic range (cTTR) patient sub-groups in accordance with the NICE scope. Sub-group analyses were performed for both the primary efficacy (stroke/SE) and safety (major bleed) outcomes. Only NMAs for these two outcomes by cTTR and $CHADS_2$ were possible for dabigatran and rivaroxaban, as insufficient data were available for other outcomes of interest.

$CHADS_2$ sub-groups were as follows:

1) $CHADS_2$ score ≤ 1 (excludes ROCKET as all enrolled patients had $CHADS_2$ score ≥ 2)
2) $CHADS_2$ score = 2
3) $CHADS_2$ score ≥ 3.

Centre TTR (cTTR) sub-groups are presented in Table 26 below. Since the average TTR differed across trials, the TTR quartiles defined for each trial were different (see appendix 10.14.6 for more details):

Table 26: Centre-TTR quartile sub-groups across the three trials in NMA1

cTTR quartile	ARISTOTLE	RE-LY	ROCKET
Lowest	<58.0%	<57.1%;	<50.6%;
2nd lowest	58.0-65.7%	57.1-65.5%	50.7-58.5%
2nd highest	65.7-72.2%	65.5-72.6%	58.6-65.7%

Highest	>72.2%	>72.6%	>65.7%

Abbreviations: cTTR, centre-level time in therapeutic range; NMA, network meta analysis

$CHADS_2$ sub-group analyses were conducted for both the warfarin suitable and unsuitable patient populations (including the AVERROES study). For cTTR analyses, only data from the warfarin suitable population was available.

The full set of results is presented in Appendix 10.14.6.

Stroke or systemic embolism

In summary, there were no statistically significant differences between apixaban and the other NOACs across $CHADS_2$ (NMA1, NMA2) or TTR (NMA1) subgroups for the primary efficacy outcome (stroke or SE). This is consistent with the base case analysis.

Major bleeding

Across the $CHADS_2$ subgroups NMA 1 and NMA 2 found that:

- Apixaban had a significantly lower risk of major bleeding compared with rivaroxaban across all subgroups
- Apixaban had a consistently lower risk of major bleeding compared with dabigatran 150mg which was statistically significant for the $CHADS_2 \geq 3$ subgroup; there were no statistically significant differences between apixaban and dabigatran 110mg across all subgroups

Across the TTR subgroups NMA 1 found that:

- Apixaban had a consistently lower risk of major bleeding compared with rivaroxaban, which was significant for the 2nd lowest TTR quartile and the highest TTR quartile
- Apixaban had a consistently lower risk of major bleeding compared with dabigatran 150mg, which was statistically significant for the highest TTR quartile; there were no statistically significant differences between apixaban and dabigatran 110mg across all subgroups

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

The following important differences were identified between studies:

- The enrolled population in the ROCKET-AF trial (rivaroxaban vs warfarin) was clinically more severe (≥ 2 prior risk factors for stroke) compared with patients in the ARISTOTLE (apixaban vs warfarin) and RE-LY (dabigatran vs warfarin) trials (both requiring 1 prior risk factor for stoke).
- In the ROCKET-AF study there was an imbalance between treatment arms for previous MI at baseline, with significantly fewer patients in the rivaroxaban group than warfarin group experiencing a previous MI.
- The comparison between dabigatran and warfarin in RE-LY employed an open-label study design, compared with the ROCKET-AF and ARISTOTLE RCTs which used a double-blind, double-dummy study design. This may potentially introduce performance bias.

- As previously discussed different analysis populations were assessed across studies for efficacy and safety outcomes. For example, all safety analyses for RE-LY were conducted using the ITT population, and only the OT population analyses for disabling stroke, non-disabling stroke and fatal stroke were identified from the publicly available ROCKET-AF data sources (i.e. ITT analyses for these outcomes could not be found).

As there was only a single study for each treatment comparison, exclusion of a particular study would mean exclusion of that treatment from the analysis. Consequently no studies were excluded from the analyses and the results should be interpreted in light of these potential sources of heterogeneity.

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

In the ARISTOTLE trial apixaban was superior to warfarin for the prevention of death due to any cause (HR 0.89; 95% CI: 0.80–0.99; p=0.047). However in NMA 1 and NMA 2, the result for this outcome just failed to reach statistical significance (HR [redacted]) and (HR [redacted]), respectively. The difference is purely due to rounding differences between the calculations, rather than the contribution of the other studies to the NMAs. This is because the HR reflects the relative treatment effect. There is only one trial and one path for apixaban versus warfarin in the networks, and therefore only data from ARISTOTLE contributes to the calculation of the relative efficacy of apixaban versus warfarin in the NMAs.

There were no other inconsistencies between hazard ratios reported in ARISTOTLE and AVERROES and those calculated in the NMAs for the other outcomes reported in this section. In summary the apixaban head to head trial data are highly consistent with the results observed in both the NMAs across all outcomes.

6.8 Non-RCT evidence

A systematic literature review was conducted to identify relevant non-RCTs on apixaban from the published literature. The literature search is described in Sections 6.1 and 6.2 and Appendix 6: Search strategy and flow diagram for Section 6.2 and 6.8. No RCTs were identified, therefore non-RCT evidence is not considered.

6.9 Adverse events

The identification of clinical evidence is described in Sections 5.1 and 5.2. All trials relevant to this submission are listed in Table 7 in Section 6.2.4.

6.9.1 ARISTOTLE

Summary

- Apixaban was superior to warfarin for adjudicated ISTH major bleeding (HR 0.69; 95% CI: 0.60–0.80; p<0.001)
- Apixaban resulted in fewer intracranial haemorrhages and fewer fatal haemorrhages than warfarin, with no increase in major GI bleeding
- The reduction in risk of major bleeding with apixaban was maintained even in the subgroups at high-risk for bleeding (e.g. age ≥ 75 years, subjects with moderate to severe renal impairment)

- When applying more rigorous bleeding criteria (such as GUSTO or TIMI major) there was an even greater reduction in the rate of serious bleeding with apixaban versus warfarin, suggesting that overall the bleeds seen with apixaban were less severe
- The rate of any bleeding was significantly lower with apixaban than warfarin, with an absolute reduction of 7.7% (HR 0.71; 95% CI: 0.68–0.75; p<0.001)
- For events other than bleeding, the safety profile of apixaban was similar to that of warfarin based on the incidence of AEs, SAEs, and discontinuation due to AEs
- The safety of apixaban was maintained:
  - Across patients at different levels of stroke risk
  - Regardless of levels of warfarin control (TTR)
  - In the patients who required dose reduction

Adverse events are reported for the treated population. The treated population dataset is usually used for safety analyses as it excludes randomised subjects never exposed to study drug, and is therefore the more conservative analysis.

Bleeding outcomes

Apixaban was superior to warfarin for the primary safety endpoint of adjudicated ISTH major bleeding (p <0.0001). Major bleeding occurred in 327 patients in the apixaban group (2.13% per year), as compared with 462 patients in the warfarin group (3.09% per year) (HR, 0.69; 95% CI: 0.60–0.80; p<0.001) (Table 27 and Figure 11). The rate of intracranial haemorrhage was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (HR, 0.42; 95% CI, 0.30–0.58; p<0.001).

Event rates were significantly lower for the apixaban group relative to the warfarin group for ISTH major or CRNM bleeding, all bleeding, and for all bleeding endpoints using Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) and Thrombolysis in Myocardial Infarction (TIMI) criteria (Table 27). The rate of any bleeding

was 25.8% per year in the warfarin group and 18.1% per year in the apixaban group, an absolute reduction of 7.7 percentage points (p<0.001).

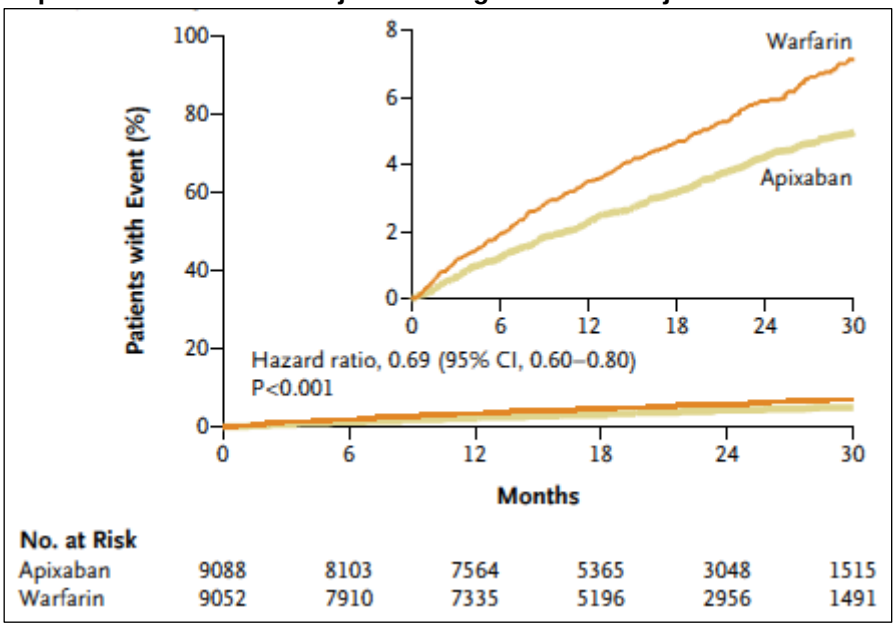
Table 27: Bleeding outcomes and net clinical outcomes – treated patients

	Apixaban (N=9,088)		Warfarin (N=9,052)		Hazard ratio (95% CI)	P Value
	Pts with event no.	Event rate %/yr	Pts with event no.	Event rate %/yr		
Primary safety outcome: ISTH major bleeding	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or CRNM bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, SE, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, SE, major bleeding or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

Source: Granger et al, 2011 (2)

Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; GUSTO, Global use of strategies to open occluded coronary arteries; HR, hazard ratio; ISTH, International society on thrombosis and haemostatsis; no., number; SE, systemic embolism; TIMI, Thrombolysis In Myocardial Infarction; yr, year

Figure 11: Kaplan-Meier curve for major bleeding – treated subjects

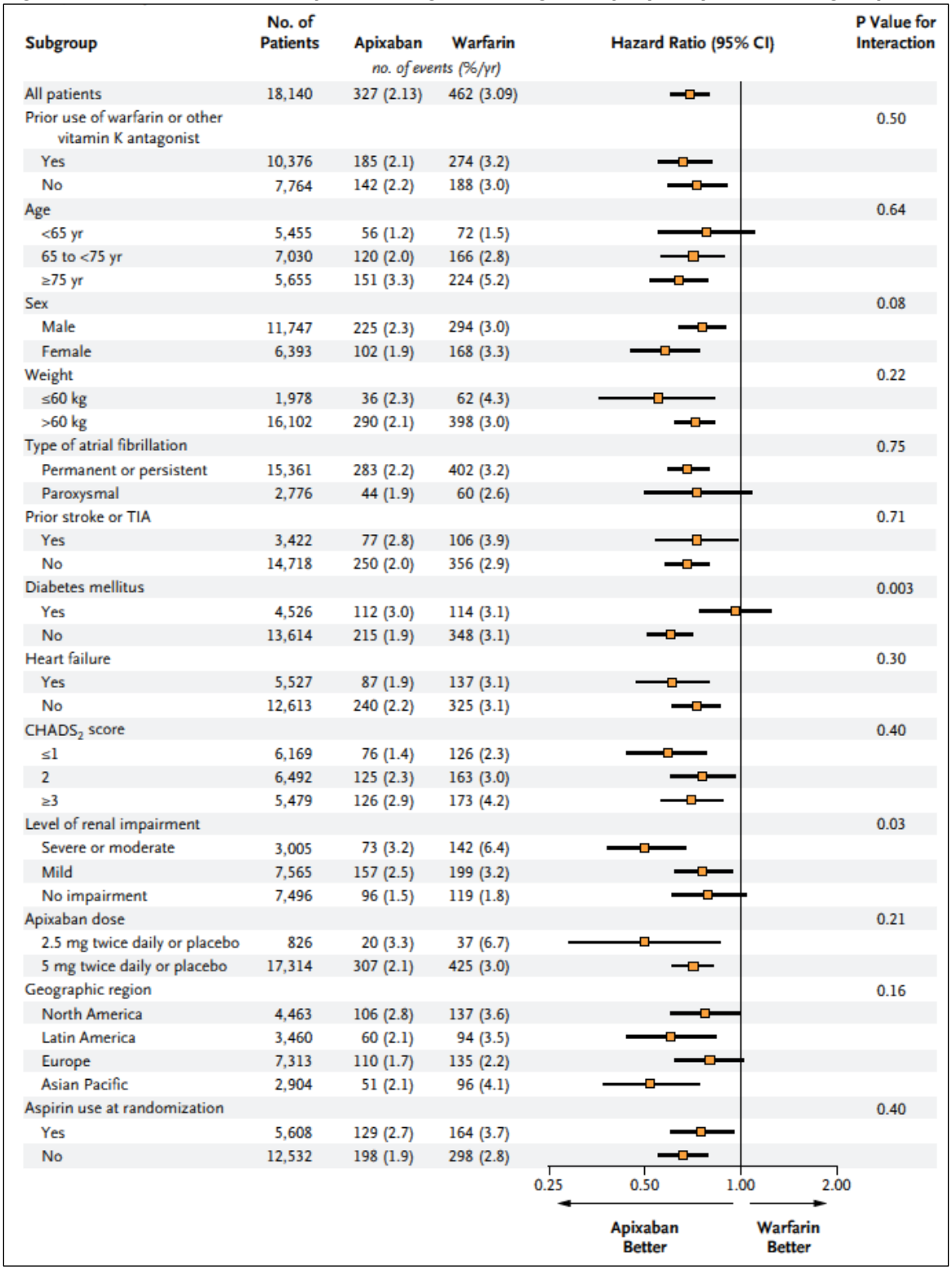


Subgroup analyses for bleeding endpoints

Subgroup analyses for bleeding endpoints occurring during the treatment period were performed for the subgroups of clinical interest used in the subgroup analysis for the primary efficacy endpoint. Overall, the results within each subgroup were consistent with the results for the study for ISTH major, composite of ISTH major or CRNM and all bleeding identified by the investigator (Figure 12). Apixaban showed a robust effect in reducing the risk of bleeding compared with warfarin in subjects at high risk, including the elderly (age ≥ 75 years), subjects with $CHADS_2$ ≥ 3, subjects with severe or moderate renal impairment, and subjects with severe renal impairment. Although the study was not powered to demonstrate superiority within subgroups, the observed HRs and upper bounds of the associated 95% CIs for all these subgroups were <1.

Statistical tests for interaction were not significant for the majority of predefined subgroups. The only baseline characteristics for which the interaction was significant were diabetes status and renal function, with a greater reduction in bleeding among patients who did not have diabetes (p=0.003 for interaction) and among patients with moderate or severe renal impairment (p=0.003 for interaction).

Figure 12: Relative risks of major bleeding according to major pre-specified subgroups



Pre-specified cTTR sub-group analysis

The reduction of major bleeding with apixaban was consistent across the TTR subgroups (Table 28).

Table 28: Relative risks of major bleeding with apixaban compared with warfarin, according to cTTR subgroup

	Apixaban		Warfarin		
cTTR (%)	**Events**	**Rate/100 person years**	**Events**	**Rate/100 person years**	**HR (95% CI)**
< 58.0	64	1.75	115	3.34	0.53 (0.39; 0.72)
58.0–65.7	61	1.60	102	2.68	0.60 (0.43; 0.82)
65.7–72.2	103	2.68	109	2.89	0.93 (0.71; 1.21)
>72.2	98	2.49	136	3.46	0.72(0.55; 0.93)

Source: Wallentin, 2011 (69)
Abbreviations: CI, confidence interval; cTTR, Centre time in therapeutic range; HR, hazard ratio

These results suggest that the benefits of apixaban over warfarin in preventing major bleeding are consistent regardless of the centre's quality of INR control.

Other safety outcomes

The overall safety profile of apixaban was similar to that of warfarin based on the incidence of deaths (based on SAEs with outcome of death), AEs, SAEs, and AEs leading to discontinuation (Table 29). The event rates for bleeding-related AEs were substantially lower for the apixaban group than the warfarin group (25.2% and 32.7%, respectively).

The frequency of SAEs was similar in both treatment groups (35.0% subjects in the apixaban group and 36.5% subjects in the warfarin group). No SAE occurred in >5% of subjects in either group. The SAEs reported in >1.0% of subjects in any treatment group were in the system organ classes of Cardiac Disorders, Infections and Infestations, and Nervous System Disorders. These occurred with similar frequency in the two treatment groups.

The incidence of AEs leading to discontinuation of double-blind study drug was lower in the apixaban group (7.6%) than the warfarin group (8.4%). All of the AEs leading to discontinuation were reported in ≤ 0.5% subjects in both treatment groups.

Table 29: Summary of adverse events – treated subjects

Adverse events **Number (%) subjects**	**Apixaban** **(N=9,088)**	**Warfarin** **(N=9,052)**
AE	7406 (81.5)	7521 (83.1)
SAE	3182 (35.0)	3302 (36.5)
Bleeding AE	2288 (25.2)	2961 (32.7)
Discontinuation due to AEs	688 (7.6)	758 (8.4)

AE, includes all serious or non-serious adverse events with onset from first dose through 2 days (for non-serious AEs) or 30 days (for serious AEs) after the last dose of blinded study drug; SAE, includes all serious adverse events with onset from first dose through 30 days after the last dose of blinded study drug; Bleeding AE, includes all serious or non-serious bleeding-related adverse events with onset from first dose through 2 days after the last dose of blinded study drug; Discontinuations due to AE, includes all serious or non-serious adverse events with onset from first dose of blinded study drug and with action taken regarding study drug (drug discontinued)

The rates of abnormalities on liver-function testing and liver-related serious adverse events were similar in the two groups.

The frequency of subjects with liver function test (LFT) elevations (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin) during the treatment period was low, and similar for the apixaban and warfarin treatment groups (Table 30). Furthermore, the number of subjects with concurrent elevations of ALT >3x ULN and total bilirubin >2x ULN was low and similar in both groups. The frequency of subjects with LFT elevations, including concurrent elevations of ALT >3x ULN, total bilirubin >2x ULN, and ALP <2x ULN on the same date was balanced between the 2 groups.

Table 30: Summary of hepatic safety – treated patients

Adverse events **Number (%) subjects**	**Apixaban** **(N=9,088)**	**Warfarin** **(N=9,052)**
ALT or AST >3x ULN and total bilirubin >2x ULN	30/8788 (0.2)	31/8756 (0.4)
ALT or AST >3x ULN and total bilirubin >2x ULN and alkaline phosphatase <2x ULN	17/8786 (0.2)	19/8755 (0.2)
ALT elevation		
3x ULN	100/8790 (1.1)	89/8759 (1.0)
5x ULN	45/8790 (0.5)	47/8759 (0.5)
10x ULN	16/8790 (0.2)	20/8759 (0.2)
20x ULN	8/8790 (<0.1)	12/8759 (0.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

6.9.2 AVERROES

Summary

- The observed event rates for bleeding were higher for apixaban than aspirin without an increase in the number of fatal bleeds or intracranial haemorrhage
- There was no statistically significant difference in the incidence of major, intracranial or GI bleeding between apixaban and aspirin, however apixaban had a significantly higher rate of the composite outcomes of major or CRNM bleeding and all bleeding
- The net-clinical benefit profile of apixaban (composite rate of stroke, SE, myocardial infarction, vascular death, and major bleeding) was favourable to that of aspirin (HR 0.64; 95% CI: 0.51–0.80, p<0.001)

Adverse events are reported for the treated population. The treated population dataset is usually used for safety analyses as it excludes randomised subjects never exposed to study drug, and is therefore the more conservative analysis. All data are taken from the clinical study report (68), as the primary study publication reports safety for the ITT population. For completeness, the safety data as reported in the primary study publication (3) are presented in Appendix 15.

Bleeding outcomes

The observed event rate for major bleeding was 1.4% per year in the apixaban group and 0.9% per year in the aspirin group (see Table 31 and Figure 13). This increased risk on apixaban (HR = 1.54) did not reach statistical significance (p=0.07) and fatal bleeds and intracranial haemorrhages occurred with similar frequency in both treatment groups (5 fatal bleeds and 11 intracranial haemorrhages in each treatment group). The event rates for the composite of major or CRNM bleeding, and for all bleeding were higher for apixaban than for aspirin (see Table 31).

Table 31: Summary of bleeding outcomes – treated subjects

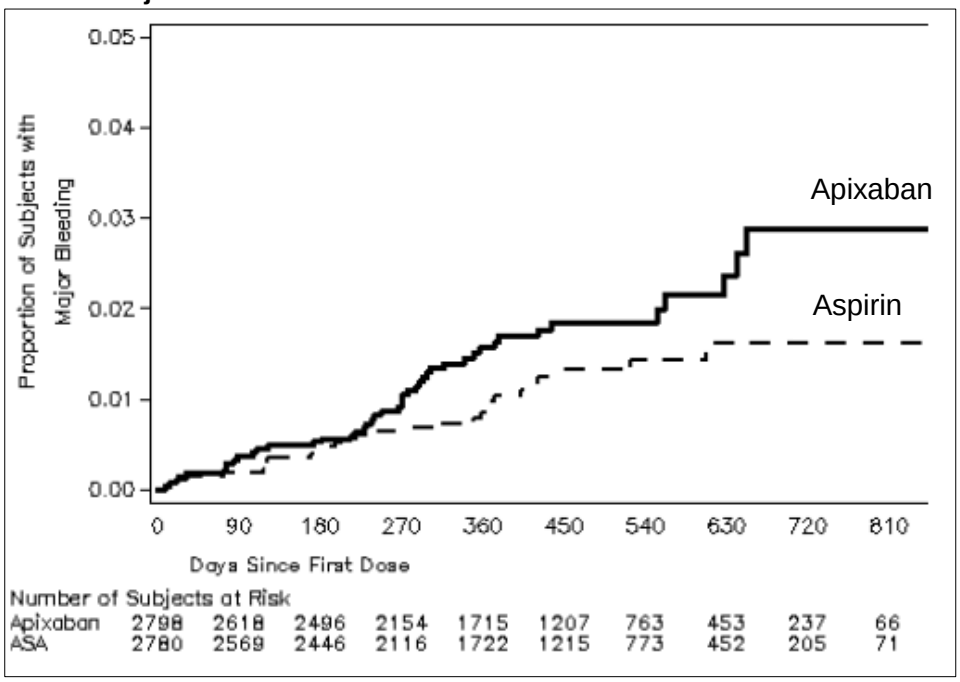
	Apixaban (N=2,798)		Aspirin (N=2,780)		Hazard ratio (95% CI)	P Value
	Pts with event	Event rate[†]	Pts with event	Event rate		
	no.	%/yr	no.	%/yr		
Major bleeding	45	1.41	29	0.92	1.54 (0.96–2.45)	0.07
Fatal Intracranial	5		5		–	–
Bleeding into a critical site	22		12		–	–
Intracranial	11		11		–	–
Intraarticular	2		1		–	–
Intraocular	6		0		–	–
Pericardial	1		0		–	–
Intramuscular	1		0		–	–
Retroperitoneal	1		0		–	–
Major or CRNM bleeding	140	4.46	101	3.24	1.38 (1.07–1.78)	0.01

	Apixaban (N=2,798)		Aspirin (N=2,780)		Hazard ratio (95% CI)	P Value
	Pts with event	Event rate[†]	Pts with event	Event rate		
	no.	%/yr	no.	%/yr		
CRNM bleeding	98		74			
Minor bleeding	200		153			
All bleeding	325	10.85	250	8.82	130 (1.10–1.53)	0.002

Source: Clinical study report (68)

Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; Pts, patients; no., number; yr, year

Figure 13: Cumulative hazard rates for major bleeding, according to treatment group – treated subjects



Abbreviations: ASA, aspirin

Net-clinical benefit

The net-clinical benefit endpoint includes both efficacy and safety events.

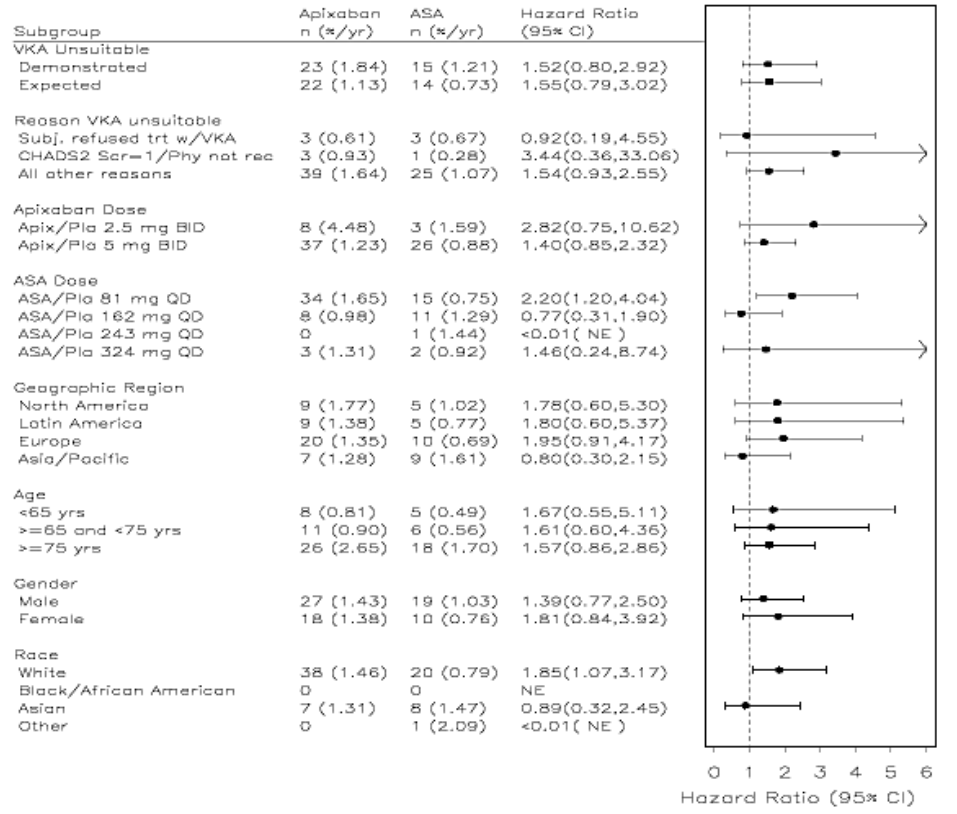
The net-clinical benefit profile of apixaban (composite rate of stroke, SE, myocardial infarction, vascular death, and major bleeding) was favourable to that of aspirin; 4.0% per year versus 6.3% per year; HR 0.64; 95% CI: 0.51–0.80, p<0.001.

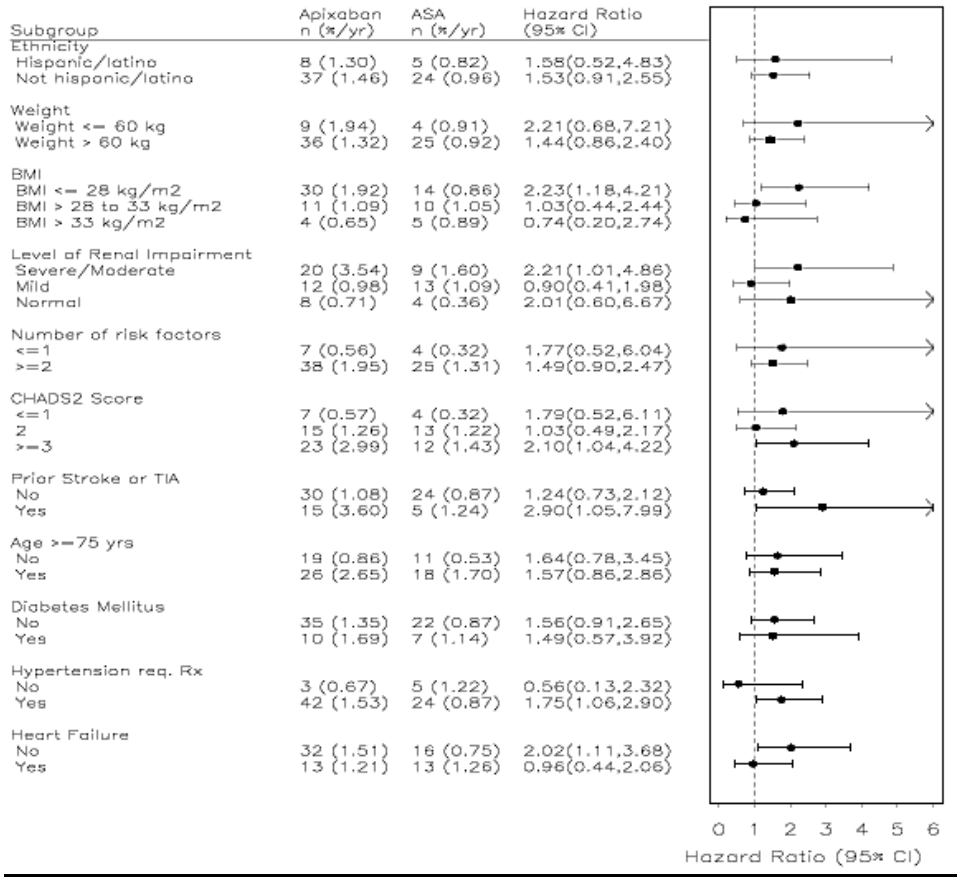
Subgroup analyses for bleeding endpoints

Subgroup analyses for bleeding endpoints (major bleeding, composite of major or CRNM bleeding, all bleeding) occurring during the Double-blind Treatment Period were performed for the subgroups of clinical interest used in the subgroup analysis for the primary efficacy endpoint.

Overall, the results within subgroups were consistent with the results for the overall population. There were no significant interactions between the treatment effects and various characteristics of the patients (see Figure 14).

Figure 14: Subgroup analyses for major bleeding – treated subjects





Abbreviations: ASA, aspirin; BID, twice daily; BMI, body mass index; Pla, placebo; QD, once daily; TIA, transient ischaemic attack; VKA, vitamin K antagonist. Horizontal bars represent 95% CIs for HRs. Source: Clinical study report (68)

Other safety outcomes

The overall safety profile of apixaban was similar or favourable to that of aspirin based on the incidence of SAEs and discontinuation due to AEs (see Table 32).

The frequency of subjects with AEs during the double-blind treatment period was similar for the apixaban and aspirin treatment groups (see Table 27). The most common AEs (in more than 5% of subjects in either treatment group) were dizziness and dyspnea. Most AEs were mild to moderate in severity in both treatment groups.

Table 32: Summary of adverse events – treated subjects

Adverse events Number (%) subjects	Apixaban (N=2,798)	Aspirin (N=2,780)
AE	1833 (65.5)	1925 (69.2)
SAE	657 (23.5)	804 (28.9)
Bleeding AE	281 (10.0)	259 (9.3)
Discontinuation due to AEs	266 (9.5)	362 (13.0)

Abbreviations: AE, adverse event; SAE, serious adverse event

The incidence of bleeding-related AEs was similar in both treatment groups. Bleeding-related AEs were reported in ≤ 1% subjects in either treatment group except for epistaxis (1.9% for both groups) and contusion (1.3% for apixaban; 1.7% for aspirin).

The incidence of AEs leading to discontinuation of double-blind study drug was lower in the apixaban group (9.5%) than the aspirin group (13.0%). The majority of AEs leading to discontinuation were reported in ≤ 0.5% subjects in both treatment groups except for cerebrovascular accident and ischaemic stroke in the aspirin group.

The incidence of SAEs was lower in the apixaban group (23.5%) than the aspirin group (28.9%). The most common SAEs were in the system organ classes of Cardiac Disorders, Infections and Infestations, and Nervous System Disorders (see Table 33). These occurred with a similar frequency in the 2 treatment groups except for the Nervous System Disorders which were lower in the apixaban group (3.0%) than the aspirin group (6.5%).

Table 33: Summary of serious adverse events (>2% in either treatment arm) – treated subjects

Number (%) subjects	Apixaban (N=2,798)	Aspirin (N=2,780)
Cardiac disorders	251 (9.0)	278 (10.0)
Atrial fibrillation	72 (2.6)	70 (2.5)
Cardiac failure	60 (2.1)	76 (2.7)
Gastrointestinal disorders	61 (2.2)	72 (2.6)
General disorders and administration site conditions	65 (2.3)	71 (2.6)
Infections and infestations	103 (3.7)	130 (4.7)
Pneumonia	37 (1.3)	55 (2.0)
Nervous system disorders	83 (3.0)	182 (6.5)

Number (%) subjects	Apixaban (N=2,798)	Aspirin (N=2,780)
Respiratory, thoracic and mediastinal disorders	64 (2.3)	65 (2.3)
Vascular disorders	28 (1.0)	60 (2.2)

The frequency of subjects with LFT elevations was low and similar for the apixaban and aspirin treatment groups (see Table 34). Furthermore, the number of subjects with concurrent elevations of ALT >3xULN and total bilirubin >2xULN was low and similar in both treatment groups.

Table 34: Summary of liver function test abnormalities – treated subjects

Number (%) subjects	Apixaban (n=2779)	Aspirin (n=2753)
ALT elevation		
>3x ULN	23	31
>10xULN	2	4
AST elevation		
>3x ULN	28	33
>10x ULN	3	3
Both ALT and AST elevation on same date		
>3x ULN	15	19
>10x ULN	1	2
AST or ALT >3x ULN and total bilirubin >2x ULN	5	9

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

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

Bleeding

Apixaban significantly reduced the risk of major bleeding by 31% compared with warfarin. Event rates were also significantly lower for apixaban relative to warfarin for ISTH major or CRNM bleeding, all bleeding, and for all bleeding endpoints using GUSTO and TIMI criteria.

There was no statistically significant difference in risk of major bleeding or intracranial haemorrhage between apixaban and aspirin.

Other AEs

The overall safety profile of apixaban was similar to that of warfarin based on the incidence of deaths, AEs, SAEs, and AEs leading to discontinuation. When compared with aspirin, the event rates for AEs, SAEs, and discontinuations due to AEs were lower with apixaban.

In conclusion, apixaban significantly reduces the risk of stroke and SE without a concomitant increased safety risk. When compared with warfarin the efficacy benefits of apixaban are accompanied by a significantly reduced bleeding risk and lower mortality.

6.10 Interpretation of clinical evidence

Summary

- Apixaban provides an alternative treatment option to both warfarin and aspirin for the prevention of stroke and SE in patients with AF
- Apixaban reduced the risk of stroke or SE by 21%, major bleeding by 31%, and death by 11%, as compared with warfarin
- In patients unsuitable for warfarin therapy, apixaban reduced the risk of stroke and SE by 55% without a significant increase in the risk of major bleeding or intracranial haemorrhage
- Both NMAs consistently show that apixaban has significantly better safety and similar efficacy compared with dabigatran 150 mg and rivaroxaban on most outcomes
- Apixaban was associated with a statistically significant reduction in myocardial infarction compared with dabigatran 150 mg and dabigatran 110 mg, but there were no statistically significant differences between the three NOACs for the other efficacy outcomes
- Apixaban had a statistically significant lower incidence of all bleeding outcomes compared with rivaroxaban, a statistically significant lower incidence of major bleeding, other major bleeding, GI bleeding, and any bleeding compared with dabigatran 150 mg, and a statistically significant lower incidence of any bleeding compared with dabigatran 110 mg
- There were no statistically significant differences between the three NOACS for the other bleeding outcomes
- Apixaban had a statistically significant lower incidence of study drug discontinuation than both dabigatran doses, and rivaroxaban
- In summary, the NMA data demonstrate that apixaban provides a combination of similar efficacy and significant reductions in the incidence of all bleeding (compared with both doses of dabigatran and rivaroxaban), major bleeding, other major bleeding and GI bleeding (compared with dabigatran 150 mg and rivaroxaban), so meeting the need for a new oral anticoagulant that is more efficacious than warfarin, but with a lower bleeding risk than the existing new oral anticoagulant treatments available for AF.

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

Efficacy of apixaban

The ARISTOTLE study demonstrated that in patients with atrial fibrillation, apixaban was superior to warfarin both for the prevention of stroke or SE (HR 0.79; 95% CI: 0.66–0.95; p=0.01), and for the prevention of death due to any cause (HR 0.89; 95% CI: 0.80–0.99;

p=0.047). Furthermore, the rate of clinically important fatal or disabling stroke was significantly lower with apixaban than warfarin (HR 0.71; 95% CI: 0.54–0.94). The reduction of stroke and SE with apixaban versus warfarin was maintained; across patients at different levels of stroke risk, regardless of levels of warfarin control, and in patients who required dose reduction.

In the AVERROES study apixaban, compared with aspirin, more than halved the rate of stroke and SE in patients with atrial fibrillation who were unsuitable for VKA therapy (HR 0.45; 95% CI: 0.32–0.62, p<0.001). The rate of clinically important fatal or disabling stroke was also significantly lower with apixaban than with aspirin (HR 0.43; 95% CI: 0.28–0.65, p<0.001). Apixaban showed a clinically important reduction in major vascular events (composite of stroke, SE, MI, or vascular death) relative to aspirin (HR 0.66; 95% CI: 0.53–0.83, p=0.003), and in addition, apixaban reduced the incidence of cardiovascular hospitalisations relative to aspirin (12.6% per year versus 15.9% per year, p<0.001).

In both trials there was no increase in the rate of MI with apixaban. Furthermore, the rate of discontinuation of study drug was significantly lower in the apixaban group (25.3%) than in the warfarin group (27.5%; p=0.001), and 12% lower in the apixaban group than in the aspirin group (HR 0.88, 95%CI: 0.78-0.99; p=0.03), indicating that patients are more likely to remain on apixaban than warfarin or aspirin treatment.

Results of the network meta-analyses consistently show that apixaban, was associated with a statistically significant reduction in myocardial infarction compared with dabigatran 150 mg and dabigatran 110 mg in patients both suitable and unsuitable for warfarin treatment, with no statistically significant differences between the three NOACs for the other efficacy outcomes. Results from the $CHADS_2$ and cTTR sub-group analyses demonstrated the consistency of apixaban treatment effects compared with dabigatran and rivaroxaban on the primary endpoint of stroke plus systemic embolism.

Safety of apixaban

In the ARISTOTLE study apixaban was superior to warfarin for adjudicated ISTH major bleeding (HR 0.69; 95% CI: 0.60–0.80; p<0.001), and resulted in fewer intracranial haemorrhages and fewer fatal haemorrhages than warfarin with no increase in major GI bleeding. Importantly, the reduction in major bleeding with apixaban was maintained in the subgroups at high-risk for bleeding (e.g. age $\geq$ 75 years, and subjects with moderate to severe renal impairment). When applying more severe bleeding criteria, such as GUSTO or TIMI major, there was an even greater reduction in the rate of serious bleeding with apixaban versus warfarin, indicating that overall the bleeds with apixaban were less severe than those with warfarin. Regardless of severity, the bleeding rate in the apixaban treated group was significantly lower than in the warfarin group, with an absolute reduction of 7.7% for any bleeding (p<0.001). For events other than bleeding the safety profile of apixaban was similar to that of warfarin – based on the incidence of AEs, SAEs, and discontinuation due to AEs.

It was expected that apixaban would outperform aspirin in terms of efficacy and therefore it was important to determine the clinical benefit versus the risk of bleeding (risk/benefit ratio) for apixaban versus aspirin. The AVERROES study demonstrated that there was

no statistically significant difference in the risk of major or intracranial bleeding between apixaban and aspirin. The net-clinical benefit profile of apixaban (composite rate of stroke, SE, MI, vascular death, and major bleeding) was favourable to that of aspirin. Overall, apixaban had an acceptable side-effect profile when compared with aspirin, and fewer patients in the apixaban group than in the aspirin group had a serious adverse event and discontinued due to an adverse event.

Results of the network meta-analyses consistently showed that in patients suitable and unsuitable for warfarin treatment apixaban has improved safety compared with both dabigatran and rivaroxaban. Apixaban had a statistically significant lower incidence of all bleeding outcomes (ICH, major bleeding, other major bleeding, GI bleeding, CRNM bleeding, and any bleeding) compared with rivaroxaban. It also had a statistically significant lower incidence of major bleeding, other major bleeding, GI bleeding, and any bleeding compared with dabigatran 150 mg, and a statistically significant lower incidence of any bleeding compared with dabigatran 110 mg. There were no statistically significant differences between the NOACS on any of the other bleeding outcomes. Results from the $CHADS_2$ and cTTR sub-group analyses demonstrated the consistency of apixaban's treatment effects compared with dabigatran and rivaroxaban on the primary safety endpoint of major bleeding. Finally, apixaban had a statistically significant lower incidence of study drug discontinuations than both doses of dabigatran, and rivaroxaban.

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

The apixaban clinical trial programme consisted of two robust, prospective, randomised, double-blind, double-dummy trials that were conducted in a large number of countries worldwide including a significant proportion of European and UK centres. Randomisation was carried out by a centrally managed interactive voice response system, and all efficacy and safety endpoints were adjudicated by an independent adjudication committee that was blinded to the treatment allocation.

The clinical trial programme included the largest warfarin-controlled study (ARISTOTLE) in patients with AF and the only aspirin-controlled NOAC study (AVERROES) reported to date in patients with AF who are unsuitable for warfarin treatment. These trials included patients with stroke risks (based on $CHADS_2$ scores) that ranged from low risk to high risk, with an even distribution. AVERROES included 40% of patients who had previously tried and discontinued warfarin. Such a population can be considered as representative as is possible (within the confines of a clinical trial) of an AF population seen within clinical practice in the UK (81).

Control of INR for warfarin subjects in ARISTOTLE was determined by TTR using central monitoring of INR measurements. Maintenance of an acceptable target INR for warfarin-treated subjects was a key component to the design of this warfarin-controlled study, because it was necessary to achieve an adequate comparison with apixaban. The mean TTR for warfarin in the ARISTOTLE study was 62%, which compares well with contemporary warfarin trials (range 55-68%, (82)), and studies observing warfarin patients in UK clinical practice, (range 52-68%, (40, 42, 43)).

In both ARISTOTLE and AVERROES apixaban was significantly superior to the comparator for stroke prevention – and the event rate was more than halved versus

aspirin in AVERROES. A pre-specified analysis of the efficacy of apixaban versus warfarin at various levels of anticoagulation control (TTR quartiles) showed a consistent benefit across all levels. This means that the benefit of apixaban over warfarin was preserved regardless of the quality of warfarin control.

In the ARISTOTLE study, apixaban showed a significant reduction compared with warfarin in all-cause mortality. The AVERROES trial was terminated early by the Data Safety Monitoring Board (as the treatment benefit in favour of apixaban for the primary outcome exceeded 4 standard deviations, and the statistics plan for AVERROES pre-specified termination of the study if this criterion was met). Data indicated that had it not been terminated early, a similar reduction in all-cause mortality would have been observed for apixaban versus aspirin.

A significant concern of anticoagulation is the risk of major bleeding, particularly intracranial bleeding which is the most feared complication of warfarin treatment. As a consequence, in clinical practice, patients deemed at risk of bleeding are often treated with aspirin instead of warfarin (26). In the ARISTOTLE study major, intracranial and any bleeding rates were all significantly lower in the apixaban arm compared with the warfarin arm and, crucially, there were no statistically significant differences in major and intracranial bleeding rates versus aspirin in AVERROES.

The efficacy/safety ratio in ARISTOTLE and AVERROES was maintained across a number of clinically relevant subgroups, including the elderly (>75 years of age) and patients with moderate to severe renal impairment.

Based on head-to-head clinical trials versus warfarin, apixaban is the only NOAC to demonstrate significant benefits for the combination of stroke reduction, major bleeding and all-cause mortality. Based on the NMAs, apixaban provides a combination of similar efficacy and significant reductions in the incidence of all bleeding (compared with both doses of dabigatran and rivaroxaban), major bleeding, other major bleeding and GI bleeding (compared with dabigatran 150 mg and rivaroxaban).

Previous research in cardiac disease patients has highlighted the morbidity and mortality consequences associated with a major bleeding event. The incidence of mortality in patients with an in-hospital major bleed was consistently higher compared with those with no bleed (1-year mortality up to 40%) (83-92), reaching statistical significance in seven studies (83-85, 89-92). Furthermore, major bleeding is also associated with a subsequent increase of major cardiac events (MACE). A higher incidence of a MACE was observed in patients with an in-hospital major bleed compared with those with no bleed (83, 88, 91-93) reaching statistical significance in four studies, with one to four years of follow-up after the major bleed event (83, 88, 91, 92). The incidence of a subsequent MI was also higher in patients experiencing a major bleed compared with those with no major bleed (83, 88, 91, 92), reaching statistical significance in two studies (83, 91). Finally, a recent retrospective study found a statistically significant increased incidence of subsequent mortality in AF patients who survived a major bleed compared to a control group of AF patients with no major bleed events (94). The existing evidence in patients with cardiovascular disease demonstrates the important morbidity and mortality consequences of a major bleed event, with a similar mortality risk found in AF patients. Since apixaban has been shown to have significantly lower major bleeding rates compared with warfarin, dabigatran 150 mg and rivaroxaban in AF patients, there

is likely to be consequent longer-term mortality and morbidity protection associated with its use.

Thus, apixaban should be considered an innovation in the management of patients with AF.

6.10.3 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.

AF increases the risk of stroke by approximately 5-fold, and more than 20% of all strokes are attributed to this arrhythmia (14). Strokes in association with AF tend to be more severe and carry a worse prognosis (4, 14), and hence constitute a considerable burden to both patients and the NHS. The risk of stroke in people with AF can be reduced with antithrombotic treatment. According to current NICE guidance anticoagulation with warfarin is recommended for people with AF at high risk of stroke, and aspirin is recommended for people with AF at low risk of stroke and for those with contraindications to warfarin (4).

Warfarin is an effective treatment when well-managed, but it is associated with a number of limitations. It has a variable response and a narrow therapeutic window which require close patient monitoring for dose adjustments, it has numerous drug/drug and food/drug interactions, and it carries a risk of bleeding (including intracranial and GI bleeds). As a result it is estimated that almost 45% of patients in the UK who could benefit from warfarin discontinue treatment or do not receive it (95), and may be prescribed aspirin instead. However, aspirin is less efficacious than warfarin and may not be any safer than oral anticoagulation (29, 54). Consequently there is a significant unmet need in the field of stroke prevention in patients with AF.

Apixaban provides an alternative treatment option to both warfarin and aspirin for the prevention of stroke and SE in patients with AF, as demonstrated by the ARISTOTLE and AVERROES studies.

ARISTOTLE and AVERROES assessed outcomes that are clinically relevant to stroke prevention in AF. The clinical goal of anticoagulation therapy is the prevention of stroke and SE, and the primary efficacy measure in both ARISTOTLE and AVERROES was the composite of stroke and SE. Anticoagulation therapy is associated with an increased bleeding risk and in both studies the primary safety measure was major bleeding.

In addition both studies assessed a number of secondary endpoints, including mortality, MI, PE or DVT and hospitalisation, which are of direct relevance to the patient population under consideration.

As AVERROES is currently the only aspirin-controlled NOAC trial, and aspirin is still being widely used in clinical practice in England, the evidence base for apixaban allows the decision problem to be addressed more credibly.

6.10.4 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?

NICE and ESC guidelines recommend anticoagulation for patients with AF and a moderate to high risk of stroke (4). ARISTOTLE and AVERROES recruited patients with AF and at least 1 additional risk factor for stroke. Risk factors for stroke included; prior stroke, transient ischaemic attack or SE; age ≥ 75 years; arterial hypertension requiring pharmacological treatment; diabetes mellitus; heart failure (NYHA class 2 or higher at time of enrolment); a left ventricular ejection fraction of 35% or less, or documented peripheral arterial disease. Thus the trials enrolled patients for whom guidelines recommend anticoagulation, and consequently the patient populations of ARISTOTLE and AVERROES are representative of patients eligible for anticoagulation treatment in England and Wales. Furthermore the patient population recruited for AVERROES is representative of those patients with atrial fibrillation at risk of stroke and who are unsuitable for VKA therapy. Approximately 40% of subjects in AVERROES had previously received but discontinued warfarin.

ARISTOTLE and AVERROES enrolled patients with various levels of stroke risk. The distribution of $CHADS_2$ scores across these patients closely mirrors that found in a recent real-world UK cohort (26, 42, 81). Table 35 below demonstrates that both the AVERROES and ARISTOTLE trials contained similar populations compared with a recent GPRD study of AF patients in UK clinical practice.

Table 35: Baseline characteristics of the apixaban trials compared with a recent GPRD study of patients in UK clinical practice

Characteristic	Gallagher 2008 (26)	Gallagher 2011 (42)	ARISTOTLE	AVERROES
Age, yrs (mean)	77	74	70 (median)	70
Male, (%)	55	52	65	59
$CHADS_2$ (%)				
0	12.57%	9.80%	0.6%	0.3%
1	30.55%	30.10%	33.4%	37.9%
2	30.67%	29.60%	35.8%	35.2%
3	14.87%	17.90%	18.0%	16.7%
4	8.14%	8.50%	8.7%	7.1%
5	2.82%	4.10% (5 & 6)	3.1%	2.4%
6	0.38%		0.4%	0.4%
Average $CHADS_2$	**1.9**		**2.1**	**2.0**

Abbreviations: GPRD, General Practice Research Database

Apixaban demonstrated the same efficacy and safety signals in both ARISTOTLE and AVERROES, thus confirming that the benefit of apixaban is reproducible and consistent across two complementary AF trial scenarios. As such the outcomes can be considered robust and reliable.

The UK licensed dose of apixaban (5 mg twice daily), as outlined in the SPC, was investigated in both ARISTOTLE and AVERROES. Based on pharmacokinetic exposure studies a dose reduction to 2.5mg twice a day was mandated in patients satisfying 2 of the following 3 criteria: >80 years of age, weight <60 kg, severe renal impairment. However, although the dose is halved, the exposure to drug is similar to that observed with the higher dose. This effectively means that only one dose of apixaban was studied in ARISTOTLE and AVERROES. Nine per cent of ARISTOTLE patients and almost 7% of AVERROES patients received the 2.5mg dose of apixaban, and the efficacy and safety profile of the 2.5mg cohort was similar to that seen in the larger cohort.

7 Cost-effectiveness

Summary

- The cost-effectiveness of apixaban was assessed using a Markov model similar to that used in NICE appraisals of dabigatran and rivaroxaban.
- The base case incremental cost-effectiveness ratio (ICER) for apixaban compared with the standard of care and most routinely used therapy, warfarin, was £12,824 per QALY. Apixaban was also cost-effective against the less commonly used anticoagulants, aspirin, rivaroxaban and dabigatran at the £20,000 per QALY threshold.
- Apixaban provided more quality adjusted life years (QALYs) than all other therapies. Compared to warfarin, apixaban produced savings for the NHS in avoided cost of stroke, intracranial haemorrhage, INR monitoring and bleeding.
- The cost effectiveness results for apixaban compared with dabigatran and rivaroxaban in the VKA unsuitable population should be interpreted with caution, as neither therapy has data in this specific patient population, and so imputed efficacy estimates from VKA suitable populations are believed to overestimate their QALYs and cost-effectiveness.
- Apixaban was cost-effective across all patient subgroups of INR control (centre time in therapeutic range) and $CHADS_2$ stroke risk categories 1 and 2.
- One-way sensitivity analyses, scenario analyses and probabilistic sensitivity analyses confirmed that the findings were robust to changes in key parameters

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic review was conducted to identify cost-effectiveness studies of interventions for the prevention of stroke and/or systemic embolism in adult patients with atrial fibrillation (AF). The following electronic databases were searched; NHS EED, OVID Medline, OVID Medline In-Process and Other Non-Indexed Citations, OVID EMBASE and Econlit. Electronic searches were supplemented by hand searching the following sources; manufacturer databases, the Cost-Effectiveness Analysis (CEA) Registry, conference proceedings and NICE HTA submissions.

Full details of the databases, conference proceedings, search strategies employed and inclusion/exclusion criteria are presented in Section 10.10.

In total, 2639 papers were identified through the electronic searches. Upon the removal of duplicate papers, 2301 titles and abstracts were reviewed. Forty-one were ordered for full paper review, of which 22 were excluded, resulting in 19 relevant papers for final inclusion (Figure 37, in Appendix 10, section 10.10). In addition, the following were identified via hand searching: one study through the manufacturer (this study was published prior to the electronic search date, but not entered into Medline), five relevant

abstracts from conference proceedings, and two on-going NICE single technology appraisals (for dabigatran and rivaroxaban).

7.1.2 Description of identified studies

Of the 20 full text papers identified, five were cost-utility analyses that evaluated currently available pharmacological interventions in an active comparator setting, and reported an ICER. These five studies were deemed relevant to this submission and are discussed further in this section.

A summary of the 20 full text papers and five conference abstracts is provided in Table 107, in Section 10.10 (Appendix 10).

The five relevant cost-utility analyses, are summarised in Table 108: Summary of relevant cost-utility studies. Three of the studies utilised a Markov model (96-98), one a semi-Markov model (99), and one was a discrete event simulation (98). They all evaluated the cost-effectiveness of dabigatran, warfarin, aspirin and/or aspirin plus clopidogrel in the prevention of stroke and SE in AF patients. Comparative cost-effectiveness of dabigatran was assessed in four studies (96, 98-100), and the cost-effectiveness of warfarin versus aspirin in one (97).

Subsequent to the systematic review a further cost-utility analysis was published, which evaluated apixaban compared with aspirin for stroke prevention in AF among patients unsuitable for warfarin (101). This study is also summarised in Table 108. The 10 year time horizon is most consistent with the NICE reference case (lifetime time horizon).

The modelling approach used in the two NICE single technology appraisals (for dabigatran and rivaroxaban) were also of relevance to this submission. A summary of the manufacturer submission and ERG critique for each appraisal is presented below.

Dabigatran etexilate

Manufacturer submission (24)

Boehringer Ingelheim presented two Markov Models: a single dose and a sequential dose model. Both models used 23 health states separated into four levels of disability: ‘independent disability’, ‘moderate disability’, ‘severe disability’ and death. The difference between the models was that in the sequential dose model patients were started on dabigatran 150 mg but at the age of 80 were reduced to dabigatran 110 mg. In the single dose model, treatment was independent of age and thus both dabigatran doses were examined separately.

Both models examined non-valvular AF patients who were at risk of SE or stroke and eligible for anticoagulation treatment. The primary comparator in the models was warfarin. Aspirin and aspirin plus clopidogrel were also considered as secondary analyses in patients unsuitable for warfarin treatment and in whom dabigatran may be appropriate. A baseline general risk of an adverse event for patients was based on warfarin treatment in the RE-LY trial, which was modified for risks of a series of AEs (ischaemic stroke, intracranial haemorrhage, haemorrhagic stroke, extracranial bleeds, SE, TIA and acute MI). In each model cycle, patients were then exposed to these relative risks and this affected how many patients were in each health state.

The base case ICER was £6,264 per QALY for dabigatran 150 mg versus warfarin, with sensitivity analysis variations ranging from £3,925 (using real-world prescribing behaviour for warfarin) to £75,601 (2 year time horizon). Probabilistic sensitivity analysis (PSA) showed that in the manufacturer's model there was a 93% chance that dabigatran 150 mg would be cost-effective at a £20,000 per QALY willingness-to-pay threshold and a 98% chance for £30,000 per QALY.

ERG critique (102)

In general, the ERG accepted the manufacturer's model. Included in the report is a table of the NICE reference checklist, and a brief summary of whether they felt the manufacturer had satisfied each criterion. The ERG noted that utility values for health states were partly elicited through EQ-5D yet some were obtained via TTO. Utility decrements for EQ-5D values were based on valuation from the US population while TTO was administered to a sample of stroke patients, rather than from a sample of the public.

Upon re-running the manufacturers economic literature searches, the ERG identified a recent publication on the cost-effectiveness of dabigatran by Freeman et al 2011 (96). There were notable differences in the ICER estimate, which the ERG attributed to a more conservative approach to certain input estimates by Freeman et al. Freeman et al estimated an acquisition cost of dabigatran of £6.30/day, compared with the manufacturers estimate of £2.52/day; for INR monitoring, Freeman et al estimated 14 visits/year compared with the manufacturers estimate of 20 visits/year; and Freeman et al evaluated a less severe AF population ($CHADS_2$ score of 1 or equivalent).

The key criticisms of the ERG were:

- The trial population modelled were not reflective of the UK AF population
- The long-term consequences of MI and SE were not incorporated
- Model cycle length could be shorter than three months and allow more than one AE per cycle
- The model allowed the evaluation of a restricted number of treatment sequences
- The cost of annual INR monitoring was over estimated in the model
- The disutility of warfarin and NOACs
- Dyspepsia should be modelled and costs accrued as long as the patient is taking dabigatran since it is a drug dependent effect

Rivaroxaban

Manufacturer submission (103)

Bayer modelled rivaroxaban using a 23 health state Markov Model with three month cycles. Each hypothetical cohort was exposed to an AE probability from major and minor stroke, SE, major and minor extracranial bleeding, intracranial bleeding, MI and death. Patients were simulated using clinical data based on the ROCKET AF RCT (63) and the manufacturer's network meta-analysis (NMA) results, supplemented by a long-term observational trial (26). AEs were considered either permanent or temporary, and health states for permanent AEs took into account the permanent reduced quality of life (QoL). Relative risks of SE and stroke were adjusted for age and $CHADS_2$.

In the base case, the population considered were stable AF patients treated with either rivaroxaban or warfarin. Further analyses considered patients poorly controlled on warfarin, vitamin k antagonist (VKA) naïve patients and treatment of AF using aspirin, placebo, dabigatran 110 mg or 150mg.

The base case ICER for rivaroxaban versus warfarin was £18,883/QALY, with sensitivity analysis showing rivaroxaban either dominating warfarin or costing below £18,883/QALY. PSA was presented as a cost-effectiveness acceptability curve (CEAC) and reported that at a willingness-to-pay threshold of £20,000 per QALY, there was a 75% chance of rivaroxaban being cost-effective, which increased to 88% for a £30,000 threshold.

ERG critique (104)

The ERG generally accepted the model methodology, noting that the model was easy and transparent.

The key criticisms of the ERG were:

- The reliability of the cost effectiveness results was limited by the uncertainty around the frequency of INR monitoring in warfarin-treated patients in the economic model (which is driven by cost of anticoagulation monitoring rather than clinical effectiveness)
- The lack of direct comparative data from a randomised controlled trial comparing rivaroxaban with dabigatran in patients suitable for anticoagulation
- The safety and clinical benefit of rivaroxaban compared with dabigatran and aspirin in warfarin unsuitable patients was not addressed
- The lack of QoL data for people taking rivaroxaban
- The assumption that treatment discontinuation rates were the same between treatments in the absence of any direct evidence to suggest otherwise had a substantial impact on the ICERs
- The data for rivaroxaban efficacy in people at moderate risk of stroke was limited.

7.1.3 Quality assessment

Of the 20 studies that were identified by the systematic review five were cost-utility analyses that evaluated currently available pharmacological interventions in an active comparator setting and reported an ICER, and therefore deemed relevant to this submission. Quality assessments have been conducted on these five relevant cost-utility studies and are provided in Appendix 11 (Section 10.11). Based on the quality assessment we consider the studies to be of good quality.

7.2 De novo analysis

7.2.1 Patients

The patient population included in the economic evaluation reflects the licensed indication; adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors, including those unsuitable for vitamin K antagonists (VKA). Within this population two subpopulations are considered to be consistent with the scope and to match the evidence base for apixaban:

- VKA suitable; patients who are suitable for warfarin
- VKA unsuitable; patients who are unsuitable for warfarin

Patient characteristics used in the model are taken from Gallagher et al, 2011 (42) and reflect a cohort of 37,907 patients with a diagnosis of AF from the UK General Practice Research Database (GPRD). GPRD data were used as they may be more representative of the UK patient population than data from clinical trials. Use of GPRD data is also consistent with sources preferred in the NICE appraisals of dabigatran (102) and rivaroxaban (104). These data were used to characterise both the VKA suitable and unsuitable populations in the model, as specific information from observational studies for these sub-groups were not available.

Characteristics of the patient cohort incorporated in the model are presented in Table 36, and compared with the patients from ARISTOTLE and AVERROES. The data from Gallagher et al (42), suggest that in comparison with the clinical trial populations; the average age of an AF patient in the UK is higher, the proportion of males is lower and, as the trials selected AF patients with at least one additional risk factor, the $CHADS_2$ distribution is slightly different, in particular there are more patients with a $CHADS_2$ score of zero.

Table 36: Patient characteristics used in base case analysis

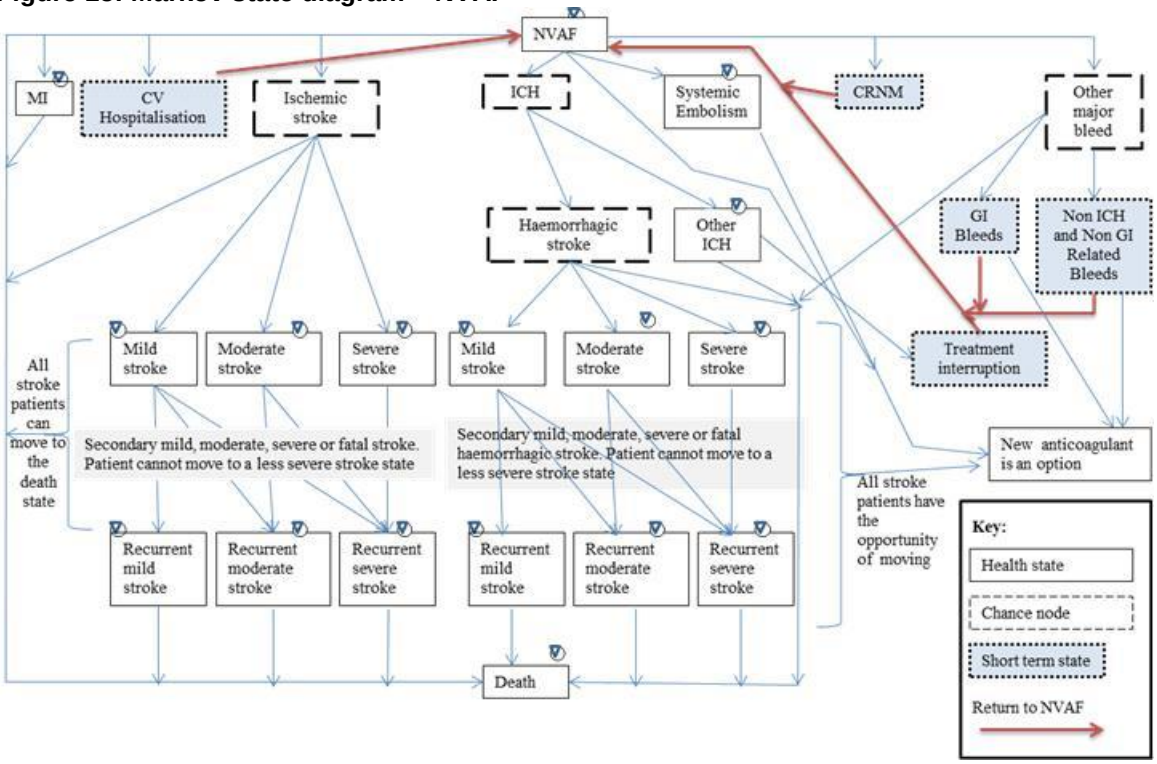
	GPRD data used in base case analysis[§]		**Patient baseline characteristics in clinical trials**	
	VKA suitable	**VKA unsuitable**	**VKA suitable[†]**	**VKA unsuitable[‡]**
Gender				
Male	52%	52%	64.7%	58.5%
Female	48%	48%	35.3%	41.5%
Mean age (years)				
Male	74	74	70	70
Female	74	74	70	70
$CHADS_2$ distribution				
$CHADS_2 = 0$	9.80%	9.80%	0.6%	0.3%
$CHADS_2 = 1$	30.10%	30.10%	33.4%	37.9%
$CHADS_2 = 2$	29.60%	29.60%	35.8%	35.2%
$CHADS_2 = 3$	17.90%	17.90%	18.0%	16.7%
$CHADS_2 = 4$	8.50%	8.50%	8.7%	7.1%
$CHADS_2 = 5$	4.10%	4.10%	3.1%	2.4%
$CHADS_2 = 6$	0%	0%	0.4%	0.4%
Average $CHADS_2$	**2.0**	**2.0**	**2.1**	**2.0**

Source of data; [§]Gallagher et al, 2011 (42); [†]ARISTOTLE clinical trial (67); [‡]AVERROES clinical trial (68)
Abbreviations: GPRD, General Practice Research Database; VKA, Vitamin K antagonist

7.2.2 Model schematic

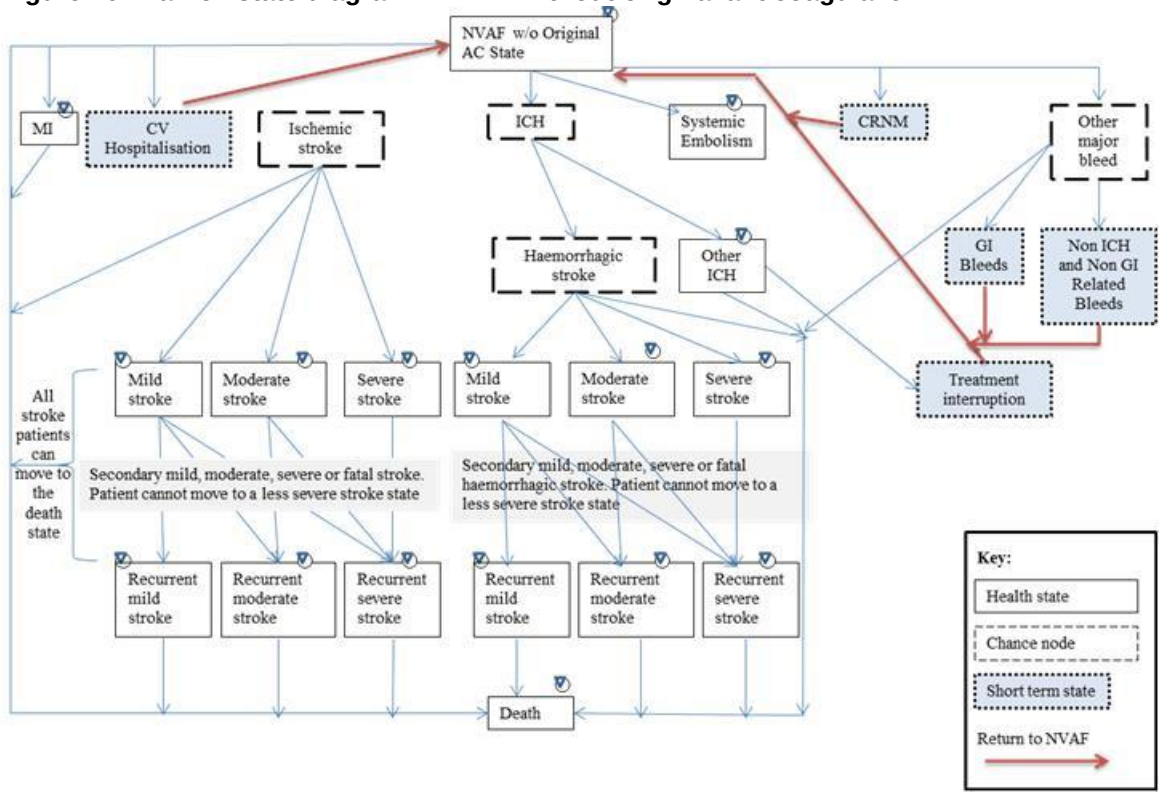
A Markov model was developed in Microsoft Excel® consisting of 18 health states, using a 6-week cycle length and a lifetime horizon. The Markov model structure is shown in Figure 15 and Figure 16. All patients start in the non-valvular atrial fibrillation (NVAF) health state (Figure 15). Patients can discontinue anticoagulant (AC) treatment due to reasons unrelated to stroke or SE, or discontinue due to ICH or other major bleed (GI bleed, non-ICH and non-GI related bleed). Patients who discontinue AC treatment, transition to the 'NVAF without original AC' health state and are assumed to start a second line aspirin treatment. For ease of understanding second line treatment ('NVAF without original AC') is presented in a separate diagram in Figure 16.

Figure 15: Markov state diagram – NVAF



Abbreviations: CRNM, clinically relevant non-major (bleed); CV, cardiovascular; GI, gastrointestinal; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Figure 16: Markov state diagram – NVAF without original anticoagulant



Abbreviations: CRNM, clinically relevant non-major (bleed); CV, cardiovascular; GI, gastrointestinal; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation; NVAF w/o original AC, non-valvular atrial fibrillation without original anticoagulant

7.2.3 Justification of model structure

The model is consistent with the clinical pathway of care identified in section 2.4. NVAF is a chronic condition in which patients' health status may change over time, and it is therefore appropriate to consider a Markov cohort model or micro simulation model e.g. discrete event simulation. NVAF can be defined according to discrete and exhaustive health states and an extended time horizon is considered. As only limited time-dependence and patient history was considered a Markov structure rather than a discrete event simulation approach was considered to be most appropriate. This approach was also adopted in the dabigatran and rivaroxaban HTA submissions (24, 103). The specific structure was developed to reflect the disease progression and the availability of clinical trial data within the apixaban clinical trial programme and the comparator RCTs.

The model was developed with reference to recent published models and those designed to support the dabigatran and rivaroxaban technology appraisals (24, 103), and where possible has addressed ERG comments (102, 104). The apixaban model provides a more comprehensive clinical representation of the health states and stroke severity than the preceding dabigatran and rivaroxaban technology appraisal models.

7.2.4 Definition of health states

The Markov model includes the following 18 health states:

Table 37: Health states

Health state	Description
Non-valvular AF (NVAF)	Patients with AF on AC who have not yet experienced any event within the model.
Ischaemic stroke Mild (mRS 0–2) Moderate (mRS 3–4) Severe (mRS 5)	3 states based on severity. Once patients have experienced a non-fatal ischaemic stroke they can transition to death or recurrent stroke (one recurrence only).
Recurrent ischaemic stroke Mild (mRS 0–2) Moderate (mRS 3–4) Severe (mRS 5)	3 states based on severity. Only one recurrence is modelled as there is limited repeat efficacy data from clinical trials
Haemorrhagic stroke Mild (mRS 0–2) Moderate (mRS 3–4) Severe (mRS 5)*	3 states based on severity. Once patients have experienced a non-fatal haemorrhagic stroke they can transition to death or recurrent stroke (one recurrence only)
Recurrent haemorrhagic stroke Mild (mRS 0–2) Moderate (mRS 3–4) Severe (mRS 5)*	3 states based on severity. Only one recurrence is modelled as there is limited repeat efficacy data from clinical trials
MI	Once patients have experienced a non-fatal MI they can only transition to death when their life expectancy has been reached
SE	Once patients have experienced a non-fatal SE they can only transition to death when their life expectancy has been reached
Other ICH	Following non-fatal other ICH patients may discontinue AC temporarily for a period of 6 weeks or discontinue AC completely.
NVAF without original AC (NVAF w/o AC)	Patients can discontinue treatment due to reasons unrelated to stroke or SE, or discontinue due to ICH or other major bleed (GI bleed, non-ICH and non-GI related bleed). Patients who discontinue treatment, transition to NVAF with original AC health state and are assumed to start a second line aspirin treatment in the base case
Death*	Death due to stroke, major bleeding (including haemorrhagic strokes, other ICH and other major bleeds), or background mortality. As per life tables and adjusted for AF impact as assessed through database studies

Abbreviations: AC, anticoagulant; AF, atrial fibrillation; ICH, intracranial haemorrhage; MI, myocardial infarction; mRS, modified Rankin scale; NVAF, non-valvular atrial fibrillation; SE, systemic embolism
* mRS 6 = death

7.2.5 Context

Atrial fibrillation (AF) is a cardiac arrhythmia and is characterised by an irregularly irregular heartbeat. AF leads to deterioration in the function of the atria preventing complete expulsion of blood from the heart. This lack of movement of blood can result in the formation of a thrombus (blood clot), which can become mobile and cause systemic

and cerebral emboli (SE), potentially resulting in stroke or systemic embolism. The disease progression is graphically represented in Figure 15 and Figure 16.

Stroke, SE and CV Events (Figure 15)
All patients, regardless of initial anticoagulation, enter the model in the nonvalvular atrial fibrillation health state (NVAF). Patients may stay in this state until death, discontinue their original anticoagulant (See Figure 16) or experience a 'Stroke, SE and CV Events' (ischemic stroke, SE, MI, CV hospitalisation) or bleeding (ICH, Other major bleed, CRNM) event.

Myocardial Infarction (MI)

NVAF patients can experience an MI, however, are assumed to discontinue anticoagulation and remain in the MI state until death (See 7.3.7.8 for model assumptions). This assumption was made to keep the model simple but to incorporate important sequelae of AF.

Cardiovascular (CV) hospitalisation

NVAF patients can experience a CV hospitalisation (not MI related). This is a short term event, impacting health related quality of life for approximately 6 days, after which patients return to the NVAF state.

Systemic Embolism (SE)

Patients entering the SE state remain in that state until death or discontinue their original anticoagulation and enter second line treatment (See the nonvalvular atrial fibrillation without original anticoagulation [NVAF w/o original AC], Figure 16).

Ischemic stroke

NVAF patients experiencing a stroke can experience a mild (mRS 0-2), moderate (mRS 3-4), severe (mRS 5) or fatal (mRS 6) stroke. Patients experiencing a nonfatal primary stroke can remain in their stroke state until death, aspirin patients are switched to warfarin second line (all others remain on their original anticoagulant) or experience a single subsequent stroke (mild, moderate, severe or fatal; See 7.3.7.8 for model assumptions). An individual can experience a milder subsequent stroke e.g. moderate stroke followed by a mild stroke, however, the individual will experience the long term health related quality of life impact of the next most severe stroke. Patients will remain in their recurrent stroke state until death.

Bleeding

Intracranial haemorrhage (ICH)

NVAF patients experiencing an ICH will either have a haemorrhagic stroke or an 'other ICH'. Patients experiencing an 'other ICH' can remain in the state until death or discontinue their original anticoagulant (enter the NVAF w/o original AC heath state, see Figure 16).

Haemorrhagic stroke is modelled in the same fashion as ischemic stroke. Patients experiencing haemorrhagic stroke can experience a mild (mRS 0-2), moderate (mRS 3-4), severe (mRS 5) or fatal (mRS 6) stroke. Patients experiencing a nonfatal primary haemorrhagic stroke discontinue anticoagulation completely. The patients can remain in

their haemorrhagic stroke state until death or experience a single subsequent haemorrhagic stroke (mild, moderate, severe or fatal; see 7.3.7.8 for model assumptions). An individual can experience a milder subsequent haemorrhagic stroke e.g. moderate stroke followed by a mild stroke, however, the individual will experience the long term health related quality of life impact of the severest haemorrhagic stroke. Patients will remain in their recurrent stroke state until death.

Clinically relevant non major bleed (CRNM)

CRNM bleeds are a short term event, affecting health related quality of life for approximately 6 weeks. Following the event, patients recover to their previous health and return to the NVAF health state.

Other Major Bleed

NVAF patients experiencing an 'other major bleed' (other than ICH) will either experience a GI bleed, 'non ICH or non GI related bleed' or die as a result of the major bleed. Patients experience a GI or 'non GI or non ICH' bleed will recover to their previous health status within approximately 6 weeks and will return to the NVAF state or discontinue their original anticoagulation and enter the NVAF w/o original AC heath state (Figure 16).

Figure 16 depicts patient progression through the health states when they have changed anticoagulation e.g. moved from apixaban to second line aspirin. Disease progression is identical to that discussed above (Figure 15) with the exception of no option to discontinue anticoagulation, except for switched to warfarin upon the occurrences of a stroke or SE.

7.2.6 Key features of the economic evaluation

The key features of the model are summarised in Table 38.

Table 38: Key features of analysis

Factor	Chosen values	Justification
Time horizon	Base case is lifetime	A lifetime horizon is the NICE reference case and is considered appropriate for AF as it is a chronic disease and the sequelae (e.g. stroke and haemorrhagic events) are likely to be life-long
Cycle length	6 weeks	Based on clinical judgement 6 weeks was considered to be the shortest duration in which pathology or symptoms were expected to change
Half-cycle correction	The model accounts for half-cycle corrections in accruing utility and resource use	In line with good practice in decision-analytic modelling (105)
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in QALYs	NICE reference case
Discount of 3.5% for utilities and costs	An annual discount of 3.5% is applied to both costs and health benefits occurring beyond the first year	NICE reference case
Perspective (NHS/PSS)	NHS perspective	NICE reference case

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years

Technology

7.2.7 Intervention and comparator

The intervention and comparators are implemented in the model according to their marketing authorisations and doses where possible (Table 39). As outlined in sections 2.3 and 2.5 above, aspirin is currently recommended for patients unsuitable for warfarin or those at low risk of strokes, and is also still widely used in clinical practice in England and Wales. Aspirin remains therefore, a relevant comparator in this submission.

Table 39: Intervention and comparator

Intervention	**Units**
Apixaban	5 mg BD†
Comparators	**Units**
Aspirin	Average daily dose approximately 150 mg OD (81–324 mg OD) (3)
Warfarin (VKA suitable population only)	Average daily dose 4.5 mg OD (106)*, target INR 2.5 (range 2.0–3.0)
Dabigatran (110 mg)	110 mg BD
Dabigatran (150 mg)	150 mg BD (switching to 110 mg at the age of 80 years as per SmPC indication)
Rivaroxaban	20 mg OD

*Average dose not recorded in CSR; mean dose taken from Blann et al, 2003 (106) as accepted in CG36 and dabigatran and rivaroxaban NICE appraisals. † 2.5mg BD was used in small sub-populations.
Abbreviations: BD, twice daily; OD, once daily; SmPC, Summary of product characteristics; VKA, Vitamin K antagonist

7.2.8 Treatment continuation rule

No explicit treatment continuation rule has been applied. The model considers treatment discontinuations from the NVAF state and permits the cessation of current treatment following stroke, haemorrhagic stroke, other ICH, GI bleeds, non ICH and non-GI major bleeds and systemic embolism.

7.3 Clinical parameters and variables

7.3.1 How were clinical data implemented in the model?

Data on the 18 health states outlined in section 7.2.2 were extracted from the AVERROES, ARISTOTLE, RE-LY and ROCKET-AF trials (2, 3, 58, 63). Apixaban was used as the reference treatment in the model. In the absence of head-to-head data, a network meta-analysis was conducted to determine the relative efficacy and safety of apixaban versus dabigatran and rivaroxaban (see Section 6.7). In the NMA, hazard ratios for efficacy outcomes were based on the ITT population and bleeding outcomes were based on the on-treatment population.

Comparisons with dabigatran and rivaroxaban within cTTR sub-groups were not possible, as data for all required outcomes were not available. Instead, the model only compares with warfarin within cTTR groups using ARISTOTLE trial data. Data on all outcomes of interest were also not available by $CHADS_2$ score for dabigatran and

rivaroxaban. Instead, these were taken from the AVERROES (3) and ARISTOTLE trials (2) for warfarin, aspirin and apixaban, and hazard ratios for dabigatran and rivaroxaban from the NMA are then applied to the apixaban stroke risk by $CHADS_2$ categories (0-1, 2, 3-6; due to sample size limitations).

Hazard ratios were used in the economic model for efficacy and adverse events rather than relative risks or odds ratios. It is not possible to use odds ratios as they cannot be directly applied to an absolute probability of an event to generate the absolute event rate for a comparator. Relative risks were not used as they represent cumulative risk over the study period and do not account for time interval, i.e. differing trial data collection periods.

7.3.2 Transition probabilities

Hazards

Hazards were transformed into probabilities in the following way:

1. Transform hazard (event rates) per year per 100 patients into hazards per day = (Hazard/number of days in a year)/number patients e.g. (1.338281/365.25)/100= 0.000037
2. Transform hazards per day into a transition probability = 1 – exponential (-(hazards per day * number of days in a cycle)) i.e. =1-EXP(-(0.000037*42))

Hazard ratios

Hazard ratios calculated from the NMA were applied to the probabilities multiplicatively to derive transition probabilities.

7.3.3 Variation of transition probabilities over time

Transition probabilities in the Markov model vary over time for stroke, ICH, other major bleed, CRNM bleeds, background death, other discontinuation and MI.

7.3.4 Linking intermediate outcome measures to final outcomes

No intermediate or surrogate measures were used in the model. All progression (transition probabilities) was based on risks identified for the progression from one health state to another.

7.3.5 Clinical experts

The choice of anti-coagulant post stroke and SE, and duration of utility decrement following bleeding events were derived from expert opinion. Expert opinion was elicited in accordance with the principles of the nominal group technique (107). Based on expertise and international reputation two experts were recruited. With two health economists, one clinician and one scribe in attendance, the experts were posed the questions outlined above. Following discussion of the key issues by the experts, the health economists formulated an answer which was then agreed or discussed until consensus was agreed by the experts. Following a two week interlude the minutes of the meeting were circulated for clarification and approval. No discrepancies were identified and a further consensus meeting was not required.

Summary of selected values

7.3.6 Summary list of variables used

Table 40 to Table 57 summarise the clinical variables and values used in the model. The base or constant intervention in this model is apixaban. Given the small absolute risks or transition probabilities of events, they are expressed for ease of reporting and interpretation, as risk per 100 patient years (PY) i.e. a risk of 0.957 per 100 PY (0.957%) is 0.00957 in absolute terms (see Table 40 for apixaban stroke risk). The transition probabilities for the remaining interventions are obtained by multiplying the base risk by the hazard ratio for the intervention (Table 41 for hazard ratios) e.g. VKA suitable stroke risk for rivaroxaban is 0.00957*1.024, and transforming as outlined in section 7.3.2.

Table 40: Stroke risk by $CHADS_2$ for apixaban (per 100 PY)

$CHADS_2$ score	VKA suitable population	VKA unsuitable population
	Apixaban‡	Apixaban†
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
Average stroke risk	[redacted]	[redacted]

‡Source: secondary analysis of ARISTOTLE data; †Source: secondary analysis of AVERROES data
Abbreviations: VKA, Vitamin K antagonist

A list of all NMA variables and values used in the economic analysis is provided in Table 41. The clinical event rates in the model were obtained from the network meta-analyses (see Section 6.7). Note that the HRs presented in Section 6.7 are versus warfarin, whereas apixaban is the reference treatment for those shown in Table 41.

Table 41: Clinical event hazard ratios (versus apixaban)

	VKA suitable [NMA 1]		VKA unsuitable [NMA 2]	
	HR	95% CrI	HR	95% CrI
ICH				
Apixaban	1.000	1.000–1.000	1.000	1.000–1.000
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Aspirin	xxxx	xxxx	xxxx	xxxx
Ischaemic stroke				
Apixaban	1.000	1.000–1.000	1.000	1.000–1.000
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Aspirin	xxxx	xxxx	xxxx	xxxx

	VKA suitable [NMA 1]		VKA unsuitable [NMA 2]	
	HR	**95% CrI**	**HR**	**95% CrI**
Other major bleeding				
Apixaban	1.000	1.000–1.000	1.000	1.000–1.000
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Aspirin	NA	NA	xxxx	xxxx
MI[$]				
Apixaban	1.000	1.000–1.000	1.000	1.000–1.000
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Aspirin	NA	NA	xxxx	xxxx
Other CV hospitalisation				
Apixaban	1.000	0.000–0.000	1.000	0.000–0.000
Aspirin	NA	NA	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Discontinuation				
Apixaban	1.000	1.000–1.000	1.000	1.000–1.000
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Aspirin	NA	NA	xxxx	xxxx
SE				
Apixaban	1.000	1.000–1.000	1.000	1.000–1.000
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Aspirin	NA	NA	xxxx	xxxx
CRNM bleeding				
Apixaban	1.000	1.000–1.000	1.000	1.000–1.000
Rivaroxaban	xxxx	xxxx	xxxx	xxxx
Dabigatran 110mg	xxxx	xxxx	xxxx	xxxx
Dabigatran 150mg	xxxx	xxxx	xxxx	xxxx
Warfarin	xxxx	xxxx	NA	NA
Aspirin	NA	NA	xxxx	xxxx

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major;CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NA, not applicable; NMA, network meta analysis; SE, systemic embolism; VKA, Vitamin K antagonist

[$] Patients experiencing an MI no longer receive an anticoagulant in the model.

Stroke severity distributions according to the mRS score (i.e., mild = mRS 0-2, moderate = mRS 3-4, severe = mRS 5 and fatality = mRS 6) for apixaban, aspirin and warfarin were obtained from secondary analysis of AVERROES and ARISTOTLE data (see Table 42). Treatment dependent stroke severity is also assessed in the sensitivity analysis (all comparators assumed to have the same distribution). Severity distribution for dabigatran (110mg and 150mg), and rivaroxaban were from the RE-LY and ROCKET-AF trials. Data for dabigatran and rivaroxaban were not available for all of the mRS categories required for the model and it was necessary to weight the percentage for mRS 3-5 for dabigatran and rivaroxaban into mRS 3-4 and mRS 5. This was done using the proportion of mRS 3-4 and 5 observed for apixaban in the secondary analysis of ARISTOTLE and AVERROES. For example, RE-LY and FDA documents report for dabigatran 110mg bd mRS 0-2 = 60/171, mRS 3-6=112/17,1 mRS 6=47/171 (108), the proportion with mRS 3-5 was (112-47)/171 was split into mRS 3-4 and mRS 5 by applying the apixaban results, mRS 3-4 = 65/171*([redacted]) and mRS5=65/171*([redacted]).

Table 42: Distribution of stroke severity

	VKA suitable population					VKA unsuitable population				
	Mild	**Moderate**	**Severe**	**Fatal**	**Source**	**Mild**	**Moderate**	**Severe**	**Fatal**	**Source**
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	[redacted]	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Aspirin (1st line)	–	–	–	–		[redacted]	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	–	–	–	–	
Dabigatran (110mg)	[redacted]	[redacted]	[redacted]	[redacted]	(58) Same distribution for all stroke types	[redacted]	[redacted]	[redacted]	[redacted]	(58) Same distribution for all stroke types
Dabigatran (150mg)	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Riva-oxaban	[redacted]	[redacted]	[redacted]	[redacted]	(63) Same distribution for all stroke types	[redacted]	[redacted]	[redacted]	[redacted]	(63) Same distribution for all stroke types

Mild = mRS (0–2), moderate = mRS (3–4), severe = mRS (5), fatal = mRS (6)
Abbreviations: Apix, apixaban; Dabi, dabigatran; NMA, network meta analysis; VKA, Vitamin K antagonist

For those patients who had experienced a stroke, the risk of a further stroke was incorporated into the model. A recurrent annual stroke rate of 0.0410 was used based on a study of patients in the South London Stroke Registry, which captured recurrence up to ten years after stroke (109). The severity of stroke distribution for apixaban was then applied to all patients who had a recurrent stroke event. As the risk of stroke increases with age in AF patients, a stroke risk adjustment factor was applied every decade in the model. An adjustment factor of 1.40 indicates that an AF patient's risk of stroke increases by 40% every decade (110). The risk adjustment factors listed in Table 43 were predominantly identified from pooled or systematic review studies.

Table 43: Risk adjustment factor (per decade)

	Value	**Source**

Ischaemic stroke	1.400	Pooled data from 5 RCTs (110)
ICH	1.970	Systematic review (111)
Other Major Bleeds	1.970	
CRNM Bleeds	1.970	
MI	1.300	(112)

Abbreviations: CRNM, clinically relevant non-major; ICH, intracranial haemorrhage; MI, myocardial infarction

Table 44 contains the base (apixaban) risks for ICH, Other major bleeds, CRNM bleed, MI, Other CV hospitalisation, Other treatment discontinuations and SE (risk per 100 PY).

Table 44: Baseline risks for non-stroke events (per 100PY)

Event	VKA suitable		VKA unsuitable	
	Apixaban	**Source**	**Apixaban**	**Source**
ICH	0.330	(2)	[redacted]	Secondary analysis of AVERROES data
Other major bleeds	1.790		[redacted]	
CRNM bleed	[redacted]	Secondary analysis of ARISTOTLE data	[redacted]	
MI	0.530	(2)	[redacted]	(68)
Other CV hospitalisation	[redacted]	Assumption‡	[redacted]	Secondary analysis of AVERROES data
Other treatment discontinuations	[redacted]	Secondary analysis of ARISTOTLE data	[redacted]	
Systemic embolism	[redacted]	(67)	[redacted]	(68)

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; VKA, Vitamin K antagonist

ICH events comprise of Haemorrhagic stroke and Other ICH. Table 45 presents the proportion of haemorrhagic stroke and other ICH. Severity distribution for dabigatran (110mg and 150mg), and rivaroxaban were from the RE-LY and ROCKET-AF trials, whilst they were taken from Secondary analysis of AVERROES and ARISTOTLE for apixaban, warfarin and aspirin.

Table 45: Distribution of ICH type

	VKA suitable population			VKA unsuitable population		
	Haemorrhagic stroke	**Other ICH**	**Source**	**Haemorrhagic stroke**	**Other ICH**	**Source**
Apixaban	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	[redacted]	[redacted]	Secondary analysis of AVERROES data‡
Aspirin	[redacted]	[redacted]	Assumption†	[redacted]	[redacted]	

	VKA suitable population			VKA unsuitable population		
	Haemorrhagic stroke	Other ICH	Source	Haemorrhagic stroke	Other ICH	Source
Warfarin	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	–	–	
Dabigatran (110mg)	64%	36%	(58)	64%	36%	(58)
Dabigatran (150mg)	41%	59%		41%	59%	
Rivaroxaban	57%	43%	(63)	57%	43%	(63)

Abbreviations: ICH, intracranial haemorrhage; VKA, Vitamin K antagonist; †Same distribution as observed in AVERROES; ‡Pooled analysis across apixaban and aspirin due to the small number of events in AVERROES

Haemorrhagic stroke severity (see Table 46) was established using the same methods as outlined above for ischemic stroke. It should be noted that the RE-LY and ROCKET-AF papers did not distinguish between ischemic and haemorrhagic strokes when reporting stroke severity. It was necessary, therefore, to assume the same severity distribution applied to both stroke types for dabigatran and rivaroxaban

Table 46: Distribution of haemorrhagic stroke severity

	VKA suitable population					VKA unsuitable population				
	Mild	Moderate	Severe	Fatal	Source	Mild	Moderate	Severe	Fatal	Source
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	[redacted]	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data‡
Aspirin (1st line)	[redacted]	[redacted]	[redacted]	[redacted]	Assumption†	[redacted]	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	–	–	–	–	
Dabigatran (110mg)	[redacted]	[redacted]	[redacted]	[redacted]	(58)	[redacted]	[redacted]	[redacted]	[redacted]	(58)
Dabigatran (150mg)	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	(63)	[redacted]	[redacted]	[redacted]	[redacted]	(63)

Abbreviations: Dabi, dabigatran; VKA, Vitamin K antagonist
Mild = mRS (0–2), moderate = mRS (3–4), severe = mRS (5), fatal = mRS (6); †Same distribution as observed in AVERROES; ‡Pooled analysis across apixaban and aspirin due to the small number of events in AVERROES

The recurrent annual risk of haemorrhagic stroke is 0.02996 (109). The severity of stroke distribution for apixaban was then applied to all patients who had a recurrent stroke event.

Other major bleeds (other than haemorrhagic and ICH) in the model comprise GI bleeds and non ICH and non-GI related bleeds. Table 47 displays the proportion of GI bleeds stroke and non ICH and non-GI related bleeds. The split between GI bleeds and 'non ICH and non-GI related' bleeds for dabigatran (110mg and 150mg), and rivaroxaban were calculated from the RE-LY and ROCKET-AF trials, whilst they were taken from AVERROES and ARISTOTLE clinical study report and Secondary analysis of ARISTOTLE data for apixaban, warfarin and aspirin. In the absence of data for aspirin in a VKA suitable population the same distribution as observed in AVERROES was assumed.

Table 47: Distribution of other major bleeds

	VKA suitable population			VKA unsuitable population		
	GI Bleeds	Non ICH and non-GI related bleeds	Source	GI Bleeds	Non ICH and non-GI related bleeds	Source
Apixaban	[redacted]	[redacted]	(67)	[redacted]	[redacted]	(68)
Aspirin	[redacted]	[redacted]	Assumption†	[redacted]	[redacted]	
Warfarin	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	–	–	
Dabi (110mg)	41%	59%	(58)	41%	59%	(58)
Dabi (150mg)	49%	51%		49%	51%	
Riva-roxaban	45%	55%	(63)	45%	55%	(63)

Abbreviations: Dabi, dabigatran; ICH, intracranial haemorrhage; GI, gastrointestinal; VKA, Vitamin K antagonist; †Same distribution as observed in AVERROES

Table 48 presents the bleeding fatality estimates for other ICH and other major bleed for the VKA suitable and unsuitable populations.

Table 48: Bleeding fatality rates (VKA suitable and unsuitable populations)

	Other ICH	Other Major Bleeds	Source
Apixaban	[redacted]	[redacted]	Secondary analysis of AVERROES and ARISTOTLE data
Aspirin	[redacted]	[redacted]	
Warfarin	[redacted]	[redacted]	
Dabigatran (110mg)	[redacted]	[redacted]	Assumption – same rate across treatments
Dabigatran (150mg)	[redacted]	[redacted]	
Rivaroxaban	[redacted]	[redacted]	

Abbreviations: ICH, intracranial haemorrhage; VKA, Vitamin K antagonist

Following an event (stroke, SE, ICH, other ICH, GI bleed or non ICH and non GI related bleed), patients may continue on their original anticoagulant or switch to an alternative treatment. Table 49 summarises for each event and treatment the percentage continuing on their original anticoagulant or switching to an alternative treatment. Patients experiencing a stroke or SE whilst receiving aspirin are assumed to be assigned warfarin following the event. Patients on any other treatment are assumed to continue on the original treatment. Patients experiencing an ICH, other ICH, GI bleed or non ICH and non GI related bleed can switch to aspirin, warfarin or no treatment, or remain on their original anticoagulant. In the base case patients switching anticoagulant are assumed to receive aspirin. Warfarin is allowed as a second line treatment only for the VKA suitable patients if the comparator analysed is not warfarin. For patients who receive aspirin as their initial AC treatment, the model assumes they continue on this therapy if second line treatment in the model is specified as aspirinUpon a switch to second-line use of aspirin or warfarin, this model assumes no subsequent treatment discontinuations and accompanying switching, with the exception of patients on aspirin or 'no treatment switching to warfarin if they experience a stroke or SE. Having switched to second-line use of aspirin or warfarin a constant risk of bleeding, stroke, SE, and MI independent of duration of second line treatment use, and prior AC treatment or patient characteristics (see Table 50) is assumed.

Table 49: Anticoagulant treatment choice post event

Stroke (mild, moderate & severe)	**No Change**	**Switch to warfarin**	**Source**
Apixaban	100%	0%	Expert opinion
Aspirin (1st line)	0%	100%	
Warfarin	–	–	
Dabigatran (110mg)	100%	0%	
Dabigatran (150mg)	100%	0%	
Rivaroxaban	100%	0%	
Systemic embolism	**No Change**	**Switch to Warfarin**	**Source**
Apixaban	100%	0%	Expert opinion
Aspirin (1st line)	0%	100%	
Warfarin	100%	0%	
Dabigatran (110mg)	100%	0%	

Dabigatran (150mg)	100%	0%	
Rivaroxaban	100%	0%	
GI bleeds	**No Change**	**Switch Treatment (VKA suitable - aspirin, warfarin or no treatment; VKA unsuitable – aspirin or no treatment)**	**Source**
Apixaban	75%	25%	(113)
Aspirin	100%	0%	Assumption
Warfarin	75%	25%	(113)
Dabigatran (110mg)	75%	25%	
Dabigatran (150mg)	75%	25%	
Rivaroxaban	75%	25%	
Other major bleeds	**No Change**	**Switch Treatment (VKA suitable - aspirin, warfarin or no treatment; VKA unsuitable – aspirin or no treatment)**	**Source**
Apixaban	75%	25%	(113)
Aspirin	100%	0%	Assumption
Warfarin	75%	25%	(113)
Dabigatran (110mg)	75%	25%	
Dabigatran (150mg)	75%	25%	
Rivaroxaban	75%	25%	
Other ICH	**Stop Treatment (6 weeks)**	**Switch Treatment (VKA suitable - aspirin, warfarin or no treatment; VKA unsuitable – aspirin or no treatment)**	**Source**
Apixaban	44%	56%	(114)
Aspirin	100%	0%	Assumption
Warfarin	44%	56%	(114)
Dabigatran (110mg)	44%	56%	
Dabigatran (150mg)	44%	56%	
Rivaroxaban	44%	56%	

Abbreviations: ICH, intracranial haemorrhage; GI, gastrointestinal; VKA, Vitamin K antagonist

Risk of events on 2nd line treatment

Above in Table 49 it was noted that patients experiencing a GI, non ICH and non GI related bleed, ICH or Other ICH could switch treatment to aspirin or no treatment and patients experiencing a stroke or SE could switch treatment to warfarin. Table 50 presents the absolute risk for patients switching to aspirin or no treatment of experiencing a stroke, ICH, other major bleed, CRNM bleed, MI, SE or other CV hospitalisation. Event rates for aspirin subsequent treatment were taken from the

secondary data analysis of the AVERROES, considering a subgroup of patients who had VKA-unsuitability "demonstrated" (i.e., previously failed warfarin).

Table 50: Absolute event risk in 2nd line therapy options (per 100 PY)

	Aspirin (2nd line)	Source	No Treatment	Source
Stroke (excl haemorrhagic stroke)	[redacted]	Secondary analysis of AVERROES data	4.186	(115)
ICH	[redacted]		0.000	Assumption
Other Major Bleeds	[redacted]		0.000	Assumption
CRNM Bleeds	[redacted]		0.000	Assumption
MI	[redacted]		1.003	(115)
SE	[redacted]	Assumption, AVERROES CSR (68)	0.959	
Other CV Hospitalization	[redacted]	Secondary analysis of AVERROES data	16.506	

Abbreviations: CRNM, Clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; GI, gastrointestinal; MI, myocardial infarction; SE, Systemic embolism; VKA, Vitamin K antagonist

Patients switched to warfarin were assumed to be exposed to the same event rates and other relevant inputs (e.g., stroke severity distribution, case fatality rates) as those who start on warfarin as the initial anticoagulant treatment. Patients on 2nd line therapy (aspirin) who experience an ischaemic stroke or systemic embolism were assumed to switch to warfarin. Stroke and ICH severity (mRS) for 2nd line aspirin (stroke severity distributions, both for stroke and haemorrhagic stroke, were assumed to be the same as those who had aspirin as the initial anticoagulation treatment) or no treatment are presented in Table 51. The model assumes patients who completely discontinued the treatment (i.e., switch to no treatment) are no longer exposed to any bleeding risks.

Table 51: Distribution of stroke severity in 2nd line therapy options

	Aspirin (2nd line)	Source	No Treatment	Source
Mild (mRS 0-2)	[redacted]	Secondary analysis of AVERROES data	22%	(116)
Moderate (mRS 3-4)	[redacted]		37%	
Severe (mRS 5)	[redacted]		36%	
Fatal (mRS 6)	[redacted]		5%	

Abbreviations: mRS, modified Rankin Scale

Other cause Mortality

Mortality comprises mortality due to events modelled and other cause mortality (all cause mortality minus event mortality). Event mortality is the mortality resulting from the events key health states modelled:

- Ischaemic stroke (see Table 42)
- Haemorrhagic stroke (see Table 46)
- SE case fatality rate of [redacted] was assumed for all therapies (67).
- Other major bleed (see Table 48)

- MI case fatality rate was assumed to be 10.8% for males and 15.6% for females (117).

In this model other cause mortality has a time specific element. Trial specific other mortality was available from Aristotle and Averroes trials for 1.2 and 1.9 years respectively and so these were used to model other cause mortality for these periods (see Table 52 for baseline risks and Table 53 for the HRs that are applied to them - dabigatran and rivaroxaban were assumed to have the same HR as apixaban).

Table 52: Absolute risk of trial based other cause mortality

	VKA Suitable Population				VKA Unsuitable Population			
	Apixaban	**Warfarin†**	**Source**	**Duration**	**Apixaban**	**Aspirin†**	**Source**	**Duration**
Death rate (per 100 patient year)	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	1.9 years	[redacted]	[redacted]	Secondary analysis of AVERROES data	1.2 years

Abbreviations: VKA, Vitamin K antagonist; †Sensitivity analysis

Table 53: Trial based other cause mortality hazard ratio versus apixaban

	VKA Suitable Population			VKA Unsuitable Population		
	Hazard Ratio	**95% CI**	**Source**	**Hazard Ratio**	**95% CI**	**Source**
Apixaban	1.000			1.000		
Aspirin (1st line)	[redacted]	[redacted]	Secondary analysis of AVERROES data	[redacted]	[redacted]	Secondary analysis of AVERROES data
Warfarin	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data	–	–	–
Dabigatran	1.000	0.900-1.100	Assumption	1.000	0.900-1.100	Assumption
Rivaroxaban	1.000	0.900-1.100	Assumption	1.000	0.900-1.100	Assumption

Abbreviations: VKA, Vitamin K antagonist

In the post trial period (>1.2 years VKA unsuitable, >1.9 years VKA suitable) it is assumed that all anticoagulants have the same other cause mortality. All cause mortality was estimated by taking the UK life table data and applying a Gompertz distribution (see Table 54), and applying a hazard ratio of 1.34 (calculated) for the AF population to reflect increased risk of mortality compared to the general population (12) as identified via a literature search (see Appendix 16, Section 10.16).

Gompertz

As life table data is available on an annual basis and the model utilises a cycle length of 6 weeks, a survival analysis extrapolation distribution was applied to improve precision in estimates. A Gompertz distribution was selected as it provided a superior fit to the log-normal, log logistic, weibull and exponential functions, closely following the shape of the

observed distribution, and yields accurate estimates of life expectancy (see appendix 17, Section 10.17).

Table 54: Gompertz regression parameters for background mortality

Gender and age	Lambda (shape)	Gamma (scale)
Males <75 years old	–9.2268	0.0745
Males ≥75 years old	–9.3652	0.0835
Females <75 years old	–9.6037	0.0717
Females ≥75 years old	–10.9334	0.0986

Source: Gompertz function fitted from the UK General Life Tables 2009

Other cause mortality for event survivors

Table 55 presents the other cause mortality HR applied for AF patients who have survived an ischaemic stroke, ICH, MI or SE.

Table 55: Additional mortality risk adjustment hazard ratios

Event	HR	Source
Stroke (excluding haemorrhagic stroke)		
Mild	3.18	(118-120)
Moderate	5.84	
Severe	15.75	
Haemorrhagic Stroke		
Mild	3.18	(118-120)
Moderate	5.84	
Severe	15.75	
MI		
Males	2.56	(121)
Females	4.16	
Systemic Embolism	1.34	Assumption. Same as AF (12)

Abbreviations: HR, hazard ratio; MI, myocardial infarction

Absolute and relative event rates by subgroup

As noted previously, comparisons with dabigatran and rivaroxaban within cTTR (center's median time in therapeutic range) sub-groups were not possible, as data for all required outcomes were not available. Instead, the model only compares with warfarin within cTTR groups using ARISTOTLE trial data. Data on all outcomes of interest were also not available by CHADS2 score for dabigatran and rivaroxaban. Instead, these were taken from the AVERROES and ARISTOTLE trials for warfarin, aspirin and apixaban, and hazard ratios for dabigatran and rivaroxaban from the NMA were then applied to the apixaban stroke risk by CHADS2 categories (0-1, 2, 3-6; due to sample size limitations).

To allow analysis by cTTR secondary analysis was required from the ARISTOTLE trial to obtain the rates of each of the events modelled for each respective cTTR range for both apixaban and warfarin (Table 56). As the purpose of the cTTR adjustment is to allow

adjustments in event risks (i.e., stroke and bleedings) based on variation in INR control, any adjustments made to the distribution of cTTR is used to re-calculate the risks of events for apixaban and warfarin.

Table 56: Risks of Stroke, ICH, CRNM, and Other Major Bleed by cTTR Ranges

	Apixaban	Warfarin	
Stroke			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of the ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	
Intracranial hemorrhage			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of the ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	
Other major bleed			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of the ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	
Clinically relevant non major bleed			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of the ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	

cTTR adjustments performed in the model

For each treatment (i.e., apixaban and warfarin), using the event rates (stroke, ICH, other major bleed, CRNM bleed) for each cTTR range as displayed in Table 56, a HR was calculated relative to the range with average TTR from the ARISTOTLE (i.e., 52.38% ≤ cTTR < 66.02%) for each event. For example, the HR for stroke for patients treated with apixaban in the cTTR range < 52.38% would be calculated in relation to patients in cTTR range between 52.38% and 66.02% as [redacted]. HRs for each cTTR range and event for each respective comparator are shown in Table 57.

Using this information, the "average HR for cTTR adjustment" for each event is determined by weighting the HRs for each cTTR range for apixaban or warfarin by the distribution of cTTR as defined at baseline. The "average HR for cTTR adjustment" obtained from this step is then applied to the event risk to generate the "cTTR-adjusted risk". Note that when the cTTR distribution is set to be trial-like (i.e., 25% in each cTTR range), the adjusted risks will be the same as the event risks reported from the trials. To

match the event risk as observed in the trials, the derived risk is multiplied by the base case risk and divided by the average HR. For example, assume a hypothetical setting INR control has distribution of cTTR as follows:

- cTTR <52.38% = 10%
- 52.38%<cTTR <66.02% = 15%
- 66.02%<cTTR <78.61% = 25%
- cTTR >78.61% = 50%

Then, the “average HR for cTTR adjustment” for apixaban in hypothetical settings, can be calculated as:

- ([redacted]*10%) + ([redacted] *15%) + ([redacted]*25%) + ([redacted] *50%) = [redacted]

In the default setting where patients are equally distributed across cTTR ranges the adjustment would be calculated as:

- ([redacted] *25%) + ([redacted] *25%) + ([redacted] *25%) + ([redacted] *25%) = [redacted]

Next, the cTTR adjusted risk can be calculated using the average stroke risk and quartile based center distribution using the following equation:

In the hypothetical setting described above this would be calculated as:

- ([redacted]

In the default setting the risk derived would be the same as the risk without the adjustment calculated as:

- ([redacted]

(Note: 0.981 is stroke risk of apixaban as reported in the ARISTOTLE; [redacted] is the average HR across all cTTR ranges).

Table 57 present the hazard ratios of stroke and ICH for apixaban and warfarin by centre time in therapeutic range (cTTR) quartile. These hazard ratios are applied in the subgroup analysis to the base case transition probabilities for the respective anticoagulants.

cTTR specific hazard ratios (for each group vs the 52.38% ≤ cTTR < 66.02% group) for ischaemic stroke, ICH, other major bleed and CRNM bleeds were calculated as secondary analyses from the ARISTOTLE clinical trial and applied to generate cTTR specific estimates of stroke events. Because data were only available from the ARISTOTLE trial, comparisons were only possible for apixaban versus warfarin.

Table 57: Hazard ratios for ischaemic stroke, ICH, Other major bleed and CRNM bleed by cTTR group

Median cTTR	Apixaban (95% CI)	Warfarin (95% CI)	Source
Ischaemic stroke			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of the ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	
ICH			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	
Other major bleed			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of the ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	
CRNM bleed			
cTTR < 52.38%	[redacted]	[redacted]	Secondary analysis of the ARISTOTLE data
52.38% ≤ cTTR < 66.02%	[redacted]	[redacted]	
66.02% ≤ cTTR < 76.51%	[redacted]	[redacted]	
cTTR ≥ 76.51%	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; cTTR, centre time in therapeutic range (INR 2.0-3.0); VKA, Vitamin K antagonist

Note: 1) Reference is the average TTR for ARISTOTLE; 2) hazard ratio is applicable if apixaban is compared to warfarin only

Table 58 contains the baseline risks of ICH, other major bleeds, CRNM bleed, MI, other CV hospitalisation, other treatment discontinuations, SE for aspirin and warfarin (apixaban risks previously presented in Table 44). These are used for non cTTR specific outcomes when analysis by cTTR is being conducted.

Table 58: Baseline risks (per 100 PY)

Event	VKA suitable		VKA unsuitable	
	Warfarin[†]	Source	Aspirin[†]	Source
ICH	0.800	(2)	[redacted]	Secondary analysis of AVERROES data
Other major bleeds	2.270		[redacted]	
CRNM bleed	[redacted]	Secondary analysis of ARISTOTLE data	[redacted]	
MI	0.610	(2)	[redacted]	(68)

Event	VKA suitable		VKA unsuitable	
	Warfarin†	Source	Aspirin†	Source
Other CV hospitalisation	10.460	Assumption‡	[redacted]	Secondary analysis of AVERROES data
Other treatment discontinuations	[redacted]	Secondary analysis of ARISTOTLE data	[redacted]	
Systemic embolism	[redacted]	(67)	[redacted]	(68)

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; VKA, Vitamin K antagonist

†Only used in the sensitivity analysis for subgroups; ‡Rate for apixaban taken from AVERROES and assumed same rate for warfarin (and all other VKA suitable comparators)

The model captures stroke risk by allowing the risk to be adjusted by the distribution of $CHADS_2$ among the cohort. Stroke risks (rate per 100 person years) by $CHADS_2$ for apixaban and aspirin were obtained from AVERROES for the VKA unsuitable patients while those for apixaban and warfarin for the VKA suitable patients were from ARISTOTLE. Stroke risks by individual score of $CHADS_2$ could not be obtained due to the insufficient sample sizes in some specific $CHADS_2$ scores. Thus, the risks were obtained for $CHADS_2$ score of 0-1, 2, and 3-6 (see Table 59). The average stroke risks (i.e., $CHADS_2$-adjusted stroke risk) for apixaban and aspirin for the VKA unsuitable population and apixaban and warfarin for the VKA suitable population were determined by weighting the risk for each category of $CHADS_2$ score (i.e., less than 2, 2, and greater than 2) for each treatment by the proportion of patients with each group of $CHADS_2$ score as defined at baseline. Baseline stroke risks for other comparators in the model are derived by applying HRs (i.e., versus apixaban) obtained from the network meta analysis (see Table 41).

Table 59: Risk of Stroke (Excluding Hemorrhagic Strokes) by $CHADS_2$ Score (Rate per 100 Person Years)

	VKA Suitable¶		VKA Unsuitable‡	
$CHADS_2$ Score	**Apixaban**	**Warfarin**	**Apixaban**	**Aspirin**
0-1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3-6	[redacted]	[redacted]	[redacted]	[redacted]
Average stroke risk†	[redacted]	[redacted]	[redacted]	[redacted]

†Adjusted by $CHADS_2$; ¶Secondary analysis of ARISTOTLE data; ‡Secondary analysis of AVERROES data

7.3.7 Extrapolation of trial outcomes

Clinical outcomes are extrapolated beyond the end of the trials. In the absence of data indicating that efficacy and adverse events would differ beyond the trial time horizons strokes, SE, MI, bleeding and CV hospitalisation were are assumed to continue at the rates seen in the anticoagulant trials (AVERROES, ARRISTOTLE, ROCKET-AF and RE-

LY). However, a discontinuation rate (discontinuation due to any cause e.g. reduced efficacy, increased adverse events, intolerability) is applied post trial duration (1.9 years) which can be varied (all treatments have the same discontinuation rates as apixaban, or continue with the observed initial rate, or do not discontinue).

7.3.8 Summary of assumptions used

Table 60: Assumptions used in the model

Assumption	Justification
General	
For transient states, patients cycle back to their original health state after the event is processed, i.e., the model assumes no impact on subsequent event risks and the anticoagulation treatment that follows	Clinical opinion
Only one clinical event can occur per cycle	Patients are unlikely to experience more than one major event during any 6-week period
The base case analysis assumes aspirin as second-line AC treatment	Patients who discontinue AC therapy can be switched to antiplatelet therapy as per NICE clinical guidelines (CG 36) (4)
For patients who receive aspirin as their initial AC treatment, the model assumes no treatment discontinuation if the second-line treatment choice is aspirin	Assumption
Upon a switch to second-line use of aspirin or warfarin, this model assumes no subsequent treatment discontinuations and a constant risk of bleeding, stroke, SE, and MI independent of duration of second line treatment use, and prior AC treatment or patient characteristics	Expert opinion (Section 7.3.5)
Stroke	
Severity of recurrent stroke (haemorrhagic or ischaemic) is conditional on severity of prior stroke. Patients transition to the most severe of the first or recurrent stroke health states	Whilst a patient can experience a less severe recurrent stroke e.g. severe stroke followed by a mild stroke, it is not clinically appropriate to assume the patient would experience the long-term effects of a milder stroke
Recurrent stroke is allowed to occur only once	It is not practical to model more than one recurrent strokes. Data on recurrent stroke was not available for patients receiving, apixaban, dabigatran, rivaroxaban or warfarin.
An average life expectancy of patients with AF and stroke (based on stroke severity) is applied upon the occurrence of stroke	Life expectancy of stroke patients is lower than for patients who have not experienced a stroke (2, 3, 58, 63, 122). The assumption is also necessary to avoid high level of complexity and 'tunnel' states associated with time dependency of mortality.
Patients discontinue AC completely upon occurrence of haemorrhagic stroke or SE	Expert opinion (Section 7.3.5)
Other ICH, GI bleeds, non-ICH and non-GI related major bleeds	
Patients discontinue AC temporarily for a period of 6 weeks	Aspirin = assumption. Other ACs =

Assumption	Justification
or discontinue completely upon occurrence of other ICH, or other major bleed	Claassen et al 2008 (114)
Apart from the acute mortality associated with other ICH, or other major bleed, no additional impact on mortality is assumed	Clinical opinion
CRNM bleeds	
CRNM bleeds are assumed to have no impact on mortality	Clinical opinion. Non-major bleeds should have no impact on mortality
Patients not receiving anticoagulation are assumed to have no bleeding risk	Clinical opinion
MI	
An average life expectancy of patient with AF and MI (based on gender) is applied upon the occurrence of MI	Necessary to avoid high level of complexity and 'tunnel' states associated with time dependency of mortality following MI.

Abbreviations: AC, anticoagulant; AF, atrial fibrillation; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; MI, myocardial infarction; NOAC, new oral anticoagulant; SE, systemic embolism

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Effects of the condition on patients' quality of life

Atrial fibrillation (AF) is a sustained cardiac arrhythmia (4), and is characterised by an erratic and rapid heartbeat. Patients with AF experience a range of symptoms including; breathlessness, palpitations, dizziness/syncope, chest pain and fatigue. AF leads to deterioration in the mechanical function of the atria preventing complete expulsion of blood from the heart. This lack of movement of blood can lead to the formation of a thrombus (blood clot), which can become mobile and cause systemic embolism (SE). Emboli in the brain may result in an ischaemic stroke.

Ischaemic stroke can have a major impact on the QoL of AF patients. AF increases the risk of stroke, and more than 20% of all strokes are attributed to this arrhythmia (14). Ischaemic strokes in association with AF are often fatal and patients who survive suffer increased levels of disability and longer hospital stays compared with stroke patients without AF (4, 14). Stroke is a primary cause of adult disability, and patients can experience speech and language problems and/or orientation, movement and memory problems.

AF is also associated with an increased risk of systemic embolism (SE) (15) which is associated with acute loss of blood flow to a peripheral artery (ARISTOTLE (2)) which would impact health related QoL.

7.4.2 Change in HRQL over time

A patient with AF is likely to experience a reduction in HRQL if they experience ischaemic stroke. Bleed events were assumed to confer a disutility from baseline whilst being experienced. Thereafter, these patients were assumed to revert to baseline utility.

MI and SE events were assumed to be associated with permanent reductions in patient utility.

HRQL data derived from clinical trials

7.4.3 Description of trial based HRQL data

HRQL data were not collected as part of the ARISTOTLE and AVERROES studies. Disutility associated with dabigatran etexilate during the first 12 months of treatment was collected in the RE-LY QoL sub-study but this information is not publicly available (24).

Mapping clinical trial HRQL data

7.4.4 Description of mapping exercise

Not applicable.

HRQL studies

7.4.5 Literature search to identify HRQL studies

A systematic review was conducted to identify relevant HRQL data from the published literature that could be used to populate health states in the model. In particular EQ-5D health state utility values (in line with the NICE preferred method) relating to adults (≥ 18 years) with AF and adults with AF who have suffered a stroke or systemic embolism. The following electronic databases were searched Medline/Medline (R) In-Process, EMBASE, Econlit and NHS EED. Electronic searches were supplemented by hand searching the following sources; primary sources of utilities used in economic evaluations, relevant NICE submission/appraisal data, conference proceedings and the CEA Registry.

Full details of the databases, conference proceedings, search strategies employed and inclusion/exclusion criteria are presented in Section 10.12. The electronic database searches identified 1,785 publications, of which 151 were potentially relevant. Hand searching of conference proceedings identified four abstracts and one poster and searches of Research Papers in Economics (RePEc), the EQ-5D website and the CEA registry found another four publications. Review of economic studies and bibliographies for the primary source of utilities identified a further 24 studies (Figure 38).

In total, 184 publications were considered for full paper review, of which 160 were excluded on the basis that they did not meet the inclusion criteria (including 46 economic evaluations that were excluded as they were not the primary source of a utility value).

In total 24 publications were identified by the systematic review (Figure 38); 11 full publications (112, 123-132),one poster (133), eight abstracts (134-141) and one economic evaluation (142), all of which presented HRQL (EQ-5D) data in an AF population. An additional three full publications (143-145) were included that reported EQ-5D values for a variety of chronic conditions after controlling for co-morbidities.

Following review of the included studies, there were still some health states for which a utility value had not been identified, therefore the studies included at first pass (n=1,785) were screened again for studies that reported bleeding, stroke or anticoagulation utilities, in an AF population, elicited by methods other than EQ-5D. A further eight studies met the new selection criteria (97, 146-152). In addition, the references quoted in the

rivaroxaban and dabigatran HTA submissions were searched and one further publication was identified (153).

Therefore a total of 33 publications were included in the final dataset, see Appendix 12 (Section 10.12.8) for complete list.

7.4.6 HRQL studies identified

Of the 33 publications identified by the systematic review and searches of the rivaroxaban and dabigatran HTA submissions, 18 reported utility values for health states used in the economic model. A summary of these 18 studies is provided in Table 109.

7.4.7 Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

Not applicable.

Adverse events

7.4.8 The impact of adverse events on HRQL

Adverse events that patients would consider significant, events that impact on areas of their HRQL such as mobility and pain, reduce the patients QoL. In the economic model death has a health state utility (HSU) of 0.0 and perfect health has a HSU score of 1.0. Decrements (reductions in health state utilities) are subtracted from the patient's pre adverse event health status for the applicable period. For example, a patient experiencing an 'other major bleed' would have a reduction of 0.159 in their utility for a period of 6 weeks. See section 6.4.9 for all the decrements applied in this economic evaluation.

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

7.4.9 Summary of HRQL values used

The utility values used in the cost-effectiveness analysis are summarised in Table 61.

Patients were assigned utilities according to their health states. A baseline utility was applied to all patients, based on a utility score specific for patients with AF. Utilities were updated upon the occurrence of stroke with different utility scores for different severity levels. Similarly utilities were applied for SE and MI. Utility decrements were applied to patients upon the occurrence of other ICHs, other major bleeds, CRNM bleeds, and CV hospitalisations (unrelated to stroke and MI) for a duration specific to each event (Table 61).

Table 61: Summary of quality of life values for cost-effectiveness analysis

State	Utility value	Source	Justification
Baseline AF	0.7800	Khan et al, 2004	The only EQ-5D utility from UK based study
Stroke		Gage et al, 1996 (149)	It is the only study reporting stroke severity for mild, moderate and severe as defined by the mRS
Mild	0.7600		
Moderate	0.3900		

Severe	0.1100		
Haemorrhagic stroke		Gage et al, 1996 (149)	It is the only study reporting stroke severity for mild, moderate and severe
Mild	0.7600		
Moderate	0.3900		
Severe	0.1100		
Systemic embolism	0.6795	Sullivan et al, 2011 (145)	Only source identified
MI	0.6830	Lacey et al, 2003 (153)	No UK based studies using EQ5D identified via the systematic review had a MI utility value. This study was identified from a search of references quoted in the rivaroxaban STA submission
State	**Utility decrement duration**	**Source**	**Justification**
Other ICH (applied upon the occurrence for a duration of six weeks)	0.1070	Thomson et al, 2000 (152)	Only source identified
	6 weeks	Expert opinion	
Other major bleeds	0.1070	Thomson et al, 2000 (152)	Only source identified
	2 weeks	Expert opinion	
CRNM bleeds	0.0582	Sullivan et al, 2011 (145)	Only source identified
	2 days	Expert opinion	
Other CV hospitalisation	0.0970	Used MI decrement	Assumption
	6 days	Expert opinion	
Anticoagulation	**Utility decrement**	**Source**	**Justification**
Apixaban	0.0020	Gage et al 1996 (149)	Anticoagulants were assumed to have an adverse impact on HRQL (for duration of treatment). Warfarin is assumed to have the highest decrement due to the requirement for routine INR monitoring and the multiple food and drug interactions. As in previous appraisals NOACs are also assumed to confer disutility upon patients – this is assumed to be at the same level as aspirin. In the Dabigatran STA the ERG recommended accounting for disutility for all anticoagulants.
Aspirin	0.0020		
Aspirin (2nd line)	0.0020		
Warfarin	0.0130		
Dabigatran (110mg)	0.0020		
Dabigatran (150mg)	0.0020		
Rivaroxaban	0.0020		

Abbreviations: AF, atrial fibrillation; CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction

7.4.10 Input from clinical experts

Clinical experts were used to estimate the duration of the utility decrement for patients experiencing other ICH, other major bleed, CRNM bleed and other CV hospitalisation. See section 7.3.5 for elicitation methods used.

7.4.11 HRQL experienced in each health state

The decrements associated with each health state are presented in section 7.4.9. The disutility is subject to between subject variance which is accounted for in this economic evaluation by conducting probabilistic sensitivity analysis.

7.4.12 Health effects excluded from the analysis

Transient ischaemic attack (TIA) is not considered in the analysis as data were not collected on this event in the ARISTOTLE clinical trial.

7.4.13 Baseline HRQL

Baseline QoL in the NVAF and NVAF w/o original anticoagulation health states was 0.780 based on published data from Khan et al (112). Patients with NVAF in UK clinical practice have a mean age of approximately 77 years (26) and typically suffer multiple co-morbidities. It is unsurprising therefore that baseline QoL is less than perfect health.

7.4.14 Changes in HRQL over time

Patients HRQL was assumed to change upon the occurrence of an event as described in 7.4.9. However, within each health state, HRQL was assumed to be constant.

7.4.15 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.

In order to produce a utility associated with systemic embolism, a decrement of -0.1004733 (145) was assumed from baseline NVAF (0.780 (112)). This resulted in a utility for systemic embolism patients of 0.6795.

The difference between MI (utility: 0.6830 (153)) and baseline NVAF (utility: 0.780) was taken as the utility decrement for other CV hospitalisation. The resulting utility decrement was 0.0970.

Similarly, to provide a utility decrement for other ICH and other major bleeds, a utility decrement of 0.1070 was estimated based on the difference between major bleed and baseline AF (152).

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 How is the clinical management of the condition currently costed in the NHS?

Table 63 to Table 73 below contain the health states, unit costs, where applicable the Health Resource Group (HRG) procedure codes and how the costs were calculated. All costs are presented in 2010/11 pounds. Where possible the HRG codes were selected

based on those employed in the NICE CG36 AF costing report (51); some codes have changed since publication of the guideline in 2006. Where HRG codes did not correspond to the resource use considered in the model, unit costs were obtained from the published literature, for example type of stroke and stroke severity.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

In the base case 2010/11 NHS reference costs are used where possible. Where procedures do not have HRG codes or the codes are not sufficiently disaggregated, such as long term care and type and severity of stroke, unit costs have been identified from the published literature. Payment by Result (PbR) Tariffs are used in a sensitivity analysis.

Resource identification, measurement and valuation studies

7.5.3 Literature search to identify resource data

A systematic review was not conducted to identify resource data from the published literature. Resource use was identified via existing technology appraisals for AF and studies identified in the cost-effectiveness and quality of life systematic reviews.

7.5.4 Input from clinical experts

Clinical expert opinion was not sought regarding the selection of cost data.

7.5.5 Intervention and comparators' costs

Costs for the interventions are provided in Table 62.

Table 62: Intervention costs

Anticoagulant	Tablet size (mg)	Cost per tablet	Average daily dose (mg)	Average daily cost	Source
Apixaban	5	£1.10	10	£2.20	BMS/Pfizer
Aspirin (gastro-resistant tablets)	75	£0.03	150	£0.07	Electronic Drug Tariff‡
Warfarin	0.5, 1.0, 3.0	£0.40	4.5	£0.12	Electronic Drug Tariff‡
Dabigatran 110mg	110	£1.10	220	£2.20	MIMS†
Dabigatran 150mg	150	£1.10	300	£2.20	MIMS†
Rivaroxaban	20	£2.10	20	£2.10	MIMS†

‡Electronic Drug Tariff, August 2012, Department of Health by the NHS Business Services Authority, NHS Prescription Services, http://www.ppa.org.uk/ppa/edt_intro.htm; †MIMS, August 2012

INR monitoring

Patients treated with warfarin were assigned costs for INR monitoring. In order to reflect the cost of monitoring accepted by NICE during previous appraisal processes, the evidence review group 2009/10 estimate of £241.54 per year from the dabigatran single technology appraisal (102) was uplifted to 2010/11 prices using the Pay & Prices Index (154) to provide an estimate of £248.19 per year. It was assumed that 18 monitoring

visits would be required per year, providing an estimated cost per visit of £13.79 (NHS reference costs 2009-10, NHS Trusts and PCTs combined, consultant led (155)).

Renal monitoring

The cost of renal monitoring was assumed to be £3 based on direct access pathology services DAP283 Haematology (156). This was cost was applied to 19.4% (58) of dabigatran patients only.

7.5.6 Health-state costs

Stroke

Post-stroke resource use and costs are separated into acute and long-term maintenance phases. Acute phase comprises the time spent in hospitalisation and rehabilitation facilities. Patients stay in the maintenance phase until death.

Acute costs

The acute costs of stroke by stroke severity were uplifted (154) from the estimates provided by Luengo-Fernandez et al, 2012 (157). Table 63 presents the acute costs of stroke, in addition to the estimated upper and lower bounds used within sensitivity analysis. Costs were assumed to depend on the severity of stroke and are per episode.

Table 63: Stroke acute costs (per episode)

	Cost	Sensitivity lower	Sensitivity upper	Source
Stroke (excluding haemorrhagic				
Mild	£3,515.64	£1,495.45	£5,535.83	Luengo-Fernandez et al, 2012 (157)
Moderate	£18,341.08	£13,375.22	£23,307.04	
Severe	£25,050.88	£17,055.07	£33,046.68	
Fatal	£3,162.11	£2,046.39	£4,277.84	
				Haemorrhagic stroke
Mild	£10,236.81	£6,150.44	£14,323.18	Luengo-Fernandez et al, 2012 (157)
Moderate	£26,299.60	£15,029.26	£37,569.94	
Severe	£44,486.65	£22,688.59	£66,284.71	
Fatal	£1,645.66	3294.70	£2,996.62	

[†]Uplifted using Pay & Prices Index (154).

Long-term maintenance costs

The long-term costs of stroke by stroke severity were uplifted (154) from the estimates provided by Luengo-Fernandez et al, 2012 (157). Table 64 presents long-term costs of stroke, in addition to the estimated upper and lower bounds used within sensitivity analysis. Costs were assumed to depend on the severity of stroke and are per month with a life time duration. Although long-term costs are applied on a 6 weekly basis in the model (cycle length duration) they are presented on a monthly basis in Table 64 as this

duration is more familiar to clinicians and prescribers. The same long term costs were used for ischaemic and haemorrhagic stroke.

Table 64: Stroke event long-term costs (per month)

	Cost	Sensitivity lower	Sensitivity upper	Source
Stroke (excluding haemorrhagic stroke)				
Mild	£183.91	£107.54	£260.29	Luengo-Fernandez et al, 2012 (157)
Moderate	£358.78	£188.79	£528.78	
Severe	£544.76	£0.00	£1,270.87	
Haemorrhagic stroke				
Mild	£183.91	£107.54	£260.29	Luengo-Fernandez et al, 2012 (157)
Moderate	£358.78	£188.79	£528.78	
Severe	£544.76	£0.00	£1,270.87	

SE

Post-SE resource use consists of acute care and maintenance costs accrued over a patient's lifetime.

Table 65: Costs of SE

	Cost	Unit	Duration	Source
Acute care	£4,077.98	Per episode	2 weeks	Luengo-Fernandez et al, 2012 (157)
Long-term maintenance	£183.91	Per month	Lifetime	

MI

Post-MI resource use consists of acute care and maintenance costs accrued over a patient's lifetime.

Acute costs

The acute cost of MI was estimated as £1,623 based on NHS Reference Costs currency code for 'Actual or Suspected Myocardial Infarction' (EB10Z) (156), (Table 66).

Table 66: MI acute costs

HRG code	HRG description	Activity	National average unit cost	Lower quartile	Upper quartile
EB10Z	Actual or Suspected MI	56,377	£1,623	£1,154	£1,911

Additional costs of £396 (cardiac rehabilitation and coronary revasculation assessment for all patients) were applied for 12 months following MI, as described in Table 67.

Table 67: Additional MI costs

Component	Unit cost	Source	% patients†	Expected cost
Cardiac rehabilitation	£463	Total cost per patient referred (158). Uplifted from 2000/2001 to 2010/11 using Pay & Prices Index (154).	56%	£259.04
Coronary revasculation assessment	£175	320 Cardiology from NHS Trusts and PCTs combined Consultant Led: First Attendance Non-Admitted Face to Face (156).	78%	£136.50
Total cost for year 1 only				**£395.54**

†NICE CG48 costing report(159)

Total acute care costs for MI were therefore estimated as £2,019.

Long-term pharmacological costs

The long-term pharmacological costs of MI were estimated as £6.65 per month (£79.80 per year) based on the co-prescribing of an ace-inhibitor, a beta-blocker and a statin for all patients following a MI (
Table 68).

Table 68: Long-term costs of pharmaco-management of MI

Therapy	Strength	Pack size	Pack price	Price per pill	Daily dose	Pills per day	Monthly cost†	Share of prescript-ions	Weighted monthly cost‡
Beta-blocker (Atenolol)	25mg tablet	28	£0.79	£0.03	100mg	4	£3.43	31.75%	£2.19
	50mg tablet	28	£0.82	£0.03		2	£1.78	53.94%	
	100mg tablet	28	£0.88	£0.03		1	£0.96	14.30%	
ACE inhibitor (Ramipril)	1.25mg capsule	28	£1.09	£0.04	10mg	8	£9.47	8.91%	£2.80
	2.5mg capsule	28	£1.17	£0.04		4	£5.08	23.36%	
	5mg capsule	28	£1.29	£0.05		2	£2.80	27.38%	
Statin (simvastatin)	10mg tablet	28	£0.87	£0.03	40mg	4	£3.78	6.12%	£1.66
	20mg tablet	28	£0.96	£0.03		2	£2.09	26.28%	
	40mg tablet	28	£1.20	£0.04		1	£1.30	67.60%	

Total		£6.65

Abbreviations: MI, myocardial infarction; †30.444 days per month, weighted average (160); ‡Electronic Drug Tariff, August 2012, Department of Health by the NHS Business Services Authority, NHS Prescription Services , http://www.ppa.org.uk/ppa/edt_intro.htm; Monthly costs are transformed to 6 weekly costs when they are applied in each cycle of the model

Other events

Other ICH

The costs of other ICH was taken from NHS Reference Costs as the average of AA23A and AA23B (Haemorrhagic Cerebrovascular Disorders with and without complications respectively) weighted by activity. This provided a cost of £3,010 and is detailed in Table 69.

Table 69: Cost per other ICH event

HRG code	HRG description	Activity	National average unit cost
AA23A	Haemorrhagic Cerebrovascular Disorders with CC	18,713	£3,069
AA23B	Haemorrhagic Cerebrovascular Disorders without CC	1,274	£2,149
Weighted average			**£3,010**

Abbreviations: CC, complication and co-morbidity; ICH, intracranial haemorrhage

GI bleeds

The costs of GI bleeds were based on the average cost of FZ38D, FZ38E and FZ38F, weighted by activity. This provided an estimated cost of £1,494 per event (Table 70).

Table 70: Cost of GI bleeds

HRG code	HRG description	Activity	National average unit cost
FZ38D	Gastrointestinal bleed with length of stay 2 days or more with Major CC	11,820	£2,011
FZ38E	Gastrointestinal bleed with length of stay 2 days or more without Major CC	14,227	£1,312
FZ38F	Gastrointestinal bleed with length of stay 1 day or less	3,350	£440
Weighted average			**£1,494**

Abbreviations: CC, complication and co-morbidity; GI, gastrointestinal

Non-ICH and non-GI related major bleeds

The cost of non-ICH and non-GI related major bleeds was estimated as £3,948. The HRG codes, average unit cost and activity for each code are shown in Table 71.

Table 71: Cost of non-ICH and non-GI related major bleeds

HRG code	HRG description	Activity	National average unit cost
HC28B	Spinal Cord Conditions with CC	1,258	£5,942
HC28C	Spinal Cord Conditions without CC	1,449	£3,475
HD24A	Non-Inflammatory Bone or Joint Disorders with Major CC	3,652	£3,439
BZ24A	Non-Surgical Ophthalmology with length of stay 2 days or more	6,904	£2,130
PA23A	Cardiac Conditions with CC	2,840	£4,414
FZ12D	General Abdominal - Very Major or Major Procedures 19 years and over with Major CC	4,164	£6,362
FZ12E	General Abdominal - Very Major or Major Procedures 19 years and over with Intermediate CC	1,838	£4,748
FZ12F	General Abdominal - Very Major or Major Procedures 19 years and over without CC	3,138	£3,865
Weighted average			**£3,948**

Abbreviations: CC, complication and co-morbidity; GI, gastrointestinal; ICH, intracranial haemorrhage

CRNM bleeding

The estimation of the cost of CRNM bleeding is detailed in Table 72.

Table 72: Cost of CRNM bleeds

Currency code	Currency description	Activity	National average unit cost
FZ38F	Gastrointestinal Bleed with length of stay 1 day or less	3,350	£440
CZ13Y	Intermediate Nose Procedures 19 years and over without CC	526	£994
LB38B	Unspecified Haematuria without Major CC	7,355	£1,460
Weighted average			**£1,134**

Abbreviations: CC, complication and co-morbidity; CRNM, clinically relevant non-major

Table 73: Cost of Other CV hospitalisation

Currency Code	Currency Description	Activity	National average unit cost
AA29A	Transient Ischaemic Attack with CC	13,028	£1,307
AA29B	Transient Ischaemic Attack without CC	612	£933
PA22Z	Chest Pain	502	£1,005
QZ20Z	Deep Vein Thrombosis	10,413	£1,561
EB03H	Heart Failure or Shock with CC	34,842	£2,758

Currency Code	Currency Description	Activity	National average unit cost
EB03I	Heart Failure or Shock without CC	38,080	£1,861
QZ17A	Non-Surgical Peripheral Vascular Disease with Major CC	1,182	£4,658
QZ17B	Non-Surgical Peripheral Vascular Disease with Intermediate CC	11,637	£2,612
QZ17C	Non-Surgical Peripheral Vascular Disease without CC	2,780	£1,831
EB01Z	Non interventional acquired cardiac conditions	116,500	£1,016
Weighted average			**£1,571**

Abbreviations: CC, complication and co-morbidity

7.5.7 Adverse-event costs

Dyspepsia

The annual cost of dyspepsia was assumed to be £27.60. This was composed of the following costs:

- Endoscopy. Total cost £6.12 based on 1% referral for endoscopy (161) and a cost of £612 per endoscopy procedure (HRG FZ42Z Wireless Capsule Endoscopy) (156)
- GP visits. Total cost £1.80 based on 5% referral rate for GP visits (161) and a cost of £36 per GP visit (154).
- Drug costs. The proton pump inhibitors licensed for dyspepsia are omeprazole and lansoprazole. Analysis of prescribing data for omeprazole and lansoprazole (160) showed that only three packs accounted for 95.7% of all prescriptions of the two medicines; the cost of each was weighted by the number of prescriptions issued (Table 74) to derive a weighted mean cost of £1.64 per month (£19.64 per year).

Table 74: Pharmacological therapies in management of dyspepsia

Therapy	Strength*	Pack size	Cost	Price per pill	Average daily dose	Pills per day	Monthly cost†	Share of prescrip-tions	Weighted monthly cost‡
Ome-prazole	10 mg	28	£1.54	£0.06	10mg	1	£1.67	7.83%	£1.64
	20 mg	28	£1.57	£0.06	20mg	1	£1.71	68.72%	
Lanso-prazole	15 mg	28	£1.31	£0.05	15mg	1	£1.42	23.46%	

*Only 10mg and 20mg doses of omeprazole are licensed for dyspepsia; †Monthly cost for each pack size; §Share of all omeprazole and lansoprazole prescriptions (160); Monthly costs are transformed to 6 weekly costs when they are applied in each cycle of the model; Electronic Drug Tariff, August 2012

7.5.8 Miscellaneous costs

No additional costs have been used.

7.5.9 Costs summary

A summary of all the costs used in the analysis is provided in Table 75. The description of how these costs have been derived is provided in section 7.5.6–7.5.7.

Table 75: Summary of costs

Item		Duration	Cost
Apixaban cost		Daily	£2.20
Warfarin cost		Daily	£0.12
Dabigatran 110 mg cost		Daily	£2.20
Dabigatran 150 mg cost		Daily	£2.20
Rivaroxaban cost		Daily	£2.10
Aspirin cost		Daily	£0.07
Ischaemic stroke	Mild acute	One-off	£3,515.64
	Mild follow-up	Monthly	£183.91
	Moderate acute	One-off	£18,341.08
	Moderate follow-up	Monthly	£358.78
	Severe acute	One-off	£25,050.88
	Severe follow-up	Monthly	£544.76
	Mortality		
Haemorrhagic stroke	Mild acute	One-off	£10,236.81
	Mild follow-up	Monthly	£183.91
	Moderate acute	One-off	£26,299.60
	Moderate follow-up	Monthly	£358.78
	Severe acute	One-off	£44,486.65
	Severe follow-up	Monthly	£544.76
	Mortality		
SE	Acute	One-off	£4,077.98
	Long-term	Monthly	£183.91
INR monitoring		Annual	£248.19
Dyspepsia management		Annual	£27.57
Renal monitoring		Annual	£3.00
MI	Acute	One-off	£2,018.84
	Follow-up	Monthly	£6.65
Other ICH		One-off	£3,010
Other CV Hospitalisation			
GI bleed		One-off	£1,494
Non-ICH and non-GI related Major bleeds		One-off	£3,948

Item	Duration	Cost
CRNM bleed	One-off	£1,134

Abbreviations: CRNM, clinically-relevant non-major; GI, gastro-intestinal; ICH, intracranial haemorrhage; INR, International normalised ratio; MI, myocardial infarction; Monthly costs are transformed to 6 weekly costs when they are applied in each cycle of the model

7.6 Sensitivity analysis

7.6.1 Uncertainty around structural assumptions

The model was developed with reference to the recent models designed to support the dabigatran and rivaroxaban technology appraisals (24, 103). The dabigatran and rivaroxaban models were considered to have an acceptable structure when evaluated by the ERGs (102, 104). We do not believe that there is structural uncertainty relating to the model.

7.6.2 Deterministic sensitivity analysis

One-way/univariate and multi-way sensitivity analyses were performed to examine the effects of changes in key model parameters. Deterministic sensitivity analysis was performed where each parameter was varied according to the measure of dispersion (95% confidence intervals and standard deviations where applicable) or as scenarios where specific values were selected, while holding all other parameters constant (Table 76). Where confidence intervals and standard deviations were unavailable, the standard deviation was assumed to be 25% of the mean. The limits identified for the sensitivity analysis are conservative and in some cases are clinically unrealistic. The one-way sensitivity analysis variables are provided in Appendix 18 (Section 10.18).

Table 76: Deterministic scenario analysis

Scenarios
Recurrent stroke (ischaemic and haemorrhagic) switched off
Trial mortality switched off
Long term mortality based on general public (AF correction switched off, HR=1)
Discontinuation set same as apixaban
Discount costs and benefits at 6% and 1.5% respectively
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic), SE cost and long-term maintenance costs equal to Youman et al (2002) (inflated to 2010/11 costs)
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and SE cost equal to NHS reference cost of stroke (estimated as £2,952 based on weighted average of AA04A, AA04B, A10A, AA10B, AA16A, AA16B,AA22A, AA22B, AA23A, AA23B; cost of fatal stroke cost=£0)
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and SE cost equal to PBR Tariff costs of stroke (estimated as £4,231 based on weighted average of AA04Z,AA10Z,AA16Z,AA22Z,AA23Z, cost of fatal stroke=£0)
Reduce health state utility decrements for Other ICH, Other Major Bleeds and CRNM Bleeds by 25%
Reduce utility values for ischaemic and haemorrhagic stroke and SE health states by 25%
Assume same (apixaban) stroke severity distribution for all interventions (mild, moderate, severe & fatal)
Age = 80, risks calculated using cTTR specific data, 100% of patients have cTTR >76.51%, All drugs have same stroke severity distribution, trial mortality off, no cost for fatal strokes, NHS

Scenarios
reference costs used for stroke and systemic embolism, utility decrements associated with bleeding reduced by 25%
Age = 70, risks calculated using cTTR specific data, 100% of patients have cTTR < 52.38%, costs of stroke and systemic embolism inflated by 15%
Apply warfarin disutility of 0.013 to all NOACs
Apply disutility of 0.0 to all anticoagulants
Gallagher et al. (2008) (26) baseline characteristics
Treatment Choice Post Other ICH/Other Major Bleeds – No treatment
Treatment Choice Post Other ICH/Other Major Bleeds – Warfarin
2nd line (after failure on warfarin)

7.6.3 Probabilistic sensitivity analysis

In order to account for variability in outcomes due to statistical uncertainty in inputs, a probabilistic sensitivity analysis (PSA) was performed. The model was run for 2,000 simulations to generate ICERs by varying event rates, costs, risks and utilities simultaneously. Time horizon, population characteristics and model settings were kept constant. Key inputs were varied from replication to replication by sampling from probability distributions. A number of probability distributions were employed including the beta, lognormal, uniform, gamma, and Dirichlet distributions.

Probabilities

The probabilities used in the model were based on the proportion of the observed outcomes of interest (for example, proportion of haemorrhagic strokes among ICH, with the patients with haemorrhagic strokes considered as events and patients without haemorrhagic stroke considered as non-events). It was therefore possible to assume a binomial distribution form with the number of events denoting the probability used in the model. Rather than using a frequentist approach to generating confidence intervals through a normal distribution which could lead to observations below 0 or above 1, a beta distribution was chosen for probabilities as it is a conjugate of the binomial and is bounded by 0 and 1 (162). The parameterisation of the beta used consists of denoting the shape parameter (i.e., alpha) as the number of events (haemorrhagic stroke observations in this example) and the scale parameter (i.e., beta) as the number of non-events (non-haemorrhagic stroke observations). The source of variation where probabilities were involved was therefore patient numbers obtained from the trials or published estimates.

Distributions

Some probabilities used in the model however cannot be described by positive and negative occurrences (event and non-event), but were however used to describe the distribution of patients amongst a number of different occurrences (e.g., in the case of assigning stroke severity where patients are segregated by mild, moderate, severe and fatal). The distribution of severity was important to include in the PSA as it varied by comparators. In addition, as noted in the methods section, alternative costs, relative risks of deaths, and utilities were assigned according to the severity level so it was imperative to capture the uncertainty around them. The Dirichlet distribution, a multivariate generalisation of the beta distribution was used for these parameters as it allowed for a

number of categories to be fit in a probabilistic manner. We followed a normalised sum of independent gamma or normal variable as described in Briggs et al. 2003 (163). This involved generating the number of patients in each of the mild, moderate, severe and fatal health states in each simulation and calculating the proportion in each health state from their total sum. A gamma distribution was used to generate the patient numbers using the number of patients observed in each category as the shape parameter (i.e., alpha) and 1 as the scale parameter (i.e., beta). Alternatively a normal distribution was used using the number of patients observed in each category as the mean and the square root of the number of patients as the standard deviation. The gamma was chosen when patient numbers were small to avoid the normal generating negative patient numbers.

Costs

With resource use and unit costs it was imperative that the distribution chosen had a lower bound of 0 to avoid the generation of any "negative" costs. The gamma distribution is therefore often used due to its constrained intervals. Standard deviations were used along with the mean to obtain the shape and scale parameters of the gamma distribution. Alternatively the lognormal distribution can be used. Both distributions can be highly skewed to reflect the natural skew in costs (163). Where standard deviations were not available, the standard deviations were derived from the 95% confidence intervals. Alternatively a 25% standard deviation of the mean was assumed. The distribution used was selected based on how well the confidence intervals produced by the distributions replicated the input values (95% confidence intervals and SEs).

HRs

For HRs, due to the nature of calculation of the confidence intervals of these parameters in the clinical trials in which the central limit theorem was employed, the natural logarithm of the parameters can often be normally distributed. A log-normal distribution was therefore used where it could replicate the confidence intervals generated from the trials. For example the stroke HR for dabigatran 110mg is 1.2 (95% CI 0.9-1.6). By assuming a standard deviation for the lognormal distribution of 0.156 the lognormal distribution will generate a 95% CI of 0.88-1.63 which is similar to the estimated HR intervals and therefore considered a good fit. If the bounds generated by the distribution did not replicate the inputs well the fit wasn't considered to be good.

A gamma distribution was compared against the log-normal to evaluate which would provide a better fit. A gamma distribution was deemed suitable for HRs due to its ability to generate only positive values. As confidence intervals were available for some of these parameters the standard deviations were derived to obtain the same confidence intervals from the distributions as those reported.

For relative risks of death, the gamma distribution was used assuming a 25% standard deviation of the mean. For the relative risk of death for AF patients, a uniform distribution was assumed with a hazard ratio of 1.34 derived from Friberg et al (2007) (12) (literature identification summarised in Zhang et al (2012) in appendix 16). The paper calculates the increase risk in death for AF patients including factors like stroke. The model already incorporates the increased risk in mortality due to strokes and bleeds therefore this risk was used as the absolute upper bound.

Utilities

For utilities, a beta distribution was used due to the bounds of the distribution (i.e., 0 to 1). Standard deviations were taken from the published literature and in some cases the published papers provided the shape and scale parameters of the distribution.

Other model parameters such as time horizon, population characteristics, anticoagulant costs, duration of utility decrements, and resource use were not varied. The PSA parameters are provided in Appendix 19 (Section 10.19).

7.7 Results

Clinical outcomes from the model

7.7.1 Summary of clinical outcomes from the model

Clinical trial results are compared against model outcomes in Table 77 and Table 78 for VKA suitable and VKA unsuitable patient populations respectively. The characteristics of the trial populations were assumed for this comparison (age, gender and $CHADS_2$ distribution).

In the VKA suitable population the number of predicted events was higher than reported in the ARISTOTLE trial, but the incremental difference between interventions was lower than seen in the trial or similar. In the VKA unsuitable population the incremental differences between interventions from the model were higher for ischaemic stroke and summed stroke and SE estimates, and lower for haemorrhagic stroke and SE. An additional 11 strokes were estimated by the model which equates to an overestimate of 0.4% (11/2,791). The model provides a good approximation of the clinical trials. The differences between the trials and the model are believed to be a consequence of assuming the subsequent treatment choice of aspirin in the model for VKA suitable patients (whilst in the trial some patients would have gone on to warfarin which has superior efficacy).

Table 77: Model results compared with clinical data in VKA suitable population

Outcome	ARISTOTLE Events‡			Model events†		
	Apixaban (N=9,120)	Warfarin (N=9,081)	Increment-al events on Warfarin	Apixaban (N=9,120)	Warfarin (N=9,081)	Incremental events on Warfarin
Primary outcome: stroke or SE	212	265	53	260§	307§	47
Stroke	199	250	51	240§	286§	46
Ischaemic or uncertain type	162	175	13	199	207	8
Haemorrhagic	40	78	38	41	79	38
SE	15	17	2	20	21	1
Death – any cause	603	669	66	593	665	72

Abbreviations: SE, systemic embolism; VKA, Vitamin K antagonist; yr, year.
†Approximation estimated at 1.84 years and patient characteristics from ARISTOTLE; ‡From Table 110
§Sum of individual events

Table 78: Model results compared with clinical data in VKA unsuitable population

Outcome	AVERROES Events‡			Model events†		
	Apixaban (N=2,808)	Aspirin (N=2,791)	Increment-al events on Aspirin	Apixaban (N=2,808)	Aspirin (N=2,791)	Incremental events on Aspirin
Primary outcome: stroke or SE	51	113	62	58§	131§	73
Stroke	49	105	56	55§	122§	67
Ischaemic	35	93	58	49	116	67
Haemorrhagic	6	9	3	6	6	0
SE	2	13	11	3	9	6
Death – any cause	111	140	29	112	138	26

Abbreviations: SE, systemic embolism; yr, year.
†Approximation estimated at 1.15 years and patient characteristics from AVERROES; ‡From Table 110
§Sum of individual events

7.7.2 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.

Simplified Markov traces are presented in Appendix 20 (Section 10.20) for all comparators and the VKA suitable and unsuitable populations.

7.7.3 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.

Simplified Markov traces are presented in Appendix 20 (Section 10.20) for all comparators and the VKA suitable and unsuitable populations.

7.7.4 Life years and QALYs accrued for each clinical outcome

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. For example:

Clinical outcomes are associated with the health states in the model. Costs and QALYs for each health state/clinical outcome are presented in 6.7.5.

7.7.5 Disaggregated incremental QALYs and costs

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.

Disaggregated QALYs by health state, the number of patients in each health state and disaggregated costs by health state for VKA suitable and VKA unsuitable patient populations respectively are resented in appendix 21 (section10.21).

Base case analysis

7.7.6 Summary of results

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.

Base case results are presented in Table 79 and Table 80. In the VKA suitable population, apixaban was associated with an ICER of £11,008 vs warfarin. Dabigatran 110 mg is dominated by dabigatran 150 & 110 mg. Apixaban extendedly dominates dabigatran 150 & 110 mg and rivaroxaban in the incremental analysis, and the ICER is therefore estimated against warfarin again as £11,008.

Table 79: Base-case results – VKA suitable population

Technol-ogies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) versus warfarin	ICER (£) incremental
	Costs (£)	LYG	QALY	Costs (£)	LYG	QALY				
Warfarin	£7,188	7.469	5.696							
Dabigatran (150/ 110 mg)	£8,437	7.537	5.788	£1,248	0.068	0.091	£581	£1,495	£13,648	Extendedly dominated
Dabigatran (110mg)	£8,684	7.503	5.756	£247	-0.034	-0.032	-£314	£277	£25,308	Strictly Dominated
Rivaroxaban	£8,778	7.553	5.809	£95	0.050	0.054	£670	£1,800	£14,071	Extendedly dominated
Apixaban	£8,983	7.614	5.860	£205	0.06	0.05	£1,466	£3,096	£11,008	£11,008

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit.
†Versus the next least costly technology

In the VKA unsuitable population, apixaban was associated with an ICER of £2,903 vs. aspirin. The incremental ICER for apixaban versus rivaroxaban is estimated as £8,401. At thresholds of £20,000 and £30,000 per QALY apixaban was the most cost-effective, providing the highest incremental net monetary benefit.

Table 80: Base-case results – VKA unsuitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus aspirin	ICER (£) incremental
	Costs (£)	LYG	QALY	Costs (£)	LYG	QALY				
Aspirin	£7,916	7.063	5.354							
Dabigatran (150 & 110 mg)	£8,228	7.357	5.635	£312	0.294	0.281	£5,309	£8,120	£1,111	£1,111
Dabigatran (110mg)	£8,531	7.311	5.592	£303	-0.046	-0.043	£4,144	£6,524	£2,587	Strictly Dominated
Rivaroxaban	£8,608	7.367	5.651	£77	0.056	0.060	£5,259	£8,235	£2,326	£23,027
Apixaban	£8,870	7.410	5.683	£262	0.043	0.031	£5,622	£8,910	£2,903	£8,401

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit.
†Vs the next least costly technology

The results show that apixaban is associated with the highest number of life-years gained (LYGs) and QALYs of all technologies included within the evaluation. Apixaban is also associated with the greatest total cost; although apixaban is associated with cost savings accruing from a reduced number of events, apixaban also has the lowest discontinuation rate of any of the therapies evaluated. These patients are therefore at less risk of moving to the (less costly) 2nd-line aspirin arm of the model and consequently incur higher anticoagulant costs.

Apixaban was the most cost-effective intervention producing the highest net monetary benefit at £20,000 and £30,000 per QALY in the VKA suitable and unsuitable populations. The cost effectiveness results for apixaban compared with dabigatran and rivaroxaban in the VKA unsuitable population should be interpreted with caution. Neither comparator has data in this specific patient population, and so the indirect comparison used in the cost-effectiveness model had to impute efficacy estimates from a different VKA suitable population (RE-LY and ROCKET trials). As was observed with apixaban, the efficacy results from the AVERROES trial (VKA unsuitable) show fewer QALYs compared with that from the ARISTOTLE trial (VKA suitable). The same would be expected for dabigatran and rivaroxaban if these data had been available, which would have resulted in more negative cost-effectiveness results.

Sensitivity analyses

7.7.7 Deterministic sensitivity analysis

Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The tornado diagram presents the 13 most influential parameters on cost-effectiveness from the 117 tested. See Appendix 18 (Section 10.18) for all parameters and values.

Figure 17 presents the tornado diagram for the VKA suitable population versus warfarin. Of parameters varied, the 6 parameters most influential on the ICER were:

- Disutility associated with warfarin use (ICER: £8,529–£15,518)
- The HR of ICH for warfarin vs apixaban (ICER: £8,149–£14,027)
- The HR of ischaemic stroke for warfarin vs apixaban (ICER: £8,518–£14,056)
- AF trial HR other (ICER: £9,049–£13,854)
- INR monitoring visit cost (ICER: £9,620-£13,917)
- Discount rate of QALYs (ICER: £8,659-£12,777)

No parameter generated an ICER exceeding £20,000. This suggests the results are robust, especially as some of the lower limits are conservative and less likely to be clinically representative e.g. the lower limit for warfarin ICH risk (ICER = £14,056) assumes 24% less strokes than apixaban. Full details of ranges varied and ICERs estimated are presented in Appendix 18 and 22 (Sections 10.18 and 10.22).

Figure 17: Tornado diagram demonstrating the effect on the ICER for apixaban vs. warfarin of varying parameter inputs in the VKA suitable population

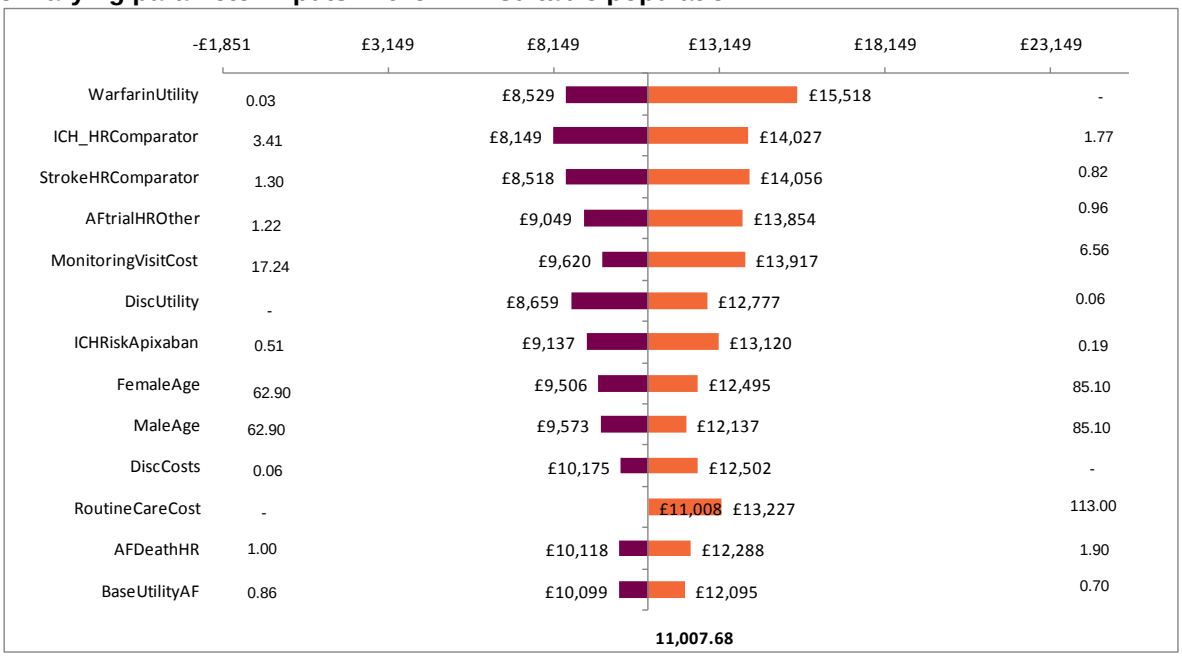


Figure 18 presents the tornado diagram for the VKA unsuitable population versus aspirin. Of parameters varied, the 5 parameters most influential on the ICER were:

- The HR of ischaemic stroke for aspirin vs apixaban (ICER: £63–£7,689)
- The absolute risk of ischaemic stroke for apixaban (ICER: £724–£6,528)
- The age of females within the model (ICER: £1,461–£3,921)
- The HR of systemic embolism for aspirin vs apixaban (ICER: £817–£3,169)
- The age of males within the model (ICER: £1,663–£3,661)

None of these parameters generated ICERs which exceeded £20,000. This suggests the results are robust, especially as some of the lower limits are conservative and less likely to be clinically representative. Full details of ranges varied and ICERs estimated are presented in Appendix 22 (Section 10.22).

Figure 18: Tornado diagram demonstrating effect on ICER vs aspirin of varying parameter inputs in VKA unsuitable population

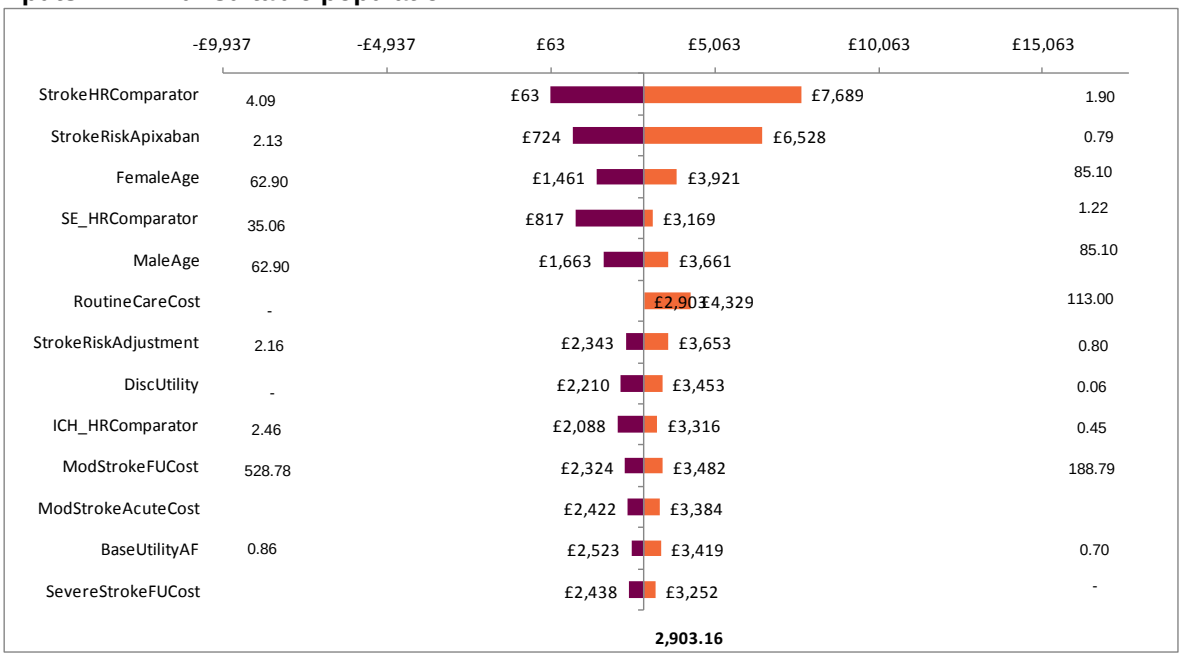


Figure 19 to Figure 24 present the tornado diagrams for apixaban versus dabigatran and rivaroxaban. Parameters which consistently appear to have an influential effect on cost-effectiveness include:

- The HRs associated with stroke for comparators vs apixaban
- The absolute stroke risk for apixaban
- Second line stroke risk for aspirin
- HR of trial mortality for comparators
- The HR of ICH for comparators vs apixaban

All one-way sensitivity analyses for apixaban vs. both doses of dabigatran in the VKA suitable population produced ICERs below £20,000 per QALY. Compared to rivaroxaban in the VKA suitable population, all ICERs were below £20,000 per QALY.

In the VKA unsuitable population, the ICER vs dabigatran 110mg & 150mg was sensitive and three parameters created ICERs exceeding £30,000. The ICERs versus dabigatran 110mg & 150mg and rivaroxaban were generally sensitive as a result of the small QALY differences between interventions. Rivaroxaban dominated apixaban when the HR for stroke (rivaroxaban vs apixaban) was reduced to 0.77. It is worth noting that some of the lower limits are conservative and less likely to be clinically representative (e.g. dropping the MI hazard ratio to 27% lower than apixaban).

Figure 19: Tornado diagram demonstrating effect on ICER vs dabigatran (110mg & 150mg) of varying parameter inputs in VKA suitable population

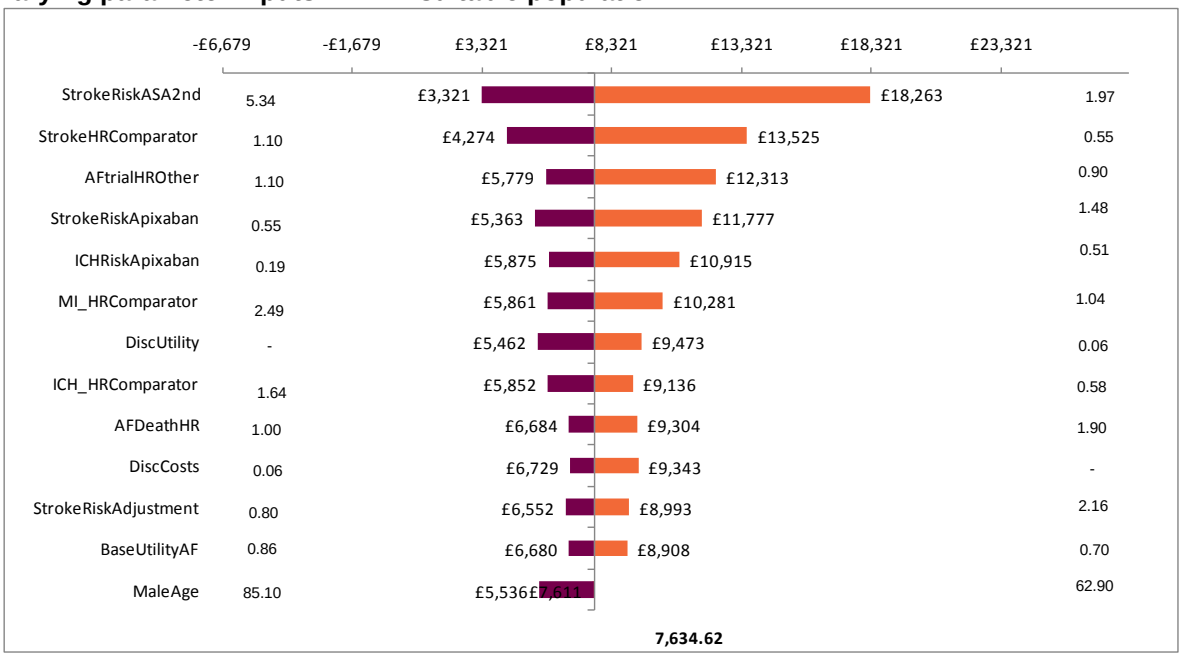


Figure 20: Tornado diagram demonstrating effect on ICER vs dabigatran (110mg) of varying parameter inputs in VKA suitable population

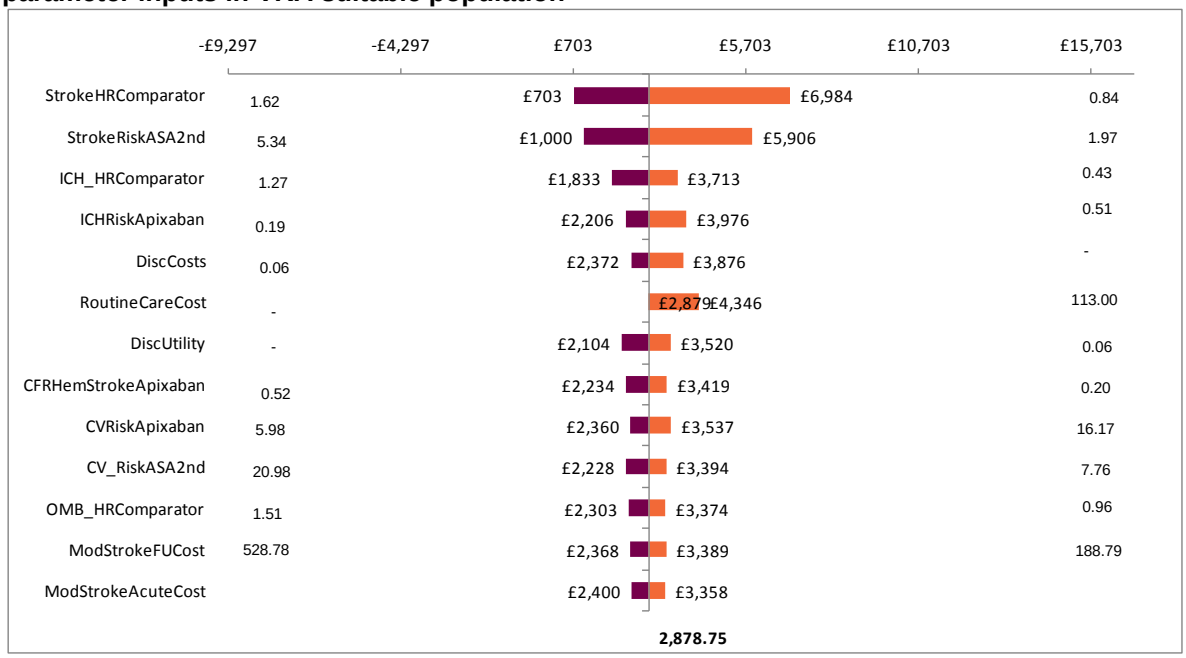


Figure 21: Tornado diagram demonstrating effect on ICER vs rivaroxaban of varying parameter inputs in VKA suitable population

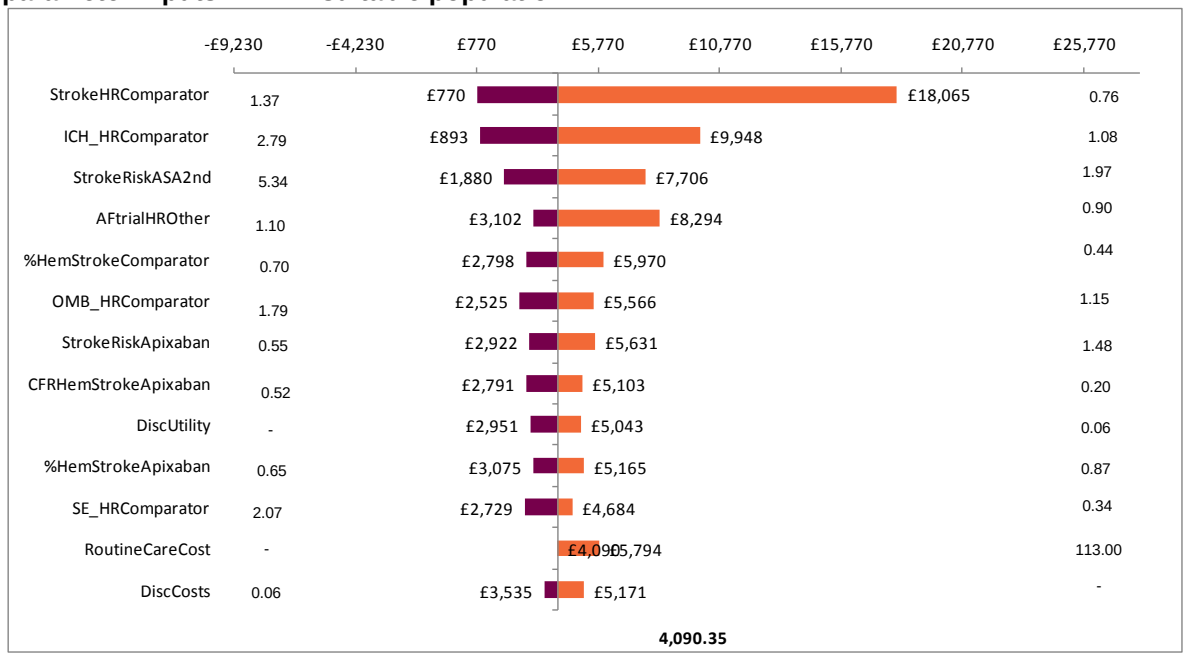


Figure 22: Tornado diagram demonstrating effect on ICER vs dabigatran (110mg & 150mg) of varying parameter inputs in VKA unsuitable population

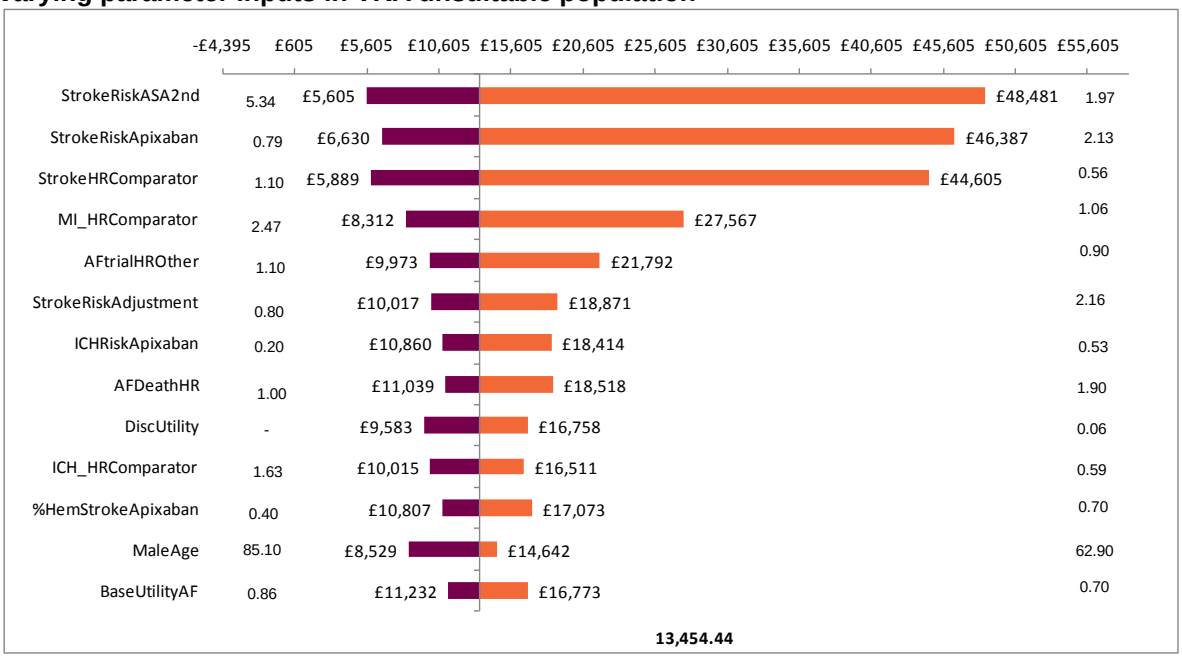


Figure 23: Tornado diagram demonstrating effect on ICER vs dabigatran (110mg) of varying parameter inputs in VKA unsuitable population

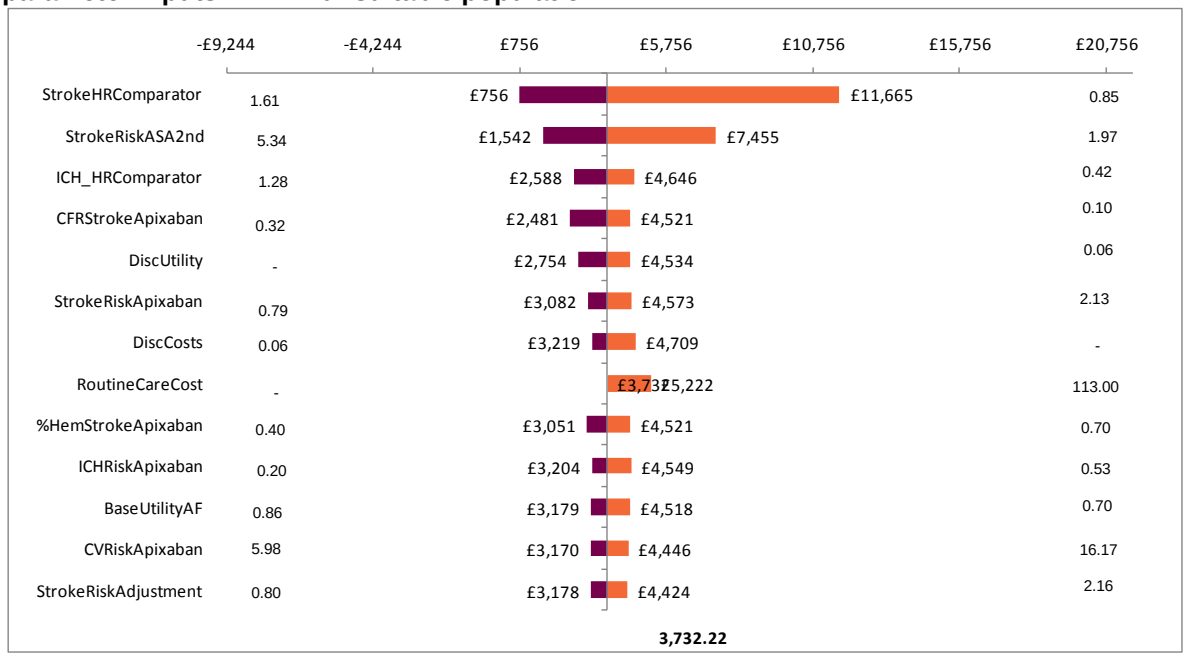
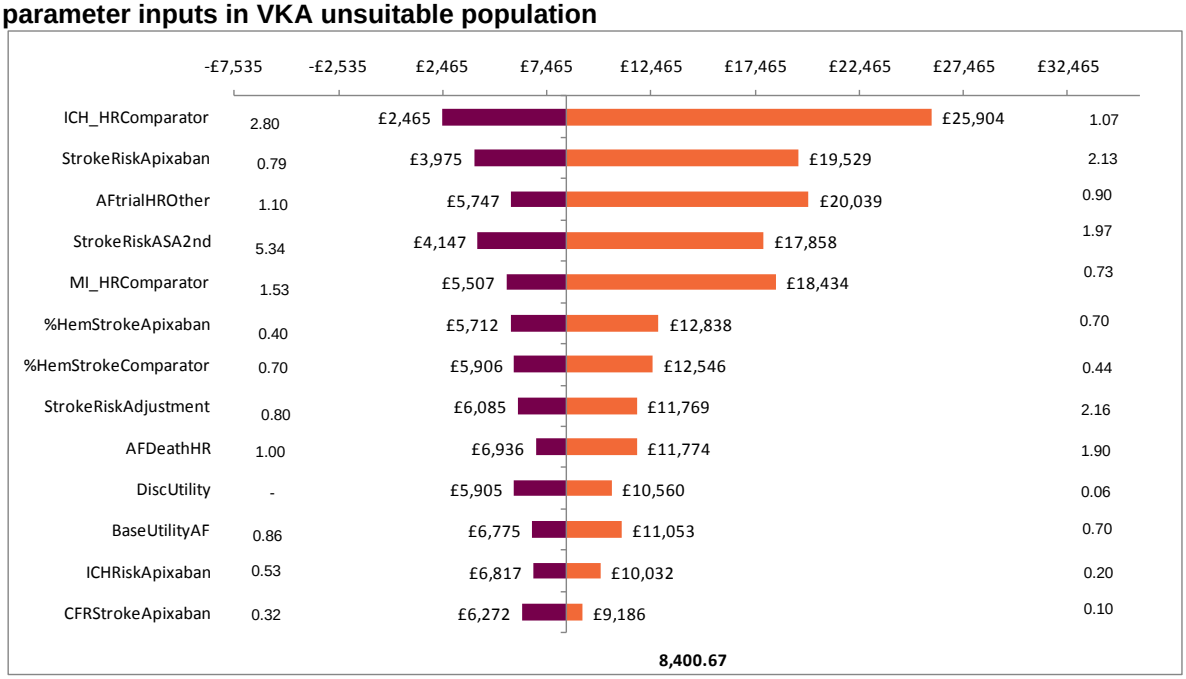


Figure 24: Tornado diagram demonstrating effect on ICER vs rivaroxaban of varying parameter inputs in VKA unsuitable population



7.7.8 Probabilistic sensitivity analysis

Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 25 to Figure 30 present scatter plots of cost-effectiveness results following PSA. Please note that the axis values may change between figures.

Figure 25: Scatter plot results of PSA in VKA suitable population, apixaban vs warfarin

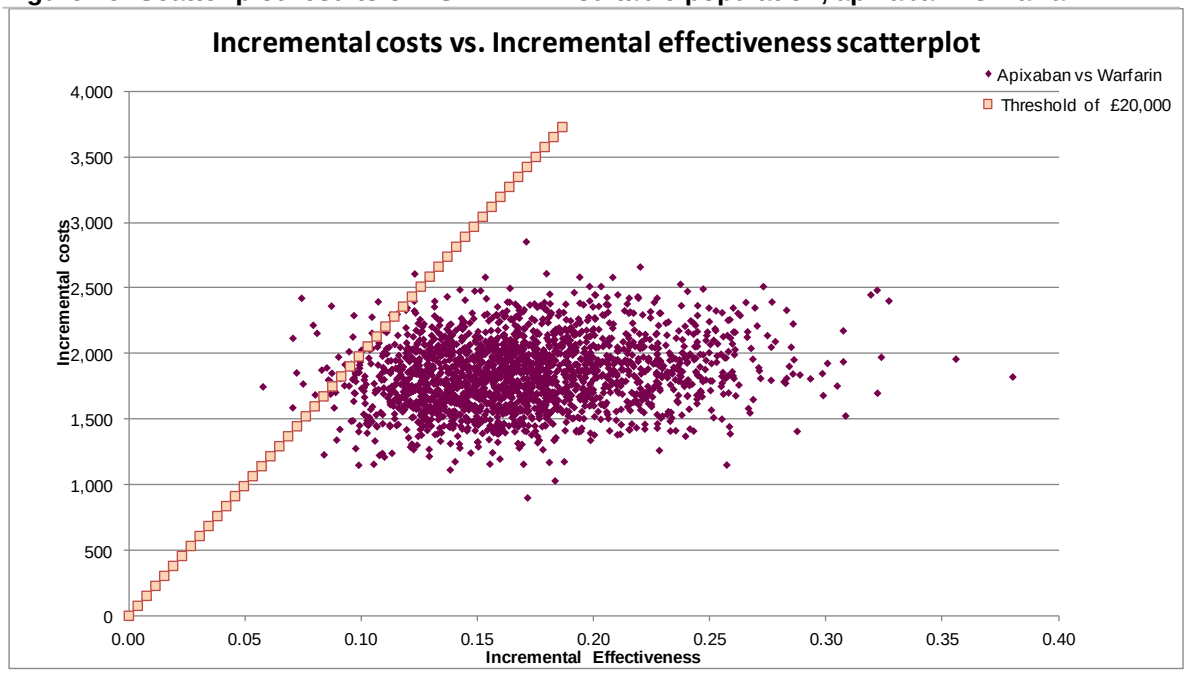


Figure 26: Scatter plot results of PSA in VKA suitable population, apixaban vs rivaroxaban

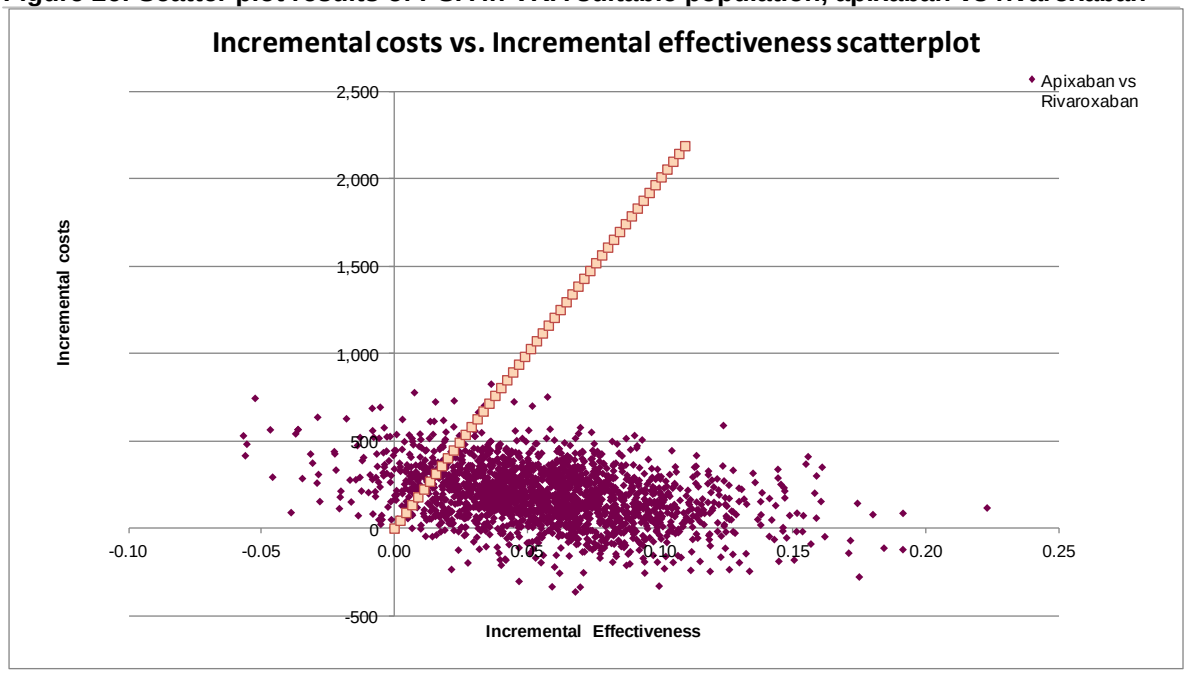


Figure 27: Scatter plot results of PSA in VKA suitable population, apixaban vs dabigatran 150mg/110mg

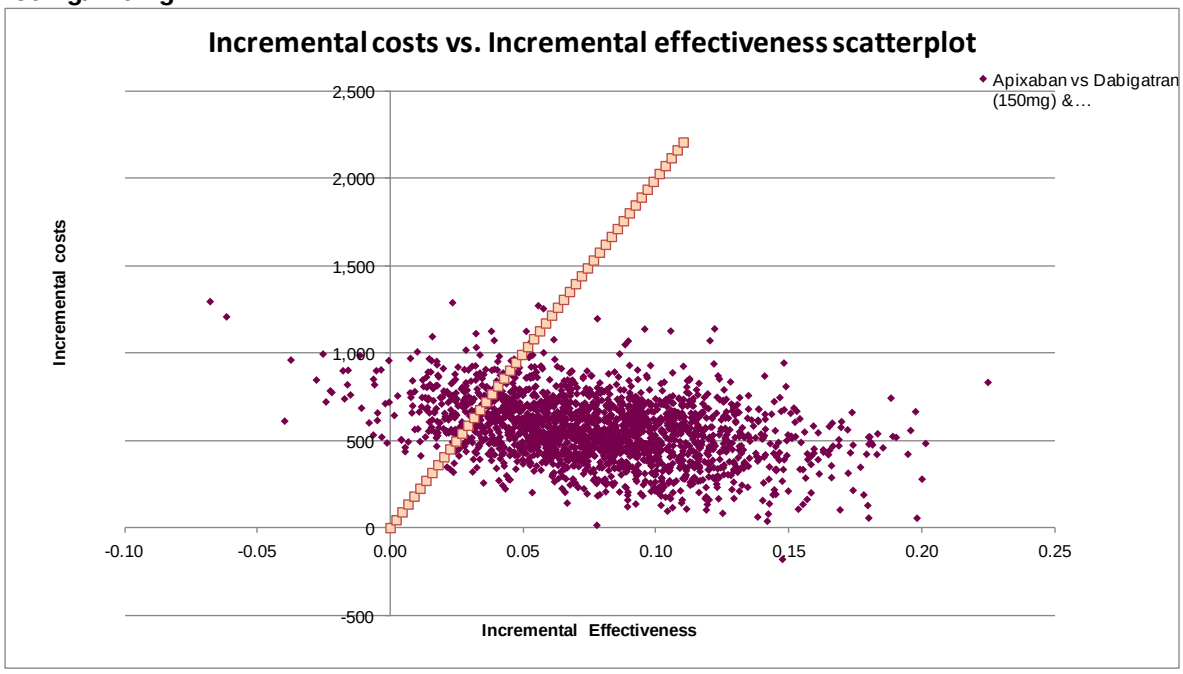


Figure 28: Scatter plot results of PSA in VKA suitable population, apixaban vs dabigatran 110mg

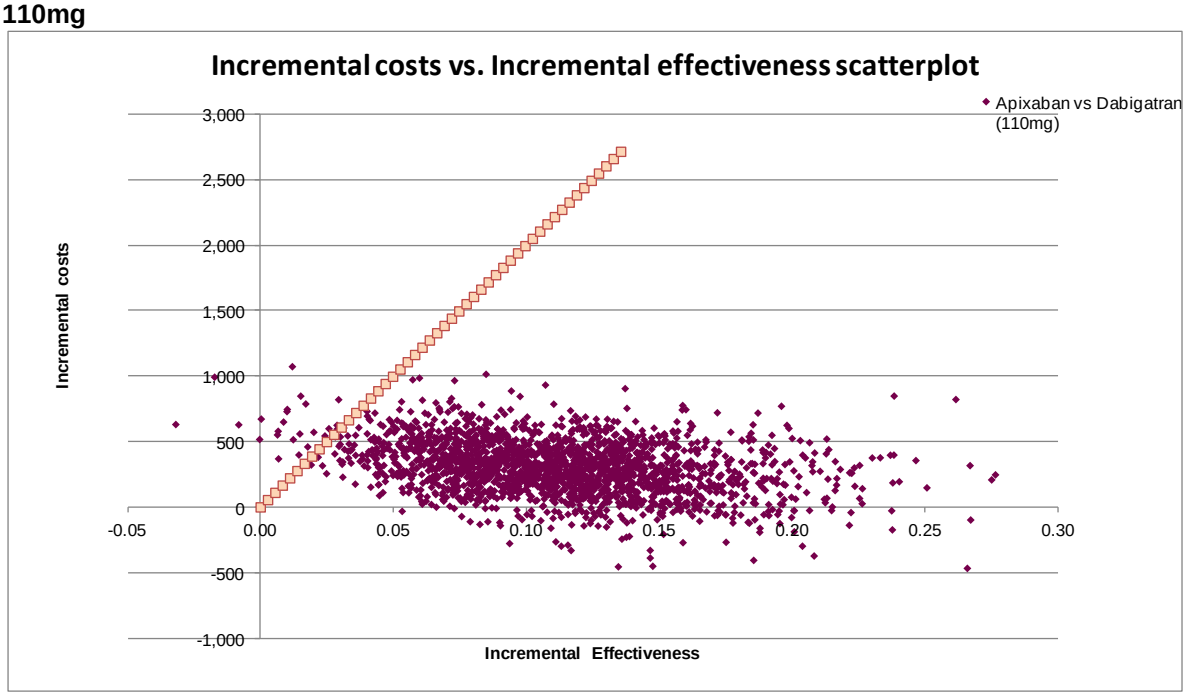


Figure 29: Scatter plot results of PSA in VKA unsuitable population, apixaban vs aspirin

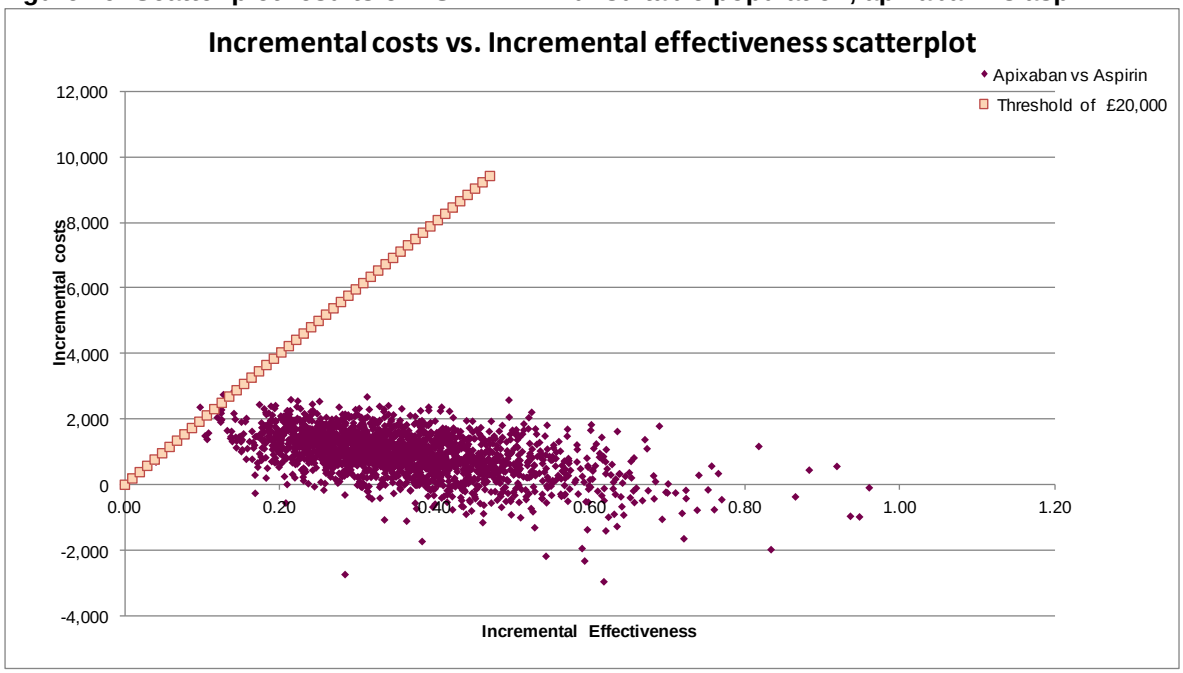


Figure 30: Scatter plot results of PSA in VKA unsuitable population, apixaban vs rivaroxaban

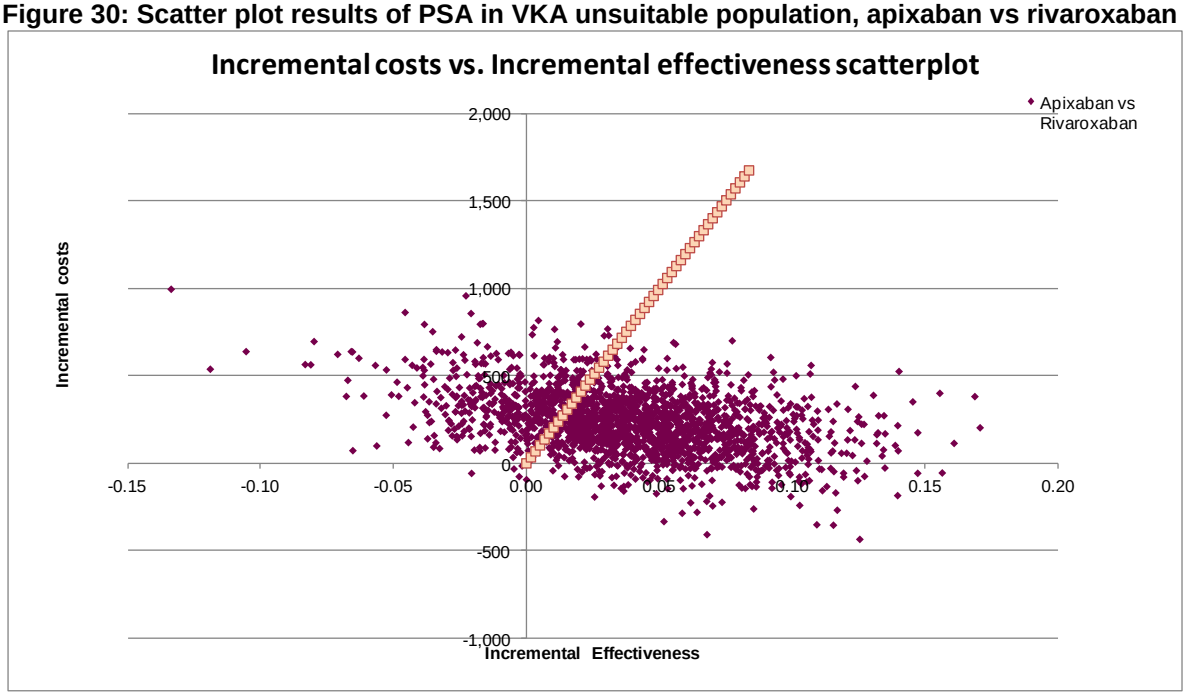


Figure 31: Scatter plot results of PSA in VKA unsuitable population, apixaban vs dabigatran 150mg/110mg

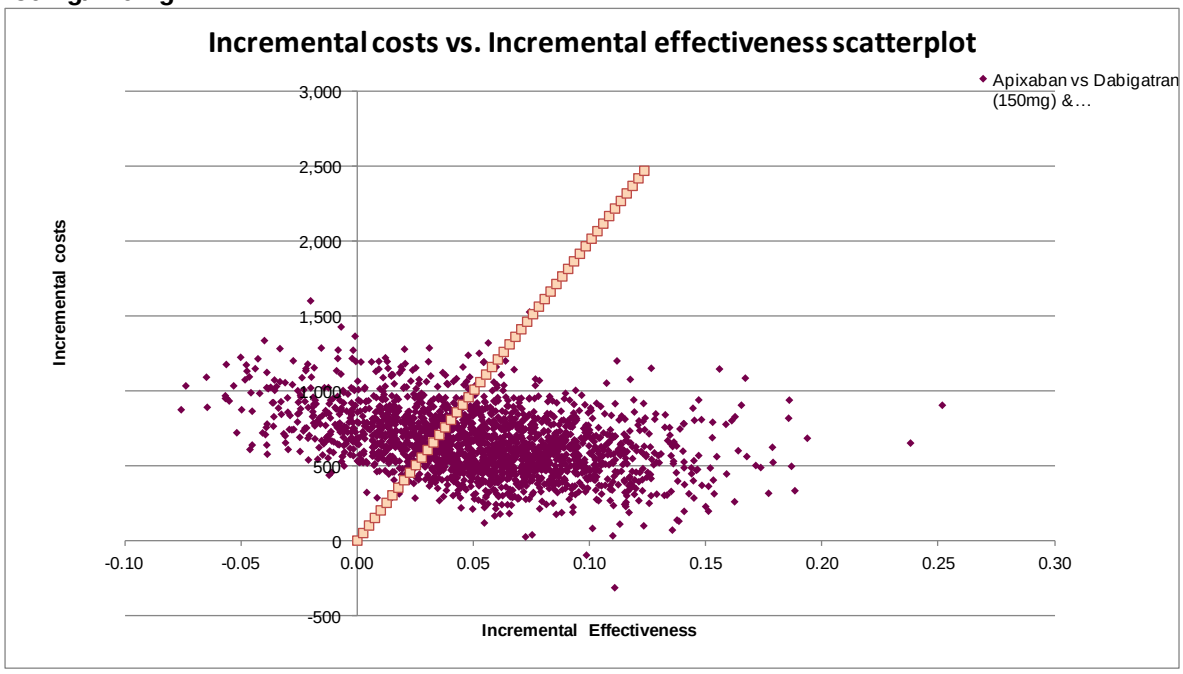


Figure 32: Scatter plot results of PSA in VKA unsuitable population, apixaban vs dabigatran 110mg

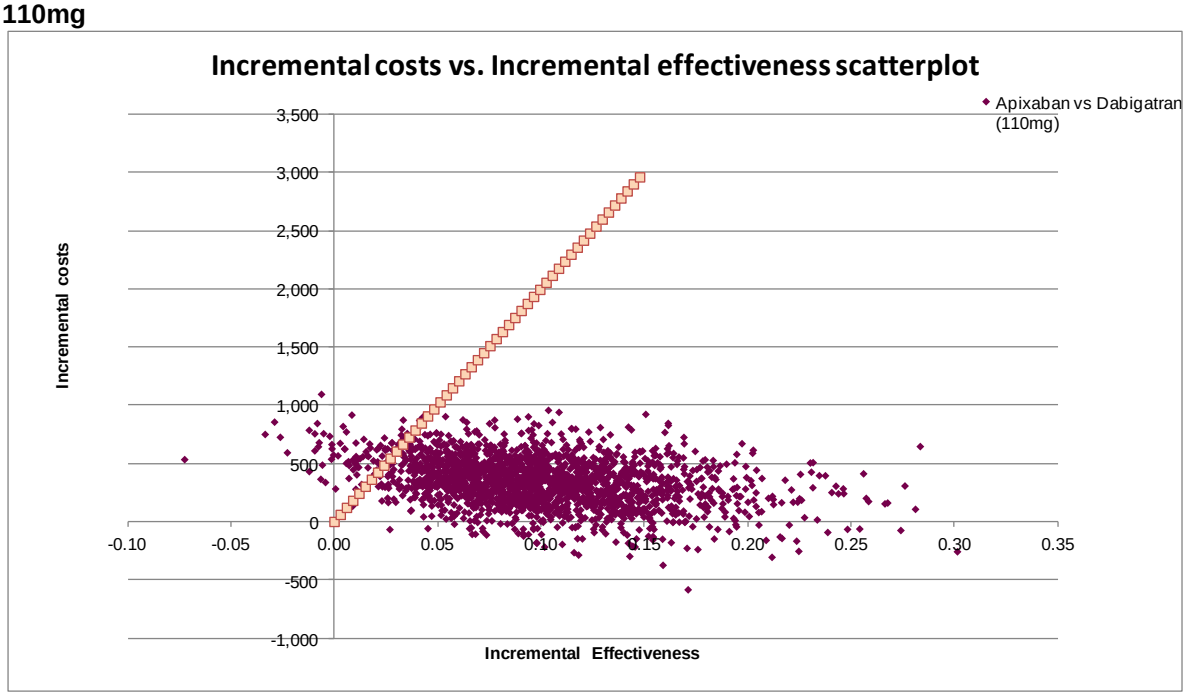


Figure 33 and Figure 34 present the cost-effectiveness acceptability curves (CEACs) for the VKA suitable and VKA unsuitable populations respectively. At willingness to pay thresholds of £20,000 and £30,000 per QALY, apixaban was estimated to have the highest probability of being the most cost-effective therapy option in the VKA unsuitable and VKA suitable populations. The probability that apixaban was the most cost-effective therapy at a

willingness to pay threshold of £20,000 was 80% (87% at £30,000) and 55% (63% at £30,000) in the VKA suitable and VKA unsuitable populations respectively.

Figure 33: Cost-effectiveness acceptability curves in VKA suitable population

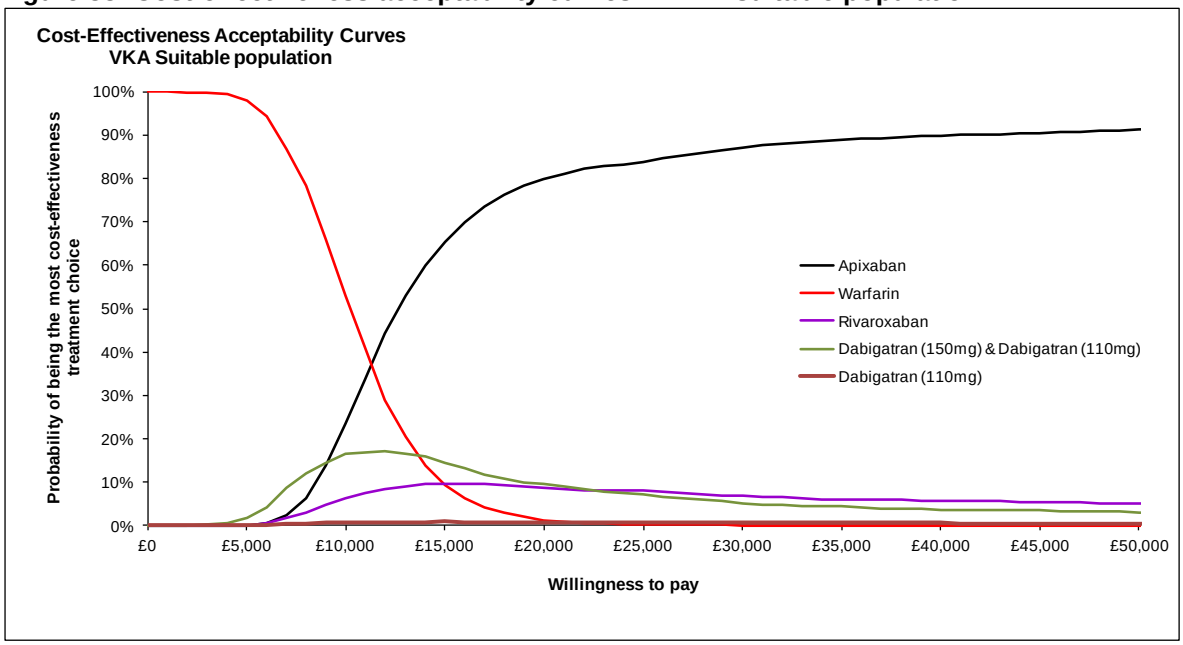


Table 81: Probability of cost-effectiveness at different WTP thresholds in VKA suitable population

	£20,000	£30,000
Apixaban	80%	87%
Dabigatran (110mg & 150mg)	10%	5%
Rivaroxaban	9%	7%
Warfarin	1%	0%
Dabigatran (110mg)	1%	1%

Figure 34: Cost-effectiveness acceptability curves in VKA unsuitable population

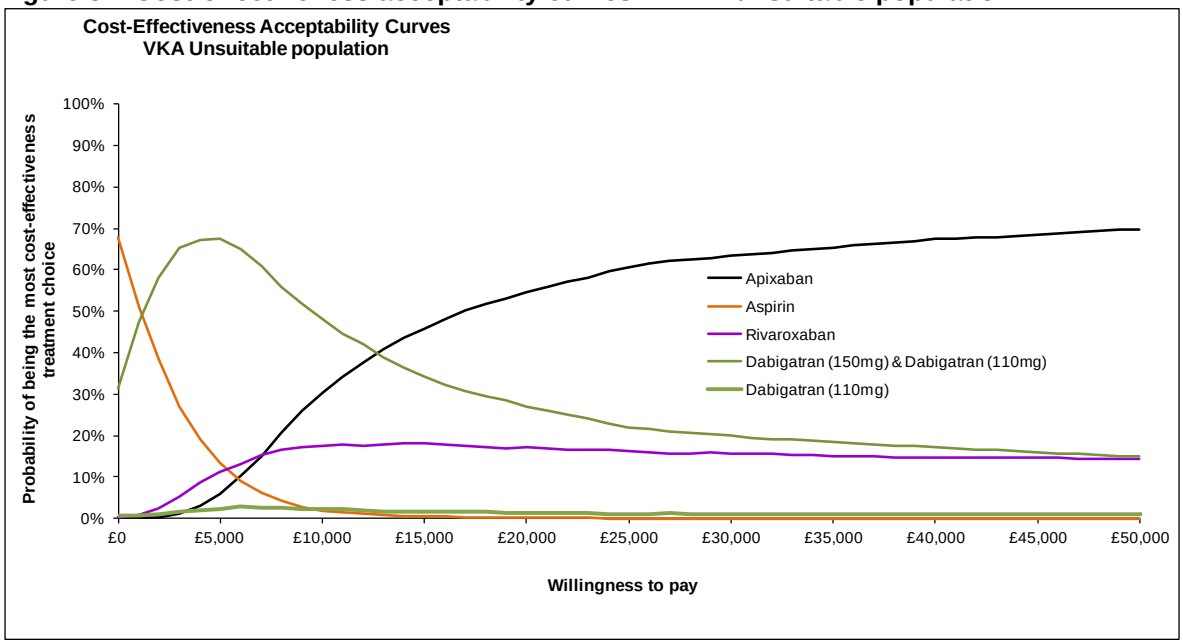


Table 82: Probability of cost-effectiveness at different WTP thresholds in VKA unsuitable population

	£20,000	£30,000
Apixaban	55%	63%
Dabigatran (110mg & 150mg)	27%	20%
Rivaroxaban	17%	16%
Dabigatran (110mg)	1%	1%
Aspirin	0%	0%

7.7.9 Scenario analysis

Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 83: Results of scenario analysis

	ICER for Apixaban vs compara				
	VKA suitable				
#	Warfarin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatra n 110 mg	Aspirin
1. Scenarios					
Recurrent stroke (ischaemic and haemorrhagic) switched off	£11,062	£4,313	£7,467	£2,898	£3,157
Trial mortality switched off	£12,830	£4,096	£7,644	£2,875	£3,096
Long term mortality based on general public (AF correction switched off, HR=1)	£10,118	£3,764	£6,684	£2,790	£2,705

	ICER for Apixaban vs compara				
	VKA suitable				
#	Warfarin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatran 110 mg	Aspirin
Discontinuation set to zero	£11,472	£3,451	£6,919	£2,212	£3,277
Discontinuation set same as apixaban	£11,203	£3,243	£7,906	£1,674	£2,770
Discount costs and benefits at 6% and 1.5% respectively	£8,914	£2,949	£5,585	£1,993	£2,327
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic), SE cost and long-term maintenance costs equal to Youman et al (2002) (inflated to 2010/11 costs)	£11,453	£3,804	£8,066	£3,697	£4,064
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and SE cost equal to NHS reference cost of stroke (estimated as £2,952 based on weighted average of AA04A, AA04B, A10A, AA10B, AA16A, AA16B,AA22A, AA22B, AA23A, AA23B; cost of fatal stroke cost=£0)	£12,152	£4,968	£8,545	£4,522	£5,236
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and SE cost equal to PBR Tariff costs of stroke (estimated as £4,231 based on weighted average of AA04Z, AA10Z, AA16Z, AA22Z, AA23Z, cost of fatal stroke=£0)	£12,096	£4,821	£8,526	£4,399	£4,953
Reduce health state utility decrements for Other ICH, Other Major Bleeds and CRNM Bleeds by 25%	£11,011	£4,095	£7,637	£2,879	£2,903
Reduce utility values for ischaemic and haemorrhagic stroke and SE health states by 25%	£10,955	£3,822	£8,064	£2,869	£2,678
Assume same (apixaban) stroke severity distribution for all interventions (mild, moderate, severe & fatal)	£11,608	£1,637	£8,421	£3,609	£4,144
Age = 80, risks calculated using cTTR specific data, 100% of patients have cTTR >76.51%, All drugs have same stroke severity distribution, trial mortality off, no cost for fatal strokes, NHS reference costs used for stroke and systemic embolism, utility decrements associated with bleeding reduced by 25%	£16,124	£2,799	£3,891	£3,815	£11,370
Age = 70, risks calculated using cTTR specific data, 100% of patients have cTTR < 52.38%, costs of stroke and systemic embolism inflated by 15%	£5,137	£2,862	£7,725	£1,917	£3,201
Apply warfarin disutility of 0.013 to all NOACs	£15,152	£4,499	£8,834	£3,148	£3,283
Apply disutility of 0.0 to all anticoagulants	£14,530	£4,105	£7,697	£2,890	£2,937
Gallagher et al (2008) baseline characteristics [1]	£11,894	£4,236	£6,135	£3,030	£3,731
Treatment Choice Post Other ICH/Other Major Bleeds – No treatment	£10,573	£2,073	£3,898	£1,074	£2,895
Treatment Choice Post Other ICH/Other Major Bleeds – Warfarin	-	£8,745	£28,695	£6,527	-
2nd line (after failure on warfarin)	-	-	-	-	£2,895

presents the results of the 20 deterministic sensitivity analysis scenarios outlined in Table 76 of the main submission. Only on one occasion did the ICER for apixaban exceed £20,000 per QALY: when warfarin was selected as the treatment choice post other ICH/other major bleeds, the ICER for apixaban versus warfarin was £28,695; this is due to the greater number of patients experiencing a bleed on dabigatran (150mg & 110 mg bd) and going on to a less costly anticoagulant.

Table 83: Results of scenario analysis

	ICER for Apixaban vs comparators							
	VKA suitable				VKA unsuitable			
#	Warfarin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatran 110 mg	Aspirin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatran 110 mg
1. Scenarios								
Recurrent stroke (ischaemic and haemorrhagic) switched off	£11,062	£4,313	£7,467	£2,898	£3,157	£9,794	£13,406	£3,896
Trial mortality switched off	£12,830	£4,096	£7,644	£2,875	£3,096	£8,399	£13,439	£3,730
Long term mortality based on general public (AF correction switched off, HR=1)	£10,118	£3,764	£6,684	£2,790	£2,705	£6,936	£11,039	£3,466
Discontinuation set to zero	£11,472	£3,451	£6,919	£2,212	£3,277	£8,215	£11,506	£3,356
Discontinuation set same as apixaban	£11,203	£3,243	£7,906	£1,674	£2,770	£7,805	£14,539	£2,465
Discount costs and benefits at 6% and 1.5% respectively	£8,914	£2,949	£5,585	£1,993	£2,327	£6,271	£10,103	£2,719
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic), SE cost and long-term maintenance costs equal to Youman et al (2002) (inflated to 2010/11 costs)	£11,453	£3,804	£8,066	£3,697	£4,064	£5,521	£12,593	£4,003
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and SE cost equal to NHS reference cost of stroke (estimated as £2,952 based on weighted average of AA04A, AA04B, A10A, AA10B, AA16A, AA16B,AA22A, AA22B, AA23A, AA23B; cost of fatal stroke cost=£0)	£12,152	£4,968	£8,545	£4,522	£5,236	£6,841	£12,610	£4,732
Set mild, moderate and severe acute stroke costs (ischaemic and haemorrhagic) and SE cost equal to PBR Tariff costs of stroke (estimated as £4,231 based on weighted average of AA04Z, AA10Z, AA16Z, AA22Z, AA23Z, cost of fatal stroke=£0)	£12,096	£4,821	£8,526	£4,399	£4,953	£6,533	£12,603	£4,573

	ICER for Apixaban vs comparators							
	VKA suitable				VKA unsuitable			
#	Warfarin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatran 110 mg	Aspirin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatran 110 mg
Reduce health state utility decrements for Other ICH, Other Major Bleeds and CRNM Bleeds by 25%	£11,011	£4,095	£7,637	£2,879	£2,903	£8,408	£13,456	£3,732
Reduce utility values for ischaemic and haemorrhagic stroke and SE health states by 25%	£10,955	£3,822	£8,064	£2,869	£2,678	£6,627	£13,615	£3,552
Assume same (apixaban) stroke severity distribution for all interventions (mild, moderate, severe & fatal)	£11,608	£1,637	£8,421	£3,609	£4,144	£811	£11,535	£3,079
Age = 80, risks calculated using cTTR specific data, 100% of patients have cTTR >76.51%, All drugs have same stroke severity distribution, trial mortality off, no cost for fatal strokes, NHS reference costs used for stroke and systemic embolism, utility decrements associated with bleeding reduced by 25%	£16,124	£2,799	£3,891	£3,815	£11,370	£4,243	£5,316	£5,103
Age = 70, risks calculated using cTTR specific data, 100% of patients have cTTR < 52.38%, costs of stroke and systemic embolism inflated by 15%	£5,137	£2,862	£7,725	£1,917	£3,201	£8,488	£14,941	£3,317
Apply warfarin disutility of 0.013 to all NOACs	£15,152	£4,499	£8,834	£3,148	£3,283	£9,653	£16,643	£4,109
Apply disutility of 0.0 to all anticoagulants	£14,530	£4,105	£7,697	£2,890	£2,937	£8,448	£13,618	£3,747
Gallagher et al (2008) baseline characteristics [1]	£11,894	£4,236	£6,135	£3,030	£3,731	£8,443	£9,879	£3,884
Treatment Choice Post Other ICH/Other Major Bleeds – No treatment	£10,573	£2,073	£3,898	£1,074	£2,895	£4,848	£7,004	£1,706
Treatment Choice Post Other ICH/Other Major Bleeds – Warfarin	-	£8,745	£28,695	£6,527	-	-	-	-

	ICER for Apixaban vs comparators							
	VKA suitable				VKA unsuitable			
#	Warfarin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatran 110 mg	Aspirin	Rivaroxaban	Dabigatran 110 mg & 150 mg	Dabigatran 110 mg
2nd line (after failure on warfarin)	-	-	-	-	£2,895	£4,848	£7,004	£1,706

7.7.10 Summary of main findings from sensitivity analysis

What were the main findings of each of the sensitivity analyses?

Deterministic sensitivity analysis suggests the parameters most influential on cost-effectiveness are:

- Key relative efficacy parameters including the HRs of events including stroke, ICH and SE and corresponding absolute rates for apixaban of ICH and stroke
- Parameters relating to mortality within the trial-period and mortality associated with AF versus the general population
- The disutility applied to users of warfarin

The results of probabilistic analysis suggest apixaban has the highest probability of being cost-effective at willingness to pay thresholds of £20,000 and £30,000 per QALY for both the VKA suitable and VKA unsuitable populations.

7.7.11 Key drivers of the cost-effectiveness results

As identified by the deterministic analysis, the key inputs driving cost-effectiveness are:

- Relative efficacy parameters, HRs of events including stroke, ICH and SE and the corresponding absolute rates for apixaban of ICH and stroke
- Parameters relating to mortality within the trial-period and mortality associated with AF vs the general population

7.8 Validation

7.8.1 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.

Validation was assessed using two primary criteria, internal (verification) and external consistency (validation). Verification was conducted by two independent economists and assessed using the techniques of extreme value analysis (substituting minimum and maximum values for appropriate parameter values), logical consistency tests and using parallel inputs for all interventions for efficacy, costs and utilities. These techniques help reveal flawed algorithms in a model and identify any irregularities between the programming of treatment arms.

External consistency was assessed by assessing the face validity and assessing the results of the model against published results. The face validity of the model was established by presenting the initial model concept, the Markov diagram, and final model structure to clinicians. External consistency with preceding models is discussed in detail in Section 7.10.1 and the comparison of model results with clinical trial results is discussed in section 7.7.1.

7.9 Subgroup analysis

7.9.1 Rationale for subgroup analysis

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.

Subgroups based on time in therapeutic range and stroke risk were specified in the decision problem (Section 5 of main submission). Since risk of stroke can be varied based on the quality of INR control (especially for warfarin), the model allows a user-selected option of having stroke and bleeding risks adjusted based on quality of INR control represented as distribution of centre's median time in therapeutic range (cTTR). Stroke risk can also be varied in the model by specifying the distribution of patients by $CHADS_2$ score.

7.9.2 Subgroup patient characteristics

Please clearly define the characteristics of patients in the subgroup.

Subgroup analyses were performed based on quality of INR control in the VKA suitable population. Four subgroups are presented based on the quartiles of median cTTR observed across centres in ARISTOTLE. Table 84 defines the cTTR ranges considered.

Table 84: cTTR subgroups considered by the analysis

Median cTTR*	Frequency across centres
cTTR < 52.38%	25%
52.38% ≤ cTTR < 66.02%	25%
66.02% ≤ cTTR < 76.51%	25%
cTTR ≥ 76.51%	25%
Total	100%

*TTR = time in therapeutic range (INR 2.0-3.0)

Subgroup analysis were performed on stroke risk ($CHADS_2$ scores) for the VKA suitable and unsuitable populations. The $CHADS_2$ distributions assumed in the base case have been presented in Table 36. Stroke risks by individual $CHADS_2$ score could not be obtained due to insufficient sample sizes in some categories, and as a result subgroup analysis is presented for $CHADS_2$ score of 1, 2, and 3-6.

7.9.3 Please describe how the statistical analysis was undertaken.

Methods of estimating transition probabilities by cTTR and $CHADS_2$ are discussed in Section 7.3.6 of the main submission (starting on page 112). For the following subgroup analysis it was assumed that all patients fell into one cTTR category per analysis, e.g. in Table 85: cTTR < 52.38% – VKA suitable population

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			Increm-ental

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
Warfarin	£7,508	7.38	5.62						
Apixaban	£8,895	7.60	5.85	£1,387	0.22	0.23	£3,177	£5,459	£6,077

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years.

all patients were allocated to the category cTTR < 52.38%.The same approach was employed for the analysis by CHADS2 score; in all patients were allocated to the category CHADS2 score =1.

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7.9.4 Results of subgroup analyses

What were the results of the subgroup analysis/analyses, if conducted?

Subgroup analyses based on median cTTR are presented in Table 85: cTTR < 52.38% – VKA suitable population

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
Warfarin	£7,508	7.38	5.62						
Apixaban	£8,895	7.60	5.85	£1,387	0.22	0.23	£3,177	£5,459	£6,077

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years.

–Table 88: cTTR ≥ 76.51% – VKA suitable population

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
Warfarin	£7,037	7.51	5.73						
Apixaban	£8,875	7.68	5.92	£1,838	0.17	0.19	£1,880	£3,739	£9,889

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years.

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Table 85: cTTR < 52.38% – VKA suitable population

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
Warfarin	£7,508	7.38	5.62						
Apixaban	£8,895	7.60	5.85	£1,387	0.22	0.23	£3,177	£5,459	£6,077

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 86: 52.38% ≤ cTTR < 66.02% – VKA suitable population

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
Warfarin	£7,202	7.47	5.69						
Apixaban	£9,156	7.55	5.80	£1,954	0.08	0.11	£205	£1,284	£18,102

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 87: 66.02% ≤ cTTR < 76.51% – VKA suitable population

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
Warfarin	£7,107	7.49	5.72						
Apixaban	£9,003	7.63	5.87	£1,896	0.14	0.15	£1,190	£2,734	£12,286

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 88: cTTR ≥ 76.51% – VKA suitable population

Technologies	Total			Incremental†			INMB vs warfarin (λ= £20,000)	INMB vs warfarin (λ= £30,000)	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
Warfarin	£7,037	7.51	5.73						
Apixaban	£8,875	7.68	5.92	£1,838	0.17	0.19	£1,880	£3,739	£9,889

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years.

When all apixaban and warfarin patients were assumed to receive care at centres with a mean TTR in the range of 52.38% to 66.02%, the ICER for apixaban compared to warfarin was £18,102 per QALY gained. This surprising result is due to the higher number of ischaemic strokes recorded by apixaban patients in this cTTR rage (ARISTOTLE trial stroke rates, apixaban: N=74, event rate =1.178; warfarin: N=68, event rate =1.078).

When all apixaban and warfarin patients are assumed to receive care at centres with a mean TTR of at least 76.51% the ICER for apixaban is more favourable than the base case ICER. This initially counter-intuitive result stems from the lower number of ischaemic and haemorrhagic strokes experienced by patients on both medications, resulting in a better incremental QALY gain for patients on apixaban compared with warfarin.

Subgroup analyses based on $CHADS_2$ are presented in Table 89: $CHADS_2$ score of 1 – VKA suitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus warfarin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Warfarin	£6,930	7.536	5.756							
Dabigatran 150mg & 110mg	£8,297	7.593	5.835	£1,367	0.056	0.079	£219	£1,012	£17,233	Extendedly dominated
Dabigatran 110mg	£8,450	7.579	5.822	£153	-0.013	-0.013	-£202	£457	£23,068	Strictly Dominated
Rivaroxaban	£8,596	7.623	5.869	£146	0.044	0.047	£586	£1,712	£14,794	Extendedly dominated
Apixaban	£8,745	7.685	5.921	£149	0.06	0.05	£1,482	£3,130	£11,010	£11,010

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

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Table 94: $CHADS_2$ score of 3-6 – VKA unsuitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus dabi 150mg & 110mg	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Dabigatran 150mg & 110mg	£8,376	7.300	5.586							
Aspirin	£8,713	6.902	5.203	£337	-0.398	-0.383	-£7,999	-£11,829	-£881	Strictly Dominated
Dabigatran (110mg)	£8,783	7.233	5.523	£70	0.331	0.320	-£1,664	-£2,293	-£6,475	Strictly Dominated
Rivaroxaban	£8,811	7.293	5.588	£28	0.060	0.065	-£385	-£360	£173,520	Extendedly dominated
Apixaban	£9,166	7.329	5.611	£355	0.036	0.022	-£295	-£48	£31,944	£31,944

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

. Analysis for $CHADS_2$ =0 is not presented as it is outside of the licensed indication for Apixaban.

Table 89: $CHADS_2$ score of 1 – VKA suitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus warfarin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Warfarin	£6,930	7.536	5.756							
Dabigatran 150mg & 110mg	£8,297	7.593	5.835	£1,367	0.056	0.079	£219	£1,012	£17,233	Extendedly dominated

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus warfarin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Dabigatran 110mg	£8,450	7.579	5.822	£153	-0.013	-0.013	-£202	£457	£23,068	Strictly Dominated
Rivaroxaban	£8,596	7.623	5.869	£146	0.044	0.047	£586	£1,712	£14,794	Extendedly dominated
Apixaban	£8,745	7.685	5.921	£149	0.06	0.05	£1,482	£3,130	£11,010	£11,010

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

Table 90: $CHADS_2$ score of 1 – VKA unsuitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus aspirin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Aspirin	£7,082	7.231	5.511							
Dabigatran 150mg & 110mg	£8,083	7.413	5.683	£1,001	0.181	0.172	£2,435	£4,153	£5,826	£5,826
Dabigatran 110mg	£8,283	7.389	5.659	£200	-0.024	-0.023	£1,771	£3,257	£8,081	Strictly Dominated
Rivaroxaban	£8,408	7.440	5.713	£124	0.051	0.054	£2,725	£4,750	£6,544	Extendedly dominated
Apixaban	£8,578	7.490	5.754	£170	0.050	0.040	£3,361	£5,789	£6,159	£4,223

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

Table 91: $CHADS_2$ score of 2 – VKA suitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus warfarin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Warfarin	£7,184	7.470	5.697							
Dabigatran 150mg & 110mg	£8,434	7.538	5.789	£1,250	0.068	0.091	£575	£1,488	£13,697	Extendedly dominated
Dabigatran 110mg	£8,680	7.504	5.757	£246	-0.034	-0.032	-£312	£280	£25,269	Strictly Dominated
Rivaroxaban	£8,776	7.554	5.810	£95	0.050	0.054	£669	£1,798	£14,083	Extendedly dominated
Apixaban	£8,979	7.615	5.860	£204	0.06	0.05	£1,466	£3,097	£11,008	£11,008

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

Table 92: $CHADS_2$ score of 2 – VKA unsuitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus aspirin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Aspirin	£8,125	7.021	5.314							

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus aspirin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Dabigatran 150mg & 110mg	£8,266	7.342	5.622	£141	0.321	0.308	£6,019	£9,100	£459	£459
Dabigatran 110mg	£8,596	7.291	5.574	£330	-0.051	-0.048	£4,725	£7,323	£1,814	Strictly Dominated
Rivaroxaban	£8,660	7.348	5.635	£64	0.057	0.061	£5,883	£9,092	£1,669	£30,622
Apixaban	£8,946	7.389	5.664	£286	0.041	0.029	£6,175	£9,673	£2,349	£9,899 (vs Rivaroxaban), £16,282 (vs Dabigatran 150mg & 110mg

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

Table 93: $CHADS_2$ score of 3-6 – VKA suitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus warfarin	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Warfarin	£7,517	7.383	5.621							
Dabigatran 150mg & 110mg	£8,615	7.465	5.727	£1,098	0.083	0.106	£1,030	£2,094	£10,321	£10,321
Dabigatran 110mg	£8,981	7.406	5.671	£366	-0.059	-0.056	-£456	£48	£29,042	Strictly Dominated
Rivaroxaban	£9,011	7.464	5.734	£29	0.058	0.063	£773	£1,907	£13,178	Extendedly dominated
Apixaban	£9,286	7.524	5.781	£275	0.06	0.05	£1,448	£3,056	£10,998	£10,998

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

Table 94: $CHADS_2$ score of 3-6 – VKA unsuitable population

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus dabi 150mg & 110mg	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Dabigatran 150mg & 110mg	£8,376	7.300	5.586							
Aspirin	£8,713	6.902	5.203	£337	-0.398	-0.383	-£7,999	-£11,829	-£881	Strictly Dominated
Dabigatran (110mg)	£8,783	7.233	5.523	£70	0.331	0.320	-£1,664	-£2,293	-£6,475	Strictly Dominated
Rivaroxaban	£8,811	7.293	5.588	£28	0.060	0.065	-£385	-£360	£173,520	Extendedly dominated

Technol-ogies	Total			Incremental†			INMB vs aspirin (λ= £20,000)	INMB vs aspirin (λ= £30,000)	ICER (£) versus dabi 150mg & 110mg	ICER (£) Increm-ental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs				
Apixaban	£9,166	7.329	5.611	£355	0.036	0.022	-£295	-£48	£31,944	£31,944

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALYs, quality-adjusted life years

Based on a cost-effectiveness threshold of £30,000, apixaban was the most cost-effective intervention for the majority of $CHADS_2$ categories, with the exception of $CHADS_2$ 3-6 in the VKA unsuitable population, for which the ICER for apixaban vs dabigatran 110mg & 150mg was £31,944.

7.9.5 Relevant subgroups not considered

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.

No obvious subgroups were omitted.

7.10 Interpretation of economic evidence

7.10.1 Comparison with published economic literature

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?

The systematic review detailed in Section 7.1 did not identify any economic evaluations which estimated the cost-effectiveness of apixaban in NVAF. Subsequent to the systematic review a cost-utility analysis that evaluated apixaban compared with aspirin for stroke prevention in AF among patients unsuitable for warfarin was published (101). In this study apixaban was an inferior strategy (more costly but no more effective) using a 1-year time horizon, but the dominant strategy (less costly and more effective) using a 10-year time horizon. According to ISPOR and NICE guidelines (164, 165), the 1-year time horizon is not appropriate. AF is a chronic condition and anticoagulation would be required for the life-time, therefore the 1-year time horizon cannot be justified according to best research practices, as it underestimates the costs and benefits of the interventions.

The manufacturer submission for dabigatran (24) estimated an ICER of £6,264 for dabigatran at the lifetime horizon. This contrasts to an estimated ICER of £13,648 (150mg & 110mg) for dabigatran vs warfarin estimated by this analysis (this analysis was also performed assuming a daily cost of £2.20 following a reduction in the cost of dabigatran).

The manufacturer submission for rivaroxaban (103) estimated the ICER for rivaroxaban vs warfarin as £18,883. The ICER estimated by this analysis is lower at £14,071 for rivaroxaban vs warfarin.

Observed differences may result from several important data input selections used between the models, notably the costs associated with stroke events, INR monitoring and HRQL inputs. The results in the submission should be given more credence than preceding evaluations due to the research methods and assumptions employed in the evaluation. The present analysis assumes conservative estimates of the costs of INR monitoring. HRQL inputs were identified following a full systematic review. Relative treatment effects were identified following a comprehensive systematic review and network meta-analysis.

7.10.2 Relevance of the economic evaluation to all patient groups

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?

The economic evaluation is relevant to all patients that could potentially use the technology as identified in the decision problem.

7.10.3 Strengths and weaknesses of the evaluation

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Primary strengths of the evaluation are:

- Clinical evidence on the efficacy and adverse events of apixaban against the most frequently used anticoagulants from approximately 24,000 patients enrolled in two double blind randomised controlled trials AVERROES (3) and ARISTOTLE (2).
- The evaluation of apixaban is the only technology appraisal to have direct head to head evidence against aspirin (apixaban versus aspirin).
- A robust NMA was conducted, which accounted for peer review comments provided by the ERGs that reviewed the dabigatran and rivaroxaban appraisals.
- The economic model (like the NMA) builds on recommendations from previous technology appraisals and good practice in published economic models.

Primary weaknesses of the evaluation are:

- Efficacy data for rivaroxaban and dabigatran were not available for the VKA unsuitable population and so data from trials in VKA suitable patients were used in the network meta-analysis.
- Trial patients may not completely representative of UK AF patients, a limitation common to all technology appraisals in this area.
- Evidence for all outcomes of interest were not published for all comparators e.g. full details of stroke severity for all modified Rankin scale categories. This necessitates assumptions being employed, possibly to the detriment of apixaban.
- Second order uncertainty in parameter values has been assessed using probabilistic sensitivity analysis.

Interpretation:

- Whilst there are concerns that efficacy in clinical practice will be less than that seen in trials and costs (and cost savings) may be underestimated, the strengths of the evaluation suggest that comparative efficacy and incremental results are robust. Additionally, the head to head data for apixaban versus aspirin supports making recommendations for VKA unsuitable patients based on this evaluation.

7.10.4 Further analyses

What further analyses could be undertaken to enhance the robustness/completeness of the results?

We believe all relevant analyses on the robustness/completeness of the results have been conducted.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 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.

Table 97 presents estimates of patient numbers for the full marketing authorisation in England and Wales. A prevalence of 1.74% was estimated for Wales, based on the number of cases of AF recorded of 55,036 and total number of patients registered with GPs nationally of 3,168,721 (166) in 2010-2011. Similarly for England a prevalence of 1.43% was estimated based of a total list size of 55,169,643 and 791,174 AF register counts. This provided a weighted average prevalence of 1.45% (with weightings based on list size for each country).

Estimates of prevalence were applied to the 2010 population size for those aged 18 years or older for England and Wales (43,570,308) (167) to provide an estimated AF prevalence of 631,996 in 2010-11. To these estimates, a mortality rate in the AF population of 2.7% (168) is applied to estimate the number of deaths. An AF incidence of 0.05% is assumed based on the manufacturer's submission for the NICE appraisal of dabigatran. From these data, the net AF population can be estimated for each year from which an estimated 80% of AF is non-valvular (25).

The marketing authorisation states that apixaban is only permitted for use in patients with $CHADS_2 \geq 1$. 87.4% of patients were assumed to have $CHADS_2 \geq 1$ (26). These patients are further divided into VKA suitable and VKA unsuitable, assuming 48.6% are VKA suitable (169). The population sizes in 2017-18 were estimated as 226,843 and 239,912 for the VKA suitable and VKA unsuitable populations respectively.

Table 95: Estimation of patients eligible for treatment

	Rate	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	Source
E + W population[†]		43,570,308	43,948,499	44,331,004	44,694,105	45,049,027	45,405,281	45,738,826	46,054,429	Population projections by the Office for National Statistics
Prevalence AF	1.45%	631,996								QOF (170)
Mortality	2.7%		17,064	17,196	17,331	17,466	17,603	17,740	17,879	
Incidence AF	0.05%		21,974	22,166	22,347	22,525	22,703	22,869	23,027	
Net AF patients			636,907	641,876	646,892	651,951	657,050	662,180	667,328	Calculated
NVAF patients	80%		509,525	513,501	517,514	521,560	525,640	529,744	533,862	
CHADS ≥ 1	87.4%		445,478	448,954	452,462	456,000	459,567	463,155	466,756	
VKA suitable	48.6%		216,502	218,191	219,897	221,616	223,350	225,093	226,843	
VKA unsuitable	51.4%		228,976	230,762	232,566	234,384	236,218	238,062	239,912	

Abbreviations: AF, atrial fibrillation; E+W, England and Wales; VKA, vitamin K antagonist
[†]Aged 18 years or older

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Growth and uptake of current treatment options including NOACs are presented in Table 96.

8.3 What assumption(s) were made about market share (when relevant)?

Table 96 presents predicted market share estimates with and without apixaban.

Table 96: Market share with and without apixaban

	2013-14	2014-15	2015-16	2016-17	2017-18
Eligible AF patients	452,462	456,000	459,567	463,155	466,756
Without apixaban					
NOAC Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With apixaban					
NOAC Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.4 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).

The annual costs of acute events are presented in Table 97. These costs were estimated using the cost-effectiveness model detailed in Section 7. Year 2 event costs (undiscounted) were halved to provide the annual cost per patient per year. 48.6% (169) of patients were assumed to be VKA suitable for NOACs (it was assumed that 100% of patients were VKA suitable for warfarin therapy, and 100% of patients were VKA unsuitable for aspirin therapy). Table 98 presents the results of applying these costs to the patient numbers estimated (using Table 96). Apixaban is associated with a net cost saving in acute event and adverse event costs.

Table 97: Annual event costs per patient by treatment

Therapy	Annual Event and AE costs	Source
Dabigatran	£406.28†	Estimated from model as acute event costs for each therapy at year 2 (divided by 2). Note discount rate=0%.
Rivaroxaban	£406.81	
Apixaban	£398.25	

Therapy	Annual Event and AE costs	Source
Warfarin	£435.00	
Aspirin	£686.50	

† Assumes 40% of individuals receive dabigatran 110 mg, 60% receive dabigatran 110 mg & 150 mg

Table 98: Acute event and adverse event costs with and without apixaban

	2013-14	2014-15	2015-16	2016-17	2017-18
Without apixaban					
Dabigatran	£4,577,284	£11,912,483	£18,353,926	£23,521,362	£30,815,510
Rivaroxaban	£957,143	£3,765,757	£7,665,213	£11,436,841	£16,842,422
Apixaban	£0	£0	£0	£0	£0
Warfarin	£123,976,889	£115,702,807	£108,471,544	£102,045,180	£94,818,582
Aspirin	£96,197,188	£93,818,981	£90,956,287	£88,486,761	£81,869,008
Total	£225,708,505	£225,200,029	£225,446,969	£225,490,145	£224,345,522
With apixaban					
Dabigatran	£3,823,595	£8,244,254	£11,818,957	£13,905,830	£17,199,795
Rivaroxaban	£699,451	£2,059,109	£3,383,911	£4,503,138	£6,740,767
Apixaban	£991,051	£5,266,405	£10,578,599	£16,213,106	£23,235,439
Warfarin	£123,976,889	£115,702,807	£108,471,544	£102,045,180	£94,818,582
Aspirin	£96,197,188	£93,818,981	£90,956,287	£88,486,761	£81,869,008
Total	£225,688,174	£225,091,555	£225,209,298	£225,154,015	£223,863,591
Total net cost with apixaban					
	-£20,330	-£108,474	-£237,671	-£336,130	-£481,931

Similarly the annual follow-up and management costs per patient were estimated from the cost-effectiveness model. Because these costs are accumulated over time, they were estimated using the 5-year costs of follow-up and management and converted to an annual cost. The 5-year costs were estimated using the same weightings of VKA suitable/unsuitable as the annual costs detailed above. Table 100 presents the results of applying these costs to the patient numbers estimated (using Table 96).

Table 99: Annual follow-up and management costs per patient by treatment

Therapy	Annual follow-up costs	Source
Dabigatran	£91†	Estimated from model as follow-up costs for each therapy at year 5
Rivaroxaban	£92	
Apixaban	£90	
Warfarin	£91	
Aspirin	£199	

*These annual costs were calculated as one-fifth of the 5-year costs
† Assumes 40% of individuals receive dabigatran 110 mg, 60% receive dabigatran 110 mg & 150 mg

Table 100: Follow-up and management costs with and without apixaban

	2013-14	2014-15	2015-16	2016-17	2017-18
Without apixaban					
Dabigatran	£1,025,741	£2,669,513	£4,113,000	£5,270,990	£6,905,563
Rivaroxaban	£217,391	£855,298	£1,740,963	£2,597,594	£3,825,338
Apixaban	£0	£0	£0	£0	£0
Warfarin	£26,076,681	£24,336,352	£22,815,364	£21,463,674	£19,943,668
Aspirin	£27,910,944	£27,220,924	£26,390,333	£25,673,817	£23,753,722
Total	£55,230,757	£55,082,087	£55,059,660	£55,006,077	£54,428,291
With apixaban					
Dabigatran	£856,844	£1,847,486	£2,648,554	£3,116,210	£3,854,367
Rivaroxaban	£158,863	£467,675	£768,571	£1,022,776	£1,530,998
Apixaban	£225,045	£1,195,880	£2,402,157	£3,681,624	£5,276,235
Warfarin	£26,076,681	£24,336,352	£22,815,364	£21,463,674	£19,943,668
Aspirin	£27,910,944	£27,220,924	£26,390,333	£25,673,817	£23,753,722
Total	£55,228,376	£55,068,316	£55,024,980	£54,958,102	£54,358,989
Total net cost with apixaban					
	-£2,381	-£13,771	-£34,680	-£47,975	-£69,302

The annual cost of INR monitoring was assumed to be £248 per year (section 7.5.5). Table 101 presents the results of applying these costs to the patient numbers estimated.

Table 101: Costs of INR monitoring with and without apixaban

	2013-14	2014-15	2015-16	2016-17	2017-18
Without Apixaban	£70,681,473	£65,964,269	£61,841,594	£58,177,808	£54,057,793
With Apixaban	£70,681,473	£65,964,269	£61,841,594	£58,177,808	£54,057,793
Total net cost with Apixaban	**£0**	**£0**	**£0**	**£0**	**£0**

8.5 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

Table 102 presents the unit costs assumed in the budget impact calculations, which are the same as those assumed in Table 62. The total treatment costs with and without apixaban are presented in Table 103.

Table 102: Unit costs assumed in budget impact calculations

Therapy	Daily cost	Annual cost	Source
Dabigatran	£2.20	£803	MIMS, June 2012
Rivaroxaban	£2.10	£767	MIMS, June 2012
Apixaban	£2.20	£803	BMS/Pfizer
Warfarin	£0.12	£44	Electronic Drug Tariff[†]
Aspirin	£0.07	£26	Electronic Drug Tariff[†]

[†]Electronic Drug Tariff, November 2011, Department of Health by the NHS Business Services Authority, NHS Prescription Services, http://www.ppa.org.uk/ppa/edt_intro.htm

Table 103: Treatment costs with and without apixaban

	2013-14	2014-15	2015-16	2016-17	2017-18
Without apixaban					
Dabigatran	£9,046,846	£23,544,616	£36,275,906	£46,489,169	£60,905,801
Rivaroxaban	£1,803,424	£7,095,341	£14,442,595	£21,548,998	£31,734,052
Apixaban	£0	£0	£0	£0	£0
Warfarin	£12,483,260	£11,650,141	£10,922,024	£10,274,952	£9,547,304
Aspirin	£3,580,259	£3,491,747	£3,385,203	£3,293,293	£3,046,994
Total	£26,913,789	£45,781,845	£65,025,728	£81,606,410	£105,234,151
With apixaban					
Dabigatran	£7,557,205	£16,294,485	£23,359,765	£27,484,396	£33,994,807
Rivaroxaban	£1,317,887	£3,879,719	£6,375,877	£8,484,696	£12,700,776
Apixaban	£1,998,299	£10,618,878	£21,330,085	£32,691,183	£46,850,616
Warfarin	£12,483,260	£11,650,141	£10,922,024	£10,274,952	£9,547,304

	2013-14	2014-15	2015-16	2016-17	2017-18
Aspirin	£3,580,259	£3,491,747	£3,385,203	£3,293,293	£3,046,994
Total	£26,936,909	£45,934,970	£65,372,954	£82,228,520	£106,140,497
Total net cost with apixaban					
	£23,121	£153,125	£347,226	£622,110	£906,346

8.6 Were there any estimates of resource savings? If so, what were they?

Resource savings associated with reduced acute event compared to rivaroxaban, warfarin and aspirin are summarised in Table 97 and Table 98, follow-up costs compared to rivaroxaban, warfarin and aspirin are summarised in Table 99 and Table 100, and INR monitoring costs were identified and detailed in Table 101 respectively.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 104 presents budget impact estimates for 2013-14 to 2017-18. Apixaban is estimated to be associated with a budget impact of £201,321 in the first year, rising to £4,955,597 in 2017-18.

Table 104: Budget impact

	2013-14	2014-15	2015-16	2016-17	2017-18
Treatment	£23,121	£153,125	£347,226	£622,110	£906,346
INR Monitoring	£0	£0	£0	£0	£0
Event	-£20,330	-£108,474	-£237,671	-£336,130	-£481,931
Follow-up	-£2,381	-£13,771	-£34,680	-£47,975	-£69,302
Annual Net	**£410**	**£30,881**	**£74,875**	**£238,005**	**£355,114**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The current BIM conservatively underestimates the cost savings with NOAC use. Whilst the BIM accounts for the introduction of NOACs inevitably lead to growth in the use of anticoagulation as patients unsuitable for warfarin and/or aspirin (no treatment group) can now be treated it does not account for the savings from avoided events for this group.

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186. Turakhia MP, Zhu PP, Bobulsky SC, Owens DK, Garber AM, Freeman JV. Cost-effectiveness of percutaneous left atrial appendage occlusion for stroke prevention in nonvalvular atrial fibrillation [abstract]. Heart Rhythm Society, May 2010.
187. Wang L. Comparison of mortality, health care utility and costs of patients with warfarin treatment for non-valvular atrial fibrillation versus patients with other treatments [abstract]. ISPOR 13th Annual Congress, November 2010.
188. Zhao Y, Lim L. Cost-effectiveness analysis comparing dabigatran and adjusted-dose warfarin for stroke prevention in atrial fibrillation [abstract]. ISPOR 16th Annual International Meeting, May 2011.
189. Oldgren J, Alings M, Darius H, Diener HC, Eikelboom J, Ezekowitz MD, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Ann Intern Med. 2011 Nov 15;155(10):660-7, W204.
190. Food and Drug Administration. Advisory Committee Briefing Document. Rivaroxaban for the prevention of stroke and non-central nervous system (CNS) systemic embolism in patients with atrial fibrillation, 2011. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM270797.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=Rivaroxaban (39039039)&utm_content=2. [Accessed 22 May 2012].

10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

See separate document.

10.2 Appendix 2: Search strategy and flow diagram for Section 6.1 and 6.2

10.2.1 Databases searched

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid)
- The Cochrane Library
- CINAHL
- BIOSIS

10.2.2 Date on which the search was conducted

The searches were conducted between 20th April and 5th May 2011.

10.2.3 Date span of the search

- Ovid MEDLINE(R) 1948 to present
- EMBASE (Ovid), 1980 to 2011 Week 15
- The Cochrane Library, to present
- CINAHL to present
- BIOSIS Previews 1969 to 2011 Week 01

10.2.4 Search strategy

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present; Searched on April 20th 2011

	Searches	Results
1	exp Atrial Fibrillation/	26543
2	exp Atrial Flutter/	4531
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	38675
4	(rivaroxaban or bay597939).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	305
5	(dabigatran or rendix or pradaxa or bibr1048).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	367
6	(apixaban or bms562247).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	127
7	exp Warfarin/	11948
8	exp Coumarins/	34427
9	(acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos	25889

	or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	
10	exp Vitamin K/ai [Antagonists & Inhibitors]	1125
11	exp Aspirin/	34016
12	(aspirin or acetylsalicylic acid or antiplatelet or anti platelet).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	57749
13	Randomized controlled trials as Topic/	72191
14	Randomized controlled trial/	303986
15	Random allocation/	70909
16	Double blind method/	109216
17	Single blind method/	14791
18	Clinical trial/	461505
19	exp Clinical Trials as Topic/	239264
20	or/13-19	768122
21	(clinic$ adj trial$1).tw.	160023
22	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	109495
23	Placebos/	29455
24	Placebo$.tw.	131635
25	Randomly allocated.tw.	13010
26	(allocated adj2 random).tw.	673
27	or/21-26	333020
28	20 or 27	876712
29	Case report.tw.	166180
30	Letter/	726472
31	Historical article/	273222
32	Review of reported cases.pt.	0
33	Review, multicase.pt.	0
34	or/29-33	1156008
35	28 not 34	851769
36	Meta-Analysis as Topic/	11091
37	meta analy$.tw.	34816
38	metaanaly$.tw.	1044
39	Meta-Analysis/	27932
40	(systematic adj (review$1 or overview$1)).tw.	27874
41	exp Review Literature as Topic/	5479
42	or/36-41	72765
43	cochrane.ab.	17309
44	embase.ab.	14663
45	(psychlit or psyclit).ab.	825

46	(psychinfo or psycinfo).ab.	5109
47	(cinahl or cinhal).ab.	5613
48	science citation index.ab.	1312
49	bids.ab.	298
50	cancerlit.ab.	500
51	or/43-50	27401
52	reference list$.ab.	6288
53	bibliograph$.ab.	9163
54	hand-search$.ab.	2739
55	relevant journals.ab.	463
56	manual search$.ab.	1559
57	or/52-56	18120
58	selection criteria.ab.	14265
59	data extraction.ab.	6741
60	58 or 59	19892
61	Review/	1594221
62	60 and 61	13153
63	Comment/	461098
64	Letter/	726472
65	Editorial/	282392
66	animal/	4708756
67	human/	11646002
68	66 not (66 and 67)	3482075
69	or/63-65,68	4542630
70	42 or 51 or 57 or 62	94247
71	70 not 69	87367
72	1 or 2 or 3	38675
73	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	98019
74	35 or 71	907475
75	72 and 73 and 74	1025
76	Edoxaban.mp.	26
77	betrixaban.mp.	12
78	(plavix or clopidogrel).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	5987
79	73 or 76 or 77 or 78	99726
80	72 and 74 and 79	1032

EMBASE 1980 to 2011 Week 15; Searched on April 20th 2011

	Searches	Results
1	exp Heart Atrium Fibrillation/	48440

2	exp Heart Atrium Flutter/	6782
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	57376
4	exp RIVAROXABAN/	1061
5	(rivaroxaban or bay597939).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1086
6	exp DABIGATRAN/	775
7	(dabigatran or rendix or pradaxa or bibr1048).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1206
8	exp APIXABAN/	517
9	(apixaban or bms562247).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	532
10	exp WARFARIN/	46092
11	exp COUMARIN/	4294
12	(acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	69002
13	(vitamin K antagonist or VKA).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	704
14	exp acetylsalicylic acid/	123719
15	(aspirin or acetylsalicylic acid or antiplatelet or anti platelet).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	139503
16	Clinical trial/	831253
17	Randomized controlled trial/	293851
18	Randomization/	54023
19	Single blind procedure/	14180
20	Double blind procedure/	102732
21	Crossover procedure/	30685
22	Placebo/	178791
23	Randomi?ed controlled trial$.tw.	61444
24	Rct.tw.	6798
25	Random allocation.tw.	1030
26	Randomly allocated.tw.	15459
27	Allocated randomly.tw.	1703
28	(allocated adj2 random).tw.	687
29	Single blind$.tw.	10954
30	Double blind$.tw.	117777
31	((treble or triple) adj blind$).tw.	239
32	Placebo$.tw.	157993

33	Prospective study/	167573
34	or/16-33	1134072
35	Case study/	11722
36	Case report.tw.	199455
37	Abstract report/ or letter/	777524
38	or/35-37	984918
39	34 not 38	1101367
40	exp Meta Analysis/	54067
41	((meta adj analy$) or metaanalys$).tw.	44122
42	(systematic adj (review$1 or overview$1)).tw.	32428
43	or/40-42	94194
44	cancerlit.ab.	595
45	cochrane.ab.	20965
46	embase.ab.	17446
47	(psychlit or psyclit).ab.	914
48	(psychinfo or psycinfo).ab.	4141
49	(cinahl or cinhal).ab.	6311
50	science citation index.ab.	1549
51	bids.ab.	360
52	or/44-51	30858
53	reference lists.ab.	6823
54	bibliograph$.ab.	11106
55	hand-search$.ab.	3108
56	manual search$.ab.	1723
57	relevant journals.ab.	607
58	or/53-57	21075
59	data extraction.ab.	8727
60	selection criteria.ab.	16946
61	59 or 60	24375
62	review.pt.	1689352
63	61 and 62	15597
64	letter.pt.	725161
65	editorial.pt.	369840
66	animal/	1653202
67	human/	12267062
68	66 not (66 and 67)	1254356
69	or/64-65,68	2336938
70	43 or 52 or 58 or 63	119258
71	70 not 69	114166
72	1 or 2 or 3	57376
73	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	192889
74	39 or 71	1151502

75	exp edoxaban/ or Edoxaban.mp.	100
76	betrixaban.mp. or exp BETRIXABAN/	99
77	clopidogrel.mp. or exp CLOPIDOGREL/	23627
78	73 or 75 or 76 or 77	196861
79	72 and 74 and 78	3469

The Cochrane Library, to present; Searched on April 20th 2011

ID	Search	Hits
#1	MeSH descriptor **Atrial Fibrillation** explode all trees	2046
#2	MeSH descriptor **Atrial Flutter** explode all trees	240
#3	(atrial or atrium or auricular) NEAR/3 (fibrillat* or flutter*)	3530
#4	rivaroxaban or bay597939	71
#5	dabigatran or rendix or pradaxa or bibr1048	58
#6	apixaban or bms562247	27
#7	MeSH descriptor **Warfarin** explode all trees	991
#8	MeSH descriptor **Coumarins** explode all trees	1438
#9	acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin	2312
#10	MeSH descriptor **Aspirin** explode all trees	4026
#11	aspirin or acetylsalicylic acid or antiplatelet or anti platelet	9724
#12	(#1 OR #2 OR #3)	3530
#13	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	11725
#14	(#12 AND #13)	581
#15	Edoxaban	5
#16	betrixaban	5
#17	plavix or clopidogrel	1082
#18	(#13 OR #15 OR #16 OR #17)	11977
#19	(#12 AND #18)	583†

†2 cochrane groups so 581 exported

CINAHL; Searched on 5th May 2011

#	Query	Results
S1	(MH "Atrial Fibrillation")	7543
S2	(MH "Atrial Flutter")	846
S3	atrial N3 fibrillat* or atrium N3 fibrillat* or auricular N3 fibrillat*	9123
S4	atrial N3 flutter* or atrium N3 flutter* or auricular N3 flutter*	1230
S5	rivaroxaban or bay597939	91
S6	dabigatran or rendix or pradaxa or bibr1048	129

S7	apixaban or bms562247	25
S8	(MH "Warfarin")	3211
S9	coumarin*	204
S10	acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin	4079
S11	Vitamin K antagonist* or Vitamin K inhibitor*	239
S12	(MH "Aspirin")	5293
S13	aspirin or acetylsalicylic acid or antiplatelet or anti platelet	7839
S14	Edoxaban	4
S15	betrixaban	3
S16	plavix or clopidogrel	1886
S17	S1 or S2 or S3 or S4	9654
S18	S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	12334
S19	(MH "Randomized Controlled Trials")	6583
S20	(MH "Random Assignment")	28868
S21	(MH "Double-Blind Studies")	19184
S22	(MH "Single-Blind Studies")	5229
S23	(MH "Clinical Trials+")	114149
S24	S19 or S20 or S21 or S22 or S23	124689
S25	clinic* N1 trial*	100442
S26	(singl* N1 blind*) or (singl* N1 mask)	5780
S27	(doubl* N1 blind*) or (doubl* N1 mask)	22593
S28	(tripl* N1 blind*) or (tripl* N1 mask)	89
S29	(MH "Placebos")	6561
S30	Placebo*	22529
S31	Randomly allocated	1651
S32	allocated N2 random	33
S33	S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32	126206
S34	S24 or S33	143516
S35	Case report	17986
S36	(MH "Historical Records") OR (MH "Historical Research")	1169
S37	PT Review	90936
S38	S35 or S36 or S37	109689
S39	S34 NOT S38	133500
S40	(MH "Meta Analysis")	12146
S41	meta analy*	16856
S42	metaanaly*	310
S43	(systematic N1 review*) OR (systematic N1 overview*)	23380
S44	S40 or S41 or S42 or S43	33048
S45	AB cochrane	7926

S46	AB embase	6075
S47	AB psychlit or psyclit	371
S48	AB psychinfo or psycinfo	5366
S49	AB cinahl or cinhal	9856
S50	AB science citation index	563
S51	AB bids	108
S52	AB cancerlit	182
S53	S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52	17468
S54	AB reference list*	2992
S55	AB bibliograph*	2990
S56	AB hand-search*	1122
S57	AB relevant journals	320
S58	AB manual search*	465
S59	S54 or S55 or S56 or S57 or S58	6967
S60	AB selection criteria	5840
S61	AB data extraction	2305
S62	S60 or S61	7428
S63	(MH "Animals")	30873
S64	(MH "Human")	846373
S65	S63 NOT (S63 AND S64)	24145
S66	S44 or S53 or S59 or S62	43633
S67	S66 NOT S65	43519
S68	S39 or S67	164551
S69	S17 and S18 and S68	249

BIOSIS Previews 1969 to 2011 Week 01

	Searches	Results
1	((atrial or atrium or auricular) adj3 (fibrillat$ or flutter$)).mp.	24846
2	(rivaroxaban or bay597939).mp.	226
3	(dabigatran or rendix or pradaxa or bibr1048).mp.	184
4	(apixaban or bms562247).mp.	105
5	(acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin).mp.	22944
6	(aspirin or acetylsalicylic acid or antiplatelet or anti platelet).mp.	48151
7	Edoxaban.mp.	22
8	betrixaban.mp.	15
9	(plavix or clopidogrel).mp.	5325
10	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	70533
11	(clinic$ adj trial$1).mp.	100063
12	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	84633

13	Placebo$.mp.	101362
14	Randomly allocated.mp.	8910
15	(allocated adj2 random).mp.	487
16	11 or 12 or 13 or 14 or 15 (225453)	225453
17	Case report.mp.	78128
18	letter.pt.	109900
19	historical article.mp.	3764
20	17 or 18 or 19	190758
21	16 not 20	224378
22	meta analy$.mp.	23998
23	metaanaly$.mp.	978
24	(systematic adj (review$1 or overview$1)).mp.	12632
25	22 or 23 or 24	32969
26	cochrane.ab.	4334
27	embase.ab.	4416
28	(psychlit or psyclit).ab.	215
29	(psychinfo or psycinfo).ab.	892
30	(cinahl or cinhal).ab.	916
31	science citation index.ab.	451
32	bids.ab.	159
33	cancerlit.ab.	179
34	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	7742
35	reference list$.ab.	2418
36	bibliograph$.ab.	9562
37	hand-search$.ab.	833
38	relevant journals.ab.	85
39	manual search$.ab.	685
40	35 or 36 or 37 or 38 or 39	12885
41	selection criteria.ab.	4494
42	data extraction.ab.	2708
43	41 or 42	7125
44	review.mp.	514861
45	"literature review".lt.	477461
46	44 or 45	830868
47	43 and 46	2952
48	editorial.lt.	104789
49	letter.pt.	109900
50	animal.or.	103457
51	human.or.	4250276
52	50 not (50 and 51)	77423
53	48 or 49 or 52	275524
54	25 or 34 or 39 or 47	37492

55	54 not 53	36454
56	21 or 55	254086
57	1 and 10 and 56	275
58	from 57 keep 1-275	275

10.2.5 Additional searches

Additional studies were identified by hand searching the following resources:

- Reference lists of retrieved articles
- Conference proceedings (2006–2010)
  - European Congress of Cardiology and meetings of the Joint Working Groups of the European Society of Cardiology (published in European Heart Journal)
  - Scientific sessions of the American Heart Association (published in Circulation)
  - Annual meeting of the American College of Cardiology (published in The Journal of the American College of Cardiology)
- clinicaltrials.gov
- NCI clinical trial database
- ISRCTN Register
- UKCCR Register of Cancer Trials
- EORTC
- UK Clinical Trials Gateway
- metaRegister (mRCT) of Controlled Trials

10.2.6 Inclusion and exclusion criteria.

	Description	**Justification**
Inclusion criteria		
Population	Adult patients (≥18 years of age), with paroxysmal, sustained or permanent non-valvular AF of any duration and any aetiology documented by electrocardiogram.	As specified by final scope
Interventions	• Vitamin K antagonist (VKA) including adjusted-dose warfarin • Acetylsalicylic acid (ASA) • Rivaroxaban • Dabigatran • Apixaban	As specified by final scope

	Description	Justification

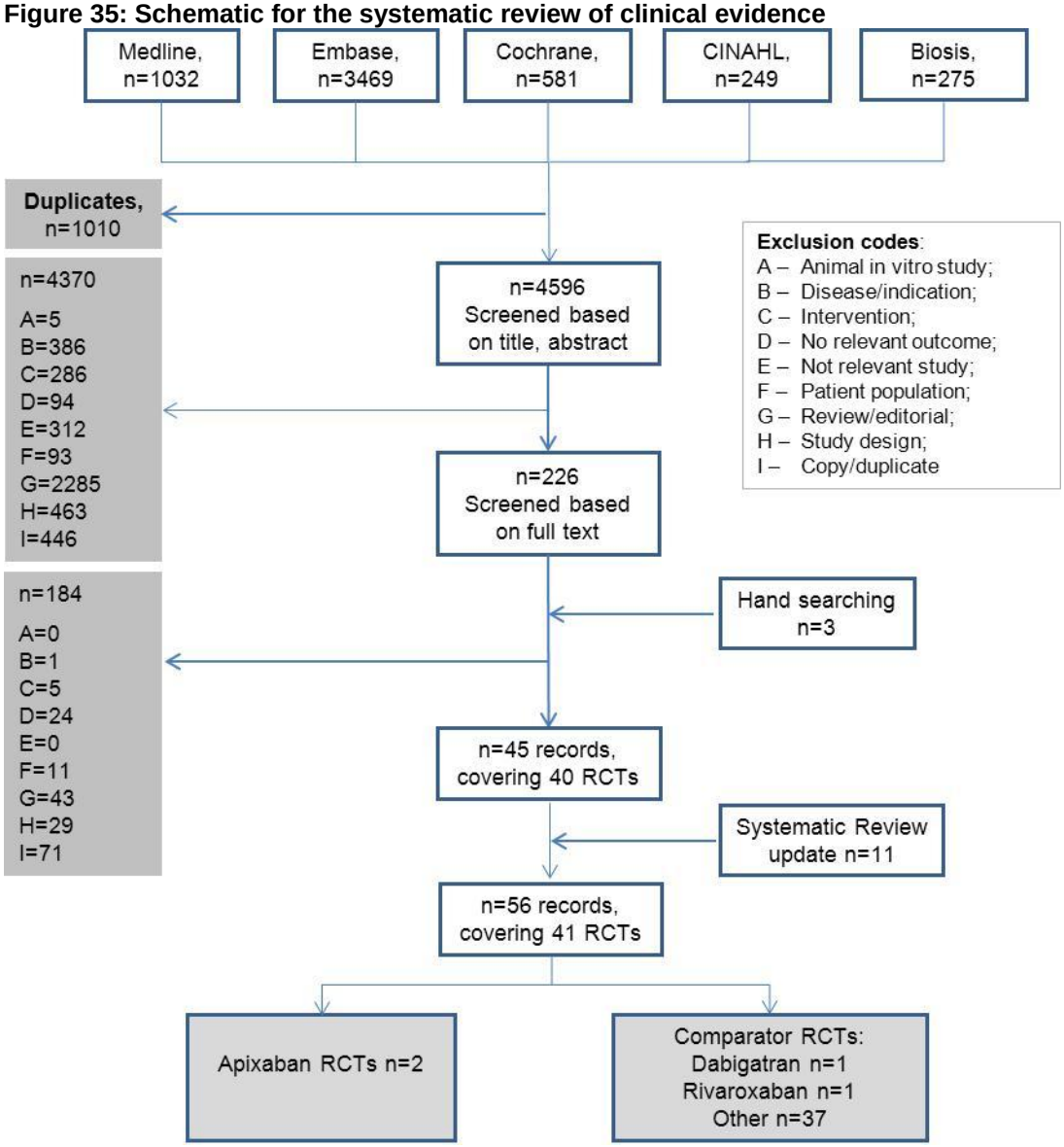
Outcomes	• Thromboembolism
	  ○ Ischaemic strokes (including both fatal and non-fatal)
	  ○ All disabling or fatal strokes (ischaemic and haemorrhagic)
	• Myocardial infarction (fatal and non-fatal)
	• Systemic (non-CNS) emboli
	• Major/minor bleeding
	  ○ All intracranial haemorrhages
	  ○ Major extracranial haemorrhages
	• Mortality
	  ○ All-cause death
	  ○ Vascular mortality
	• Readmission rates
	• Composite outcomes (e.g. all strokes, myocardial infarction or vascular death)
		As specified by final scope

Study design	Prospective randomised controlled trials	Non-RCT studies were identified through a separate search
Language restrictions	No restriction	
Exclusion criteria		
Population	Subjects <18 years of age, patients with valvular/rheumatic AF	As specified by final scope
Interventions	Studies not investigating apixaban or relevant comparator	As specified by final scope
Study design	Non-RCT	Non-RCT studies were identified through a separate search
Language restrictions	No restriction	

10.2.7 Data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into a pre-defined Microsoft Word® document by a reviewer. A second reviewer independently extracted relevant outcome data and any inconsistencies were resolved through a discussion.

Figure 35: Schematic for the systematic review of clinical evidence



10.3 Appendix 3: Quality assessment of RCT(s)

Table 105: Quality assessment of ARISTOTLE

ARISTOTLE (2)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/ not clear/NA)**
Was randomisation carried out appropriately?	At the time of enrolment, each subject was assigned a unique sequential subject number via IVRS. Subjects were randomised 1:1 to apixaban or warfarin via IVRS. Randomisation was stratified by investigative site and prior warfarin/VKA status (experienced or naïve). Subjects were randomised in blocks of 2.	Yes
Was the concealment of treatment allocation adequate?	Study medications were prepared in a double dummy design using placebo matching the active treatments. Dosing for warfarin/warfarin-placebo was based on INR monitoring using a blinded, encrypted, point-of-care INR device. An algorithm was provided to guide the adjustment of the warfarin dose	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The two treatment groups were well balanced with respect to both baseline demographic and disease characteristics.	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)?	Subjects, investigators, administrative/adjudication committees, and the Sponsor's staff conducting the study were blind to treatment assignments.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Fewer subjects discontinued study drug permanently in the apixaban group (25.3%) than in the warfarin group (27.5%) (p=0.001). The most common reasons for discontinuation in both treatment arms were subject's request to discontinue study treatment and AEs.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes planned to be measured in the study protocol appear to be reported in the clinical study report.	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?	The primary and secondary efficacy analyses included all patients who underwent randomisation (ITT). The analyses of bleeding events included all patients who received at least one dose of a study drug. This was considered appropriate.	Yes

Table 106: Quality assessment of AVERROES

AVERROES (3)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/ not clear/NA)**
Was randomisation carried out appropriately?	At the time of enrolment, each subject was assigned a unique sequential subject number via IVRS. Subjects were randomised 1:1 to apixaban or aspirin via IVRS. Randomisation was stratified by study site. The subjects were randomised in blocks of 4.	Yes
Was the concealment of treatment allocation adequate?	Study medications were prepared in a double dummy design using placebo matching the active treatments.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The treatment groups were well balanced for the baseline characteristics and physical measurements with no clinically relevant differences for randomised subjects.	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)?	Subjects, investigators, administrative/adjudication committees, and the Sponsor's staff conducting the study were blind to treatment assignments.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Fewer subjects discontinued study drug permanently in the apixaban group (19.9%) than in the aspirin group (23.3%). The most common reasons for discontinuation in both treatment arms were subject's request to discontinue study treatment and AEs.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes planned to be measured in the study protocol appear to be reported in the clinical study report.	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?	All primary efficacy and safety analyses were based on the intention-to-treat (ITT) principle. This was considered appropriate.	Yes

10.4 Appendix 4: Search strategy for Section 6.7

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for comparator interventions, relevant to the decision problem.

10.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 6.7

Study question	Study name			
	ARISTOTLE (2, 67)	ROCKET-AF (63)	RE-LY (58)	AVERROES (3, 68)
Overall grading	++	+	+	++
Overall risk of bias	Low risk of bias	Unclear/ unknown	Unclear/ unknown	Low risk of bias
A. Selection bias (systematic differences between the comparison groups				
A1. An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	Yes	Yes	Yes
A2. There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Ye	Yes	Yes	Yes
A3. The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Yes	Yes
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?	Low risk of bias	Unclear/ unknown	Low risk of bias	Low risk of bias
B. Performance bias (systemic differences between groups in the care provided, apart from the intervention under investigation				
B1. The comparison groups received the same care apart from the intervention(s) studied	Yes	Yes	No	Yes
B2. Participants receiving care were kept 'blind' to treatment allocation	Yes	Yes	No	Yes
B3. Individuals administering care were kept 'blind' to treatment allocation	Yes	Yes	No	Yes
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias

Study question	Study name			
	ARISTOTLE (2, 67)	ROCKET-AF (63)	RE-LY (58)	AVERROES (3, 68)
C. Attrition bias (systematic differences between the comparison groups with respect to the loss of participants)				
C1. All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	Yes	Yes	Yes
C2a. How many participants did not complete treatment in each group?	Apix:2310 Warf: 2493	Riva:1691 Warf: 1584	Dabi 110: 2023 Dabi 150:2146 Warf: 1510	At 2 yrs: apix: 17.9%/yr Asp: 20.5%/yr
C2b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	Yes	Yes	Yes
C3a. For how many participants in each group were no outcome data available	NR	NR	NR	NR
C3b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Unclear	Unclear	Unclear	Unclear
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?	Unclear/ unknown	Unclear/ unknown	Unclear/ unknown	Unclear/ unknown
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)				
D1. The study had an appropriate length of follow-up	Yes	Yes	Yes	Yes
D2. The study used a precise definition of outcome	Yes	Yes	Yes	Yes
D3. A valid and reliable method was used to determine the outcome	Yes	Yes	Unclear	Unclear
D4. Investigators were kept ‘blind’ to participants’ exposure to the intervention	Yes	Yes	Yes	Yes
D5. Investigators were kept ‘blind’ to other important confounding and prognostic factors	Unclear	Unclear	Unclear	Yes

Study question	Study name			
	ARISTOTLE (2, 67)	ROCKET-AF (63)	RE-LY (58)	AVERROES (3, 68)
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?	Low risk of bias	Low risk of bias	Unclear/ unknown	Low risk of bias

10.6 Appendix 6: Search strategy and flow diagram for Section 6.2 and 6.8

10.6.1 Databases searched

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE
- The Cochrane Library, incorporating the;
  - Cochrane Database of Systematic Reviews
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Database of Abstracts of Reviews of Effects (DARE)
  - Health Technology Assessment Database (HTA)

10.6.2 Date on which the search was conducted

The searches were conducted on 13th December 2011.

10.6.3 Date span of the search

- Ovid MEDLINE(R) 1948 to present
- EMBASE (Ovid), 1980 to Week 49 2011
- The Cochrane Library,1968 to present

10.6.4 Search strategy

All the following searches were combined and inclusion/exclusion criteria applied.

Embase 1980 to 2011 Week 49; Searched on December 13th 2011

	Searches	Results
1	Clinical study/	35333
2	Case control study/	56026
3	Family study/	9344
4	Longitudinal study/	47195
5	Retrospective study/	244680
6	Prospective study/	177986
7	Randomized controlled trials/	10742
8	6 not 7	177724
9	Cohort analysis/	105908
10	(Cohort adj (study or studies)).mp.	70727
11	(Case control adj (study or studies)).tw.	55392
12	(follow up adj (study or studies)).tw.	36984
13	(observational adj (study or studies)).tw.	38757
14	(epidemiologic$ adj (study or studies)).tw.	59992
15	(cross sectional adj (study or studies)).tw.	53988
16	or/1-5,8-15	819385
17	heart atrium fibrillation.mp. or exp heart atrium fibrillation/	54002

18	heart atrium flutter.mp. or exp heart atrium flutter/	7249
19	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	63319
20	apixaban.mp. or exp apixaban/	742
21	eliquis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	6
22	(bms562247 or bms-562247-01).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	6
23	17 or 18 or 19	63319
24	20 or 21 or 22	742
25	16 and 23 and 24	9

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present; Searched December 13th 2011

	Searches	Results
1	Epidemiologic studies/	5258
2	exp case control studies/	538109
3	exp cohort studies/	1153303
4	Case control.tw.	62088
5	(cohort adj (study or studies)).tw.	61852
6	Cohort analy$.tw.	2775
7	(Follow up adj (study or studies)).tw.	33989
8	(observational adj (study or studies)).tw.	31641
9	Longitudinal.tw.	115867
10	Retrospective.tw.	217085
11	Cross sectional.tw.	127005
12	Cross-sectional studies/	135354
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1575364
14	atrial fibrillation.mp. or exp Atrial Fibrillation/	38699
15	atrial flutter.mp. or exp Atrial Flutter/	6133
16	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	41750
17	(apixaban or bms562247 or bms-562247-01).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	207
18	eliquis.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	0
19	14 or 15 or 16	41750
20	17 or 18	207
21	13 and 19 and 20	3

Cochrane Library 1986 to present; Searched on December 13th 2011

ID	Search	Hits
#1	MeSH descriptor **Atrial Fibrillation** explode all trees	2056
#2	MeSH descriptor **Atrial Flutter** explode all trees	245
#3	(atrial or atrium or auricular) NEAR/3 (fibrillat* or flutt*)	3616
#4	apixaban or bms562247 or bms-562247-01 or eliquis	39
#5	(#1 OR #2 OR #3)	3616
#6	(#4 AND #5)	9
	Cochrane Reviews [2] | Other Reviews [0] | Clinical Trials [6] | Methods Studies [0] | Technology Assessments [1]	

10.6.5 Additional searches

Additional studies were identified by hand searching the following resources:

- Relevant systematic reviews
- Conference proceedings (2009–2011, inclusive)
  - ISPOR – International Society for Pharmacoeconomics and Outcomes Research
  - ESC – European Congress of Cardiology
  - AHA – American Heart Association
  - ACC – American College of Cardiology
  - iHEA – International Health Economics Association
  - Heart Rhythm Society

10.6.6 Inclusion and exclusion criteria.

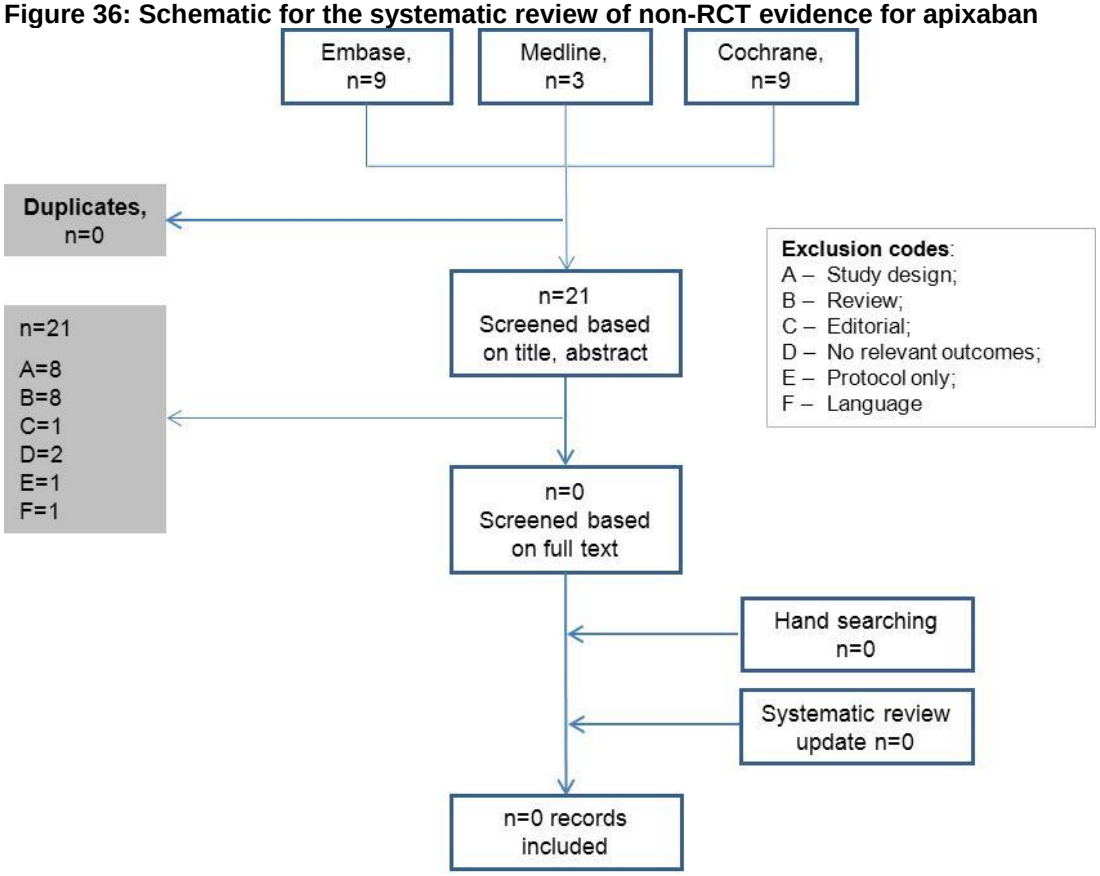
	Description	Justification
Inclusion criteria		
Population	Adult patients (≥18 years of age), with paroxysmal, sustained or permanent AF who are at mild, moderate, or high risk of stroke or systemic embolism	As specified by final scope
Interventions	• Apixaban • No restriction on comparator	As specified by final scope
Outcomes	• Stroke • Systemic embolism • Myocardial infarction (fatal and non-fatal) • Composite outcomes (e.g. all strokes, myocardial infarction or vascular death) • Major/minor bleeding • Intracranial bleeding • Gastrointestinal bleeding • Mortality • Readmission rates	

	Description	Justification
Study design	Non-RCTs including: • Prospective cohorts • Case-control/case-referent studies • Retrospective cohorts • Database studies • Cross-sectional studies	RCTs were identified through a separate search
Exclusion criteria		
Population	Subjects <18 years of age, patients with acute AF	
Interventions	Studies not investigating apixaban	
Study design	RCTs	RCTs were identified through a separate search
Language restrictions	Non-English publications	

10.6.7 Data abstraction strategy.

N/A

Figure 36: Schematic for the systematic review of non-RCT evidence for apixaban



10.7 Appendix 7: Quality assessment of non-RCT(s) in Section 6.8

No relevant studies were identified for apixaban.

10.8 Appendix 8: Search strategy for Section 6.9

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for adverse events associated with intervention name.

10.9 Appendix 9: Quality assessment of adverse event data in Section 6.9

A quality assessment of relevant studies can be found in Section 10.3.

10.10 Appendix 10: Search strategy for Section 7.1 – cost-effectiveness

10.10.1 Databases searched

The following databases were searched via OVID and the Cochrane library:

- Medline® In-Process & Other Non-Indexed Citations and OVID MEDLINE 1948-present
- Embase 1980-present
- EconLit 1961-present
- Cochrane's NHS Economic Evaluation Database (NHS EED) 1968-present

10.10.2 Date on which the search was conducted

The searches were performed on the 12th December 2011.

10.10.3 Date span of the search

All databases were search from 1990 to the 12th December 2011.

10.10.4 Search strategy

Embase 1980-present, searched 12th December 2011

	Searches	Results
1	exp Atrial Fibrillation/	53967
2	exp Atrial Flutter/	7249
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	63319
4	exp economics/ or exp health economics/	630303
5	Socioeconomics/	93173
6	Cost benefit analysis/	56921
7	Cost effectiveness analysis/	76829
8	Economic aspect/	86469
9	Health economics/	30734
10	Cost minimization analysis/	1977
11	exp economic evaluation/	174957
12	exp pharmacoeconomics/	142146
13	exp "cost utility analysis"/	3878
14	(cost effective* or cost utilit* or CEA or CUA).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	135572
15	exp statistical model/ or exp hidden Markov model/	78965
16	exp "decision tree"/	4145
17	exp medical decision making/	58588
18	exp theoretical model/	52124
19	exp quality adjusted life year/	8137
20	(incremental cost effectiveness ratio or icer).mp. [mp=title, abstract, subject	3019

	headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	
21	or/1-3	63319
22	or/4-20	963285
23	21 and 22	3293
24	limit 23 to yr="1990 -Current"	3275
25	limit 24 to english	3034
26	limit 25 to (adult <18 to 64 years> or aged <65+ years>)	938
27	limit 26 to human	917

Medline and Medline InProcess 1948-present, searched 12th December 2011

	Searches	Results
1	exp Atrial Fibrillation/	28533
2	exp Atrial Flutter/	4658
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	41750
4	Economics/	26513
5	"costs and cost analysis"/	39377
6	Cost-benefit analysis/	52908
7	Health expenditures/	12037
8	Value of life/	5202
9	exp economics, medical/	13589
10	Economics, nursing/	3855
11	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	145030
12	exp Economics, Hospital/	17734
13	exp economics, pharmaceutical/	2307
14	exp Quality-Adjusted Life Years/	5364
15	(cost effective* or cost utilit* or CEA or CUA).mp.	78166
16	exp Models, Statistical/ or exp Markov Chains/ or exp Computer Simulation/ or exp Models, Theoretical/	1120210
17	exp Patient Simulation/	2326
18	exp Decision Trees/	7837
19	exp Models, Theoretical/	1088235
20	(incremental cost effectiveness ratio or icer).mp.	2118
21	1 or 2 or 3	41750
22	or/4-20	1425716
23	21 and 22	3010
24	limit 23 to yr="1990 -Current"	2929
25	limit 24 to english	2772
26	limit 25 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)")	1590

EconLit 1961-present, searched 12th December 2011

	Searches	Results
1	atrial fibrillat*.mp.	7
2	atrial flutter.mp.	0
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp.	7
4	1 or 2 or 3	7

Cochrane – NHS EED 1968-present, searched 12th December 2011

ID	Search	Hits
#1	MeSH descriptor Atrial Fibrillation explode all trees	2056
#2	MeSH descriptor Atrial Flutter explode all trees	245
#3	(atrial or atrium or auricular) NEAR/3 (fibrillat* or flutter*)	3616
#4	(#1 OR #2 OR #3)	3616
#5	(#4), from 1990 to 2011	3391
#6	#5 in NHS EED†	125

†This confines the search to NHS EED

10.10.5 Additional searches

Additional studies were identified by hand searching the following resources:

- Manufacturer databases
- Cost Effectiveness Analysis (CEA) Registry
- Relevant NICE submission/appraisal data (e.g. for dabigatran and rivaroxaban)
- The following conference proceedings (2009-2011 inclusive)
    - ISPOR – International Society for Pharmacoeconomics and Outcomes Research
    - ESC – European Congress of Cardiology
    - HRS – Heart Rhythm Society
    - AHA – American Heart Association
    - ACC – American College of Cardiology
    - iHEA – International Health Economics Association

10.10.6 Inclusion and exclusion criteria.

Inclusion criteria

- Study design – Any form of economic evaluation presenting both costs and outcomes
- At least one treatment arm including stroke/systemic embolism prophylaxis in patients with AF

Exclusion criteria

- Clinical results only
- Studies reporting only costs or only benefits
- Prevention of adverse events (AEs) other than stroke or SE

- Treatment of AF rather than stroke or SE prophylaxis
- Non-English language

10.10.7 Data abstraction strategy.

Identified studies were independently assessed by a reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria. Any uncertainties were resolved by a second analyst or project lead. Data were extracted from eligible publications into a pre-defined table by a reviewer and verified by a second analyst or project lead.

10.10.8 Description of identified studies

A summary of the 20 full text papers identified via the systematic literature search and five conference abstracts identified via hand searching is provided in Table 107.

Figure 37: Schematic for the systematic review of cost-effectiveness evidence

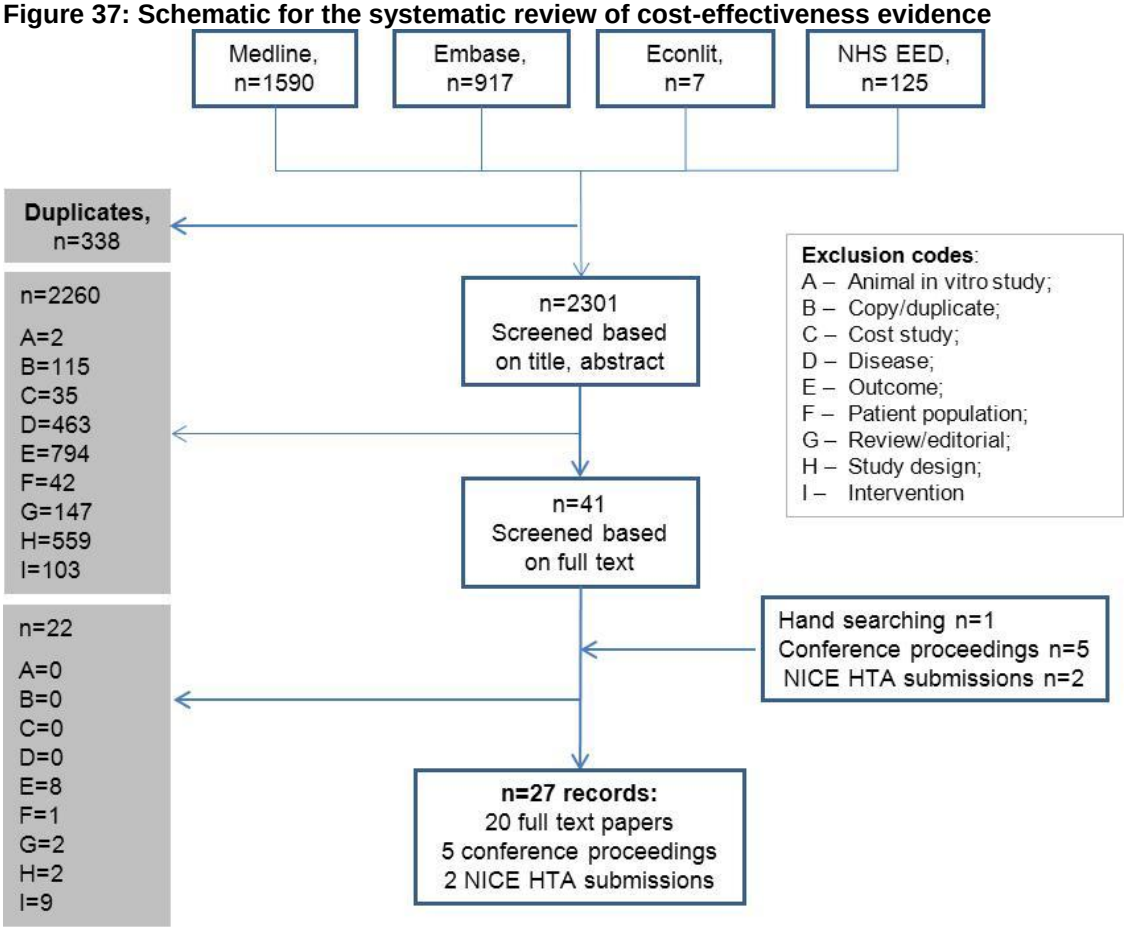


Table 107: Summary of identified cost-effectiveness studies and conference abstracts

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
Caro 2004 (171) US	No economic model - statistical analysis of US macro-economic data. 1-year time horizon	• Warfarin (in different clinical scenarios)	All US patients with AF aged ≥ 65. Baseline characteristics based on Medicare-aged patients in SPORTIF trial	NR	Current cost of strokes: • ~£8bn total • $3,435 per AF patient on average • $4,586bn in untreated AF patients Potential savings if 50% of untreated AF patients were treated with warfarin: $1,140bn	NR
Catherwood 1999 (172) US	Markov Model adapted from Gage 1995 (97). 3-month time horizon	• CV then warfarin upon relapse • CV then aspirin upon relapse	Hypothetical cohort of 70 year old NVAF patients with different baseline risks for stroke	High stroke risk (5.3% p.a.): • CV then warfarin: 8.68 • CV then aspirin: 8.41 Moderate stroke risk (3.6% p.a.): • CV then warfarin: 8.86 • CV then aspirin: 8.76 Low stroke risk of (1.6% p.a.): • CV then warfarin: 9.07 • CV then aspirin: 9.21	High stroke risk (5.3% p.a.): • CV then warfarin: $18,400 • CV then aspirin: $21,300 Moderate stroke risk (3.6% p.a.): • CV then warfarin: $16,900 • CV then aspirin: $18,300 Low stroke risk (1.6% p.a.): • CV then warfarin: $14,800 • CV then aspirin: $14,000	Moderate or high risk of stroke: • CV followed by warfarin dominates CV followed by aspirin Low risk of stroke: • CV followed by aspirin dominates CV followed by warfarin
Desbiens 2002 (173) US	Markov Model.	• Warfarin • No anti-coagulation	AF patients aged 65-100. History of stroke/TIA, diabetes or hypertension	• 65 year-old: 2.2 QALYs • 85 year-old: 0.5 QALYs	• 65 year-old: $1,434 • 85 year-old: $1,767	95 year-old patient: $30,000/QALY
Eckman 2009 (174) US	Markov Model with a 1 month cycle. Lifetime horizon	• Genotype-guided warfarin dosing • Standard warfarin induction	US 69 year old male with recently-diagnosed NVAF and no contra-indication to warfarin therapy	Using a 3% Discount • Standard anticoagulation: 7.5759 • Genotype-guided dosing: 7.5780 No discount	Using a 3% Discount • Standard anticoagulation: $19,315 • Genotype-guided dosing: $19,684 No Discount • Standard anticoagulation: $23,243 • Genotype-guided dosing: $23,610	3% Discount • Genotype-guided dosing vs standard induction: $171,750 No Discount • Genotype-guided dosing

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
				• Standard anticoagulation: 8.9873 • Genotype-guided dosing: 8.9898		vs standard induction: $114,057
Freeman 2011 (96) US	Markov Model with 15 health states. Lifetime horizon	• Dabigatran 2x110mg/day • Dabigatran 2x150mg/day • Warfarin	NVAF patients, aged 65 or older, with $CHADS_2$ score >0	• Warfarin: 10.28 • Dabigatran 110 mg: 10.70 • Dabigatran 150 mg: 10.84	• Warfarin: $143,193 • Dabigatran 110 mg: $164,576 • Dabigatran 150 mg: $168, 398	• Dabigatran 110 mg vs warfarin: $51,229 per QALY • Dabigatran 150 mg vs warfarin: $45,372 per QALY
Gage1995 (97) US	Markov Model. 10-year time horizon	• Warfarin • Aspirin • No treatment	65 year-old US NVAF patients, with varying risks of stroke and good candidates for warfarin and aspirin therapy	High risk of stroke: • Warfarin: 6.51 • Aspirin: 6.27 • No therapy: 6.01 Medium risk of stroke: • Warfarin: 6.60 • Aspirin: 6.46 • No therapy: 6.23 Low risk of stroke: • Warfarin: 6.70 • Aspirin: 6.69 • No therapy: 6.51	High risk of stroke: • Warfarin: $12,500 • Aspirin: $13,200 • No therapy: $15,300 Medium risk of stroke: • Warfarin: $10,900 • Aspirin: $9,700 • No therapy: $11,400 Low risk of stroke: • Warfarin: $9,000 • Aspirin: $5,400 • No therapy: $6,300	High risk of stroke: • Warfarin dominates aspirin and no therapy Medium risk of stroke: • Warfarin vs Aspirin: $8,000 • Warfarin dominates no therapy Low risk of stroke: • Warfarin vs Aspirin: $370,000 • Warfarin vs no therapy: $14,000
Gage 1998 (175) US	Markov Model. 10-year time horizon	• Warfarin • Warfarin or aspirin (patient preference)	US 65-year-old patients with NVAF and no contra-indications to antithrombotic therapy	Low-Risk Patients • Warfarin: 6.7 • Preference-based therapy: 6.75 Medium-Risk Patients • Warfarin: 6.6	Low-Risk Patients (over 10 years) • Warfarin: $9,000 • Preference-based therapy: $8,330 • Aspirin (used in preference-based therapy) would save $3,560 per patient	Low-Risk Patients • Preference-based therapy resulted in an additional 0.05 QALYs for $670 less Medium-Risk Patients

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
				• Preference-based therapy: 6.62 Low-Risk Patients • Warfarin: 6.51 • Preference-based therapy: 6.52	Medium-Risk Patients (over 10 years) • Warfarin: $10,860 • Preference-based therapy: $10,770 High-Risk Patients (over 10 years) • Warfarin: $12,490 • Preference-based therapy: $12,600	• Preference-based therapy resulted in 0.02 additional QALYs and saved $90 per person High-Risk Patients • Preference-based therapy resulted in 0.01 QALYs and cost an additional $110
Gustafsson 1992 (176) Sweden	No model - Statistical analysis of macro-economic data. 1-year time horizon	• Anticoagulation • Aspirin	An estimated 83,000 Swedish patients aged 50–89 years with AF	NR	Net cost per stroke prevented (direct and indirect costs) • Aspirin: Kr–262 • Anticoagulation (0.3% risk of haemorrhage): Kr–99 • Anticoagulation (1.3% risk of haemorrhage): Kr–3 • Anticoagulation (2% risk of haemorrhage): Kr–147	NR
Jowett 2011 (177) UK	None - direct analysis of clinical trial data (BAFTA), compared to associated cost data. 4-year time horizon	• Warfarin • Aspirin	Patients with AF (≥ 75 years) based on clinical trials, in particular BAFTA trial	Adjusted QALYs, 4 year period • Warfarin: 1.685 • Aspirin: 1.665	Mean Total Costs • Warfarin: £1,382 • Aspirin: £1,548	Warfarin is dominant, but differences in costs and effects are small
Lightowlers 1998 (178) UK	No model - analysis of clinical trial data. 10-year time horizon	• Warfarin (using different clinical inputs)	Patient population based on clinical trials, in particular BAATAF Trial	NR – paper only reports life years gained without stroke	• 10-Year cost of stroke (warfarin group) (discounted) £316,422.81–£743,974.58 (depending on source of clinical data) • 10-Year No-Treatment Group	NR – papers only reports cost per life year gained without stroke

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
					(discounted) £696,531.87–£1,484,875.90	
Mercaldi 2011 (179) US	No model - direct analysis of Medicare and Medicaid patients' clinical data, compared with estimated cost data. 1-year time horizon	• Warfarin • No treatment	5% Sample of 2004-2005 Medicare and Medicaid NVAF patients with irreversible causes of AF, aged ≥75	NR	Total Mean Annual Medical Costs: • All AF patients: $19,888 • Warfarin patients: $18,621 • Patients not taking Warfarin: $22,135	NR
O'Brien 2005 (180) US	Semi-Markov Model. 20-year time horizon	• Ximelagatran • Warfarin • Aspirin	Hypothetical cohort of 70 year-old patients with chronic atrial fibrillation and moderate risk of stroke and lower risk of ICH	• Ximelagatran: 9.51 • Warfarin: 9.39 • Aspirin: 8.58	• Ximelagatran: $32,000 • Warfarin: $19,000 • Aspirin: $17,000	• Ximelagatran vs aspirin: $16,200 • Ximelagatran vs warfarin: $116,000 • Warfarin vs aspirin: $2,000
Patrick 2009 (181) US	Markov Model with 3-month cycles. Lifetime horizon	• Genotype-guided warfarin dosing • Standard warfarin induction	Hypothetical cohort of 70-year-old patients with newly-diagnosed AF	Warfarin (discounted): 7.28	Warfarin: $22,541 lifetime	If genotyping increases time spent in INR range by 5 percentage points (e.g. from 57.7% to 62.7%), ICER would be $100,000 per QALY for genotype-guided warfarin vs. warfarin
Pink 2011 (98) UK	Discrete event simulation. Lifetime horizon	• Dabigatran 2x110mg/day • Dabigatran 2x150mg/day	Cohort of 50,000 simulated patients at moderate to high risk of stroke with a mean baseline	Incremental QALYs: • Dabigatran 110mg vs warfarin: 0.094 (95% central range –0.083 to 0.267)	Lifetime: • Dabigatran 110mg: £10,529 • Dabigatran 150mg: £9,850 • Warfarin: £6,480	• Dabigatran 110mg vs warfarin: £43,074 per QALY • Dabigatran 150mg vs warfarin: £23,082 per

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
		• Warfarin	$CHADS_2$ score of 2.1	• Dabigatran 150mg vs warfarin: 0.146 (central range –0.029 to 0.322) • Dabigatran 150mg vs dabigatran 110mg: 0.052 (central range –0.122 to 0.228)		QALY • Dabigatran 150mg vs dabigatran 110mg: Dominated (costs an additional £679 for 0.052 fewer QALYs)
Quinn 2007 (182) US	Markov Model, 1 month cycles. Lifetime horizon	• Warfarin • Aspirin • No Treatment	60 year old haemodialysis patient with permanent AF	Discounted: • No treatment: 1.51 • ASA: 1.57 • Warfarin: 1.66 Incremental QALYs: • Warfarin vs ASA: 0.09 • ASA vs no treatment: 0.06	Discounted • No treatment: $256,059 • ASA: $260,546 • Warfarin: $268,555 Incremental cost • Warfarin vs ASA: $8,009 • ASA vs no treatment: $4,487	• Warfarin vs ASA: $88,400 per QALY • ASA vs no treatment: $82,100 per QALY
Shah 2011 (100) US	Markov Model with 8 health states and a 1 month cycle. 20-year time horizon	• Dabigatran 2x110mg/day • Dabigatran 2x150mg/day • Warfarin • Aspirin+ Clopidogrel • Aspirin • No therapy	Hypothetical cohort of 70-year-old patients based on the RE-LY clinical trial with moderate risk of stroke and no contra-indication to anti-coagulation. Risk of stroke varied in sensitivity analysis	• Dabigatran 2x150mg/day: 8.65 • Dabigatran 2x110mg/day: 8.54 • Warfarin: 8.40 • Dual Therapy: 8.32 • Aspirin: 8.17	• Dabigatran 2x150mg/day: $43,700 • Dabigatran 2x110mg/day: $44,300 • Warfarin: $23,000 • Dual Therapy: $34,000 • Aspirin: $20,000	Vs Aspirin (per QALY) • Dabigatran 2x150mg/day: $50,000 • Dabigatran 2x110mg/day: $66,000 • Warfarin: $12,500 • Dual Therapy: $99,000 Vs Warfarin (per QALY) • Dabigatran 2x150mg/day: $86,000 • Dabigatran 2x110mg/day: $150,000 • Dual Therapy: Dominated
Sorensen	Semi-Markov Model	• Warfarin	70 year-old patient	• Scenario 1: 7.21	Total Costs:	NR

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
2009 (113) US	with 3-month cycle, using 4 health states representing temporary discontinuation. Lifetime horizon	(different clinical scenarios)	with nontransient, NVAF at moderate to high risk of ischaemic stroke (based on $CHADS_2$ score)	• Scenario 2: 6.92 • Scenario 3: 6.75 • Scenario 4: 6.67	• Scenario 1: $68,039 • Scenario 2: $77,764 • Scenario 3: $84,518 • Scenario 4: $87,248	
Sorensen 2011 (99) Canada	Semi-Markov Model with 3-month cycle, using 11 primary health states with 4 additional health states representing temporary discontinuation of therapy. Lifetime horizon	• Dabigatran • Warfarin	Canadian AF patients based on the RE-LY trial, with at least one additional risk factor for stroke/ embolism or impaired left ventricular ejection fraction, mean $CHADS_2$ score of 2.1 and mean age 69 years	• Dabigatran: 7.29 • 'trial-like' warfarin: 7.08 • Incremental: 0.21	Drug Costs • Dabigatran: CAN$8,285 • 'trial-like' warfarin: CAN$2,962 Event Costs • Dabigatran: CAN$9,107 • 'trial-like' warfarin: CAN$9,825 Follow-up Costs • Dabigatran: CAN$27,732 • 'trial-like' warfarin: CAN$30,159 Total Costs • Dabigatran: CAN$45,124 • 'trial-like' warfarin: CAN$42,946 • Incremental: CAN$2,178	• Base case: Dabigatran vs 'trial-like' warfarin: CAN$10,440 • Scenario 1: Dabigatran vs 'real-world prescribing': CAN$3,962 per QALY • Scenario 2: Dabigatran 2x150mg/day vs 'trial-like' warfarin: CAN$9,041 • Scenario 3: Dabigatran 2x110mg/day vs 'trial-like' warfarin: CAN$29,994
Sullivan 2006 (143) US	Semi-Markov model with 30-day cycles. 10-year time horizon	• Warfarin (different clinical scenarios)	Population based on SPORTIF III and V trial - 70 year old cohort at high risk of stroke	• Anticoagulation monitoring service: 6.617 QALYs • Usual care: 6.559 QALYs • Incremental: 0.057 QALYs	Total costs • Anticoagulation monitoring service: $8,661 • Usual care: $10,746 • Incremental: $-2,100	Anticoagulation monitoring service dominates usual care
Valiya 2005 (183) Australia	Decision Tree.	• Ximelagatran • Warfarin • Aspirin	65-75 year old (mean 69) chronic NVAF patients	• Warfarin: 0.748 • Aspirin: 0.546 • Ximelagatran: 0.757	NR	• Ximeligatran vs Warfarin: $272,000 per stroke avoided per patient per year • Ximeligatran vs Aspirin:

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
						$13,000 per stroke avoided/patient/year
Conference abstracts						
Fragoulakis 2011 [abstract] (184) Greece	Markov Model. Lifetime horizon	• Dabigatran 2x150mg/day • Acenocoumarol • Aspirin • Aspirin + Clopidogrel • Best Supportive Care • No Treatment	Greek AF patients	• Dabigatran: 9.86 • Sintrom: 9.83	Total costs • Dabigatran: €20,103 • Sintrom: €11,639	• Dabigatran vs Sintrom: €25,952 • Dabigatran vs aspirin-clopidogrel: €8,223 • Dabigatran vs aspirin: €10,392 • Dabigatran vs no treatment: €7,536
Freeman 2010 [abstract] (185) US	Markov Model. 35-year time horizon	• Dabigatran 2x110mg/day • Dabigatran 2x150mg/day • Warfarin	Patients aged 65 years or older with NVAF and moderate-to-high stroke risk	• Warfarin: 11.33 • Dabigatran 110 mg: 11.68 • Dabigatran 150 mg: 11.75	Total costs • Warfarin: $135,800 • Dabigatran 110 mg: $151,900 • Dabigatran 150 mg: $141,100	• Dabigatran 110 mg vs warfarin: $46,200 per QALY • Dabigatran 150 mg vs warfarin: $12,600 per QALY
Turakhia 2010 [abstract] (186) US	Markov Model. 35-year time horizon	• Percutaneous left atrial appendage occlusion • Warfarin	Hypothetical cohort of 65 year-old patients with AF at moderate-to-high risk of stroke	• Warfarin: 11.33 years • PLAAO: 11.49 years	Total costs • Warfarin: $135,800 • PLAAO: $137,600	• PLAAO vs warfarin: $11,200
Wang 2010 [abstract] (187) US	No model - direct analysis of real-life data.	• Warfarin • No Warfarin	US Medicare patients (recruited 2005-2007), aged ≥ 65 years, with ≥ 2 primary diagnoses for NVAF within 30	NR	Total risk-adjusted healthcare costs: • Warfarin: $12,739 • Non-warfarin patients: $15,359	NR

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
			days			
Zhao 2011 [abstract] (188) US	Markov Model with 3 health states. Lifetime horizon	• Dabigatran 2x150mg/day • Warfarin	Hypothetical cohort of 65 year-old AF patients at moderate risk of stroke ($CHADS_2$=1)	• Dabigatran: 12.9 • Warfarin: 12.2	Total costs • Dabigatran: $146,649 • Warfarin: $118,904	• Dabigatran vs warfarin: $40,850

Abbreviations: AF, atrial fibrillation; CEAC, cost-effectiveness acceptability curve; $CHADS_2$, clinical prediction rule for estimating the risk of stroke in AF patients; CV, cardiovascular; ICER, incremental cost effectiveness ratio; NR, not reported; NVAF, non-valvular atrial fibrillation; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; RCT, randomised controlled trial; RE-LY, Randomized Evaluation of Long-Tern Anticoagulation Therapy; SA, sensitivity analysis; vs, versus

Table 108: Summary of relevant cost-utility studies

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
Studies identified via the systematic review						
Freeman 2011 (96) US	Markov Model with 15 health states. Lifetime horizon	• Dabigatran 2x110mg/day • Dabigatran 2x150mg/day • Warfarin	NVAF patients, aged 65 or older, with $CHADS_2$ score >0	• Warfarin: 10.28 • Dabigatran 110 mg: 10.70 • Dabigatran 150 mg: 10.84	• Warfarin: $143,193 • Dabigatran 110 mg: $164,576 • Dabigatran 150 mg: $168, 398	• Dabigatran 110 mg vs warfarin: $51,229 per QALY • Dabigatran 150 mg vs warfarin: $45,372 per QALY
Gage 1995 (97) US	Markov Model. 10 year time horizon	• Warfarin • Aspirin • No treatment	65 year-old US NVAF patients, with varying risks of stroke and good candidates for warfarin and aspirin therapy	High risk of stroke: • Warfarin: 6.51 • Aspirin: 6.27 • No therapy: 6.01 Medium risk of stroke: • Warfarin: 6.60 • Aspirin: 6.46 • No therapy: 6.23 Low risk of stroke: • Warfarin: 6.70	High risk of stroke: • Warfarin: $12,500 • Aspirin: $13,200 • No therapy: $15,300 Medium risk of stroke: • Warfarin: $10,900 • Aspirin: $9,700 • No therapy: $11,400 Low risk of stroke: • Warfarin: $9,000	High risk of stroke: • Warfarin dominates aspirin and no therapy Medium risk of stroke: • Warfarin vs Aspirin: $8,000 • Warfarin dominates no therapy Low risk of stroke: • Warfarin vs Aspirin: $370,000

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
				• Aspirin: 6.69 • No therapy: 6.51	• Aspirin: $5,400 • No therapy: $6,300	• Warfarin vs no therapy: $14,000
Pink 2011 (98) UK	Discrete event simulation Lifetime horizon	• Dabigatran 2x110mg/day • Dabigatran 2x150mg/day • Warfarin	Cohort of 50,000 simulated patients at moderate to high risk of stroke with a mean baseline $CHADS_2$ score of 2.1	Incremental QALYs: • Dabigatran 110mg vs warfarin: 0.094 (95% central range –0.083 to 0.267) • Dabigatran 150mg vs warfarin: 0.146 (central range –0.029 to 0.322) • Dabigatran 150mg vs dabigatran 110mg: 0.052 (central range –0.122 to 0.228)	Lifetime: • Dabigatran 110mg: £10,529 • Dabigatran 150mg: £9,850 • Warfarin: £6,480	• Dabigatran 110mg vs warfarin: £43,074 per QALY • Dabigatran 150mg vs warfarin: £23,082 per QALY • Dabigatran 150mg vs dabigatran 110mg: Dominated (costs an additional £679 for 0.052 fewer QALYs)
Shah 2011 (100) US	Markov Model with 8 health states and a 1 month cycle. 20 year time horizon	• Dabigatran 2x110mg/day • Dabigatran 2x150mg/day • Warfarin • Aspirin+ Clopidogrel • Aspirin • No therapy	Hypothetical cohort of 70-year-old patients based on the RE-LY clinical trial with moderate risk of stroke and no contra-indication to anti-coagulation. Risk of stroke varied in sensitivity analysis	• Dabigatran 2x150mg/day: 8.65 • Dabigatran 2x110mg/day: 8.54 • Warfarin: 8.40 • Dual Therapy: 8.32 • Aspirin: 8.17	• Dabigatran 2x150mg/day: $43,700 • Dabigatran 2x110mg/day: $44,300 • Warfarin: $23,000 • Dual Therapy: $34,000 • Aspirin: $20,000	Vs Aspirin (per QALY) • Dabigatran 2x150mg/day: $50,000 • Dabigatran 2x110mg/day: $66,000 • Warfarin: $12,500 • Dual Therapy: $99,000 Vs Warfarin (per QALY) • Dabigatran 2x150mg/day: $86,000 • Dabigatran 2x110mg/day: $150,000 • Dual Therapy: Dominated
Sorensen 2011 (99) Canada	Semi-Markov Model with 3-month cycle, using 11	• Dabigatran • Warfarin	Canadian AF patients based on the RE-LY trial, with at least one	• Dabigatran: 7.29 • 'trial-like' warfarin: 7.08 • Incremental: 0.21	Drug Costs • Dabigatran: CAN$8,285 • 'trial-like' warfarin: CAN$2,962 Event Costs	• Base case: Dabigatran vs 'trial-like' warfarin: CAN$10,440 • Scenario 1: Dabigatran vs

Study, Country	Summary of model	Treatments considered	Patient population	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
	primary health states with 4 additional health states representing temporary discontinuation of therapy. Lifetime horizon		additional risk factor for stroke/ embolism or impaired left ventricular ejection fraction, mean $CHADS_2$ score of 2.1 and mean age 69 years		• Dabigatran: CAN$9,107 • 'trial-like' warfarin: CAN$9,825 Follow-up Costs • Dabigatran: CAN$27,732 • 'trial-like' warfarin: CAN$30,159 Total Costs • Dabigatran: CAN$45,124 • 'trial-like' warfarin: CAN$42,946 • Incremental: CAN$2,178	'real-world prescribing': CAN$3,962 per QALY • Scenario 2: Dabigatran 2x150mg/day vs 'trial-like' warfarin: CAN$9,041 • Scenario 3: Dabigatran 2x110mg/day vs 'trial-like' warfarin: CAN$29,994
Studies identified subsequent to the systematic review						
Lee 2012 (101)	Markov model with 9 health states 1 and 10 year time horizons	• Apixaban • Aspirin	Hypothetical cohort of 70 year old patients with AF, a $CHADS_2$ score of 2 and a low risk of bleeding	1-year time horizon • Apixaban: 0.96 • Aspirin: 0.96 10-year time horizon • Apixaban: 6.87 • Aspirin: 6.51	1-year time horizon • Apixaban: $3,454 • Aspirin: $1,805 10-year time horizon • Apixaban: $44,232 Aspirin: $50,066	1-year model • Apixaban inferior strategy (most costly but no more effective) 10-year model • Apixaban dominant (less costly and more effective)

Abbreviations: AF, atrial fibrillation; CEAC, cost-effectiveness acceptability curve; $CHADS_2$, clinical prediction rule for estimating the risk of stroke in AF patients; ICER, incremental cost effectiveness ratio; NR, not reported; NVAF, non-valvular atrial fibrillation; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; RCT, randomised controlled trial; RE-LY, Randomized Evaluation of Long-Tern Anticoagulation Therapy; SA, sensitivity analysis; vs, versus

10.11 Appendix 11: Quality assessment of cost-effectiveness studies

Study question	Study name				
	Freeman 2011 (96)	Gage 1995 (97)	Pink 2011 (98)	Shah 2011 (100)	Sorensen 2011 (99)
Study design					
1. Was the research question stated?	Yes	Yes	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	No	Yes	Yes	Not clear
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Yes	Yes	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes	Yes	Yes	Yes
5. Were the alternatives being compared clearly described?	Yes	No	Yes	Yes	Yes
6. Was the form of economic evaluation stated?	Yes	Yes	Yes	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	Yes	Yes	Yes	Yes
Data collection					
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	Yes	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	N/A	N/A	N/A	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	No	Yes	No	No
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	No	Yes	Yes	No	Yes
13. Were the details of the subjects from whom valuations were obtained given?	No	Yes	No	No	No
14. Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	No	Yes	No	No	No
16. Were quantities of resources reported separately from their unit cost?	No	No	No	No	No

Study question	Study name				
	Freeman 2011 (96)	Gage 1995 (97)	Pink 2011 (98)	Shah 2011 (100)	Sorensen 2011 (99)
17. Were the methods for the estimation of quantities and unit costs described?	Yes	No	Yes	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No	No	Yes	No	No
20. Were details of any model used given?	Yes	Yes	Yes	Yes	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Yes	Yes	No	Yes
Analysis and interpretation of results					
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes	Yes	Yes
23. Was the discount rate stated?	Yes	Yes	Yes	Yes	Yes
24. Was the choice of rate justified?	No	No	No	No	No
25. Was an explanation given if cost or benefits were not discounted?	N/A	N/A	N/A	N/A	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No	Yes	No	No
27. Was the approach to sensitivity analysis described?	Yes	Yes	Yes	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	N/A	Yes	Yes	No	No
29. Were the ranges over which the parameters were varied stated?	Yes	Yes	Yes	Yes	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes	Yes	Yes	Yes
31. Was an incremental analysis reported?	Yes	Yes	Yes	Yes	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Yes	Yes	Yes	Yes
33. Was the answer to the study question given?	Yes	Yes	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes	Yes	Yes	Yes
36. Were generalisability issues addressed?	Yes	Yes	Yes	Yes	Yes

10.12 Appendix 12: Search strategy for Section 7.4

10.12.1 Databases searched

The following databases were searched via OVID and the Cochrane library:

- Medline/Medline (R) In-Process 1948 to date of search
- Embase 1980 to date of search
- EconLit 1961 to date of search
- Cochrane Library to date of search

10.12.2 Date on which the search was conducted

The searches were performed on the 1st December 2011.

10.12.3 Date span of the search

No date restrictions were imposed on the search

10.12.4 Search strategy

Medline and Medline InProcess 1948-present, searched 1st December 2011

#	Searches	Results
1	exp Atrial Fibrillation/	28533
2	exp Atrial Flutter/	4658
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	41695
4	1 or 2 or 3	41695
5	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	2638
6	(time trade off or TTO).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	826
7	(standard gamble or SG).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	5145
8	quality of life.mp. or *"quality of life"/	155009
9	quality adjusted life years.mp. or *quality adjusted life year/	6431
10	(QOL or HRQOL or HRQL or QALY*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	24812
11	5 or 6 or 7 or 8 or 9 or 10	161155
12	4 and 11	896
13	limit 12 to (english language and humans)	716
14	limit 13 to (autobiography or bibliography or comment or dictionary or directory or editorial or historical article or interactive tutorial or interview or lectures or legal cases or legislation or letter or newspaper article)	48
15	13 not 14	668

Embase 1980-present, searched 1st December 2011

#	Searches	Results
1	exp Heart Atrium Fibrillation/	53709
2	exp Heart Atrium Flutter/	7231
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	63043
4	1 or 2 or 3	63043
5	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3814
6	(time trade off or TTO).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1014
7	(standard gamble or SG).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	6121
8	quality of life.mp. or *"quality of life"/	219462
9	quality adjusted life years.mp. or *quality adjusted life year/	3587
10	(QOL or HRQOL or HRQL or QALY*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	33885
11	5 or 6 or 7 or 8 or 9 or 10	228038
12	4 and 11	2035
13	limit 12 to (human and english language)	1628
14	limit 13 to (book or book series or editorial or letter or note or trade journal)	246
15	13 not 14	1382

EconLit 1961-present, searched 1st December 2011

#	Searches	Results
1	atrial fibrillat*.mp.	7
2	atrial flutter.mp.	0
3	((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).mp.	7
4	1 or 2 or 3	7

Cochrane library, searched 1st December 2011

#	Searches	Results
1	MeSH descriptor **Atrial Fibrillation** explode all trees	2056
2	MeSH descriptor **Atrial Flutter** explode all trees	245
3	(atrial or atrium or auricular) NEAR/3 (fibrillat* or flutter*)	3610
4	(#1 OR #2 OR #3)	3610
5	Euroqol 5D or EQ-5D or EQ5D or Euroqol or EQ 5D or EQ 5 D	1366
6	time trade off or TTO	705
7	standard gamble or SG	5023

8	MeSH descriptor **Quality of Life** explode all trees	11312
9	MeSH descriptor **Quality-Adjusted Life Years** explode all trees	2348
10	QoI OR HRQoL OR HRQL OR QALY	6898
11	(#5 OR #6 OR #7 OR #8 OR #9 OR #10)	21420
12	(#4 AND #11)	219

Cochrane Reviews [37] | Other Reviews [6] | Clinical Trials [126] | Methods Studies [0] | Technology Assessments [5] | Economic Evaluations [42] | Cochrane Groups [3]
Cannot export Cochrane Groups therefore only 216 exported

10.12.5 Additional searches

Additional studies were identified by hand searching the following sources:

- Bibliographies of selected articles and systematic reviews
- Primary sources of health state utility values used in economic evaluations
- Relevant NICE submission/appraisal data
- The following conference proceedings:
    - American Heart Association (AHA),
    - European Society of Cardiology (ESC),
    - International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
    - The European Heart Journal (EHJ)

The CEA registry, EQ-5D website and Research Papers in Economics (**RePEc)** were searched using terms including “AF”, “atrial flutter”, “atrial arrhythmia” or “ cardiac arrhythmias

10.12.6 The inclusion and exclusion criteria.

Publications were screened on the basis of title and abstract, and studies that reported EQ-5D values for relevant health states were selected for full review. Economic evaluations that focused on an AF population were included to allow the identification of primary sources of utilities used in the model. Studies that were relevant to the decision model in terms of health states, but reported utilities derived from measures other than EQ-5D were excluded.

On full paper review the priority was to identify EQ-5D values for relevant health states in an AF population.

Papers were initially included if they:

- Reported EQ-5D values for relevant health states in a defined AF population
- Considered a population aged 18 or over
- Included either the original source of EQ-5D utility values or reported EQ-5D values not captured elsewhere in the review

Papers reviewed at this stage were excluded if they:

- Were not derived on an EQ-5D basis
- Did not define an AF population behind the estimation of the utility

- Did not report a single index value for EQ-5D, suitable for use in an economic evaluation

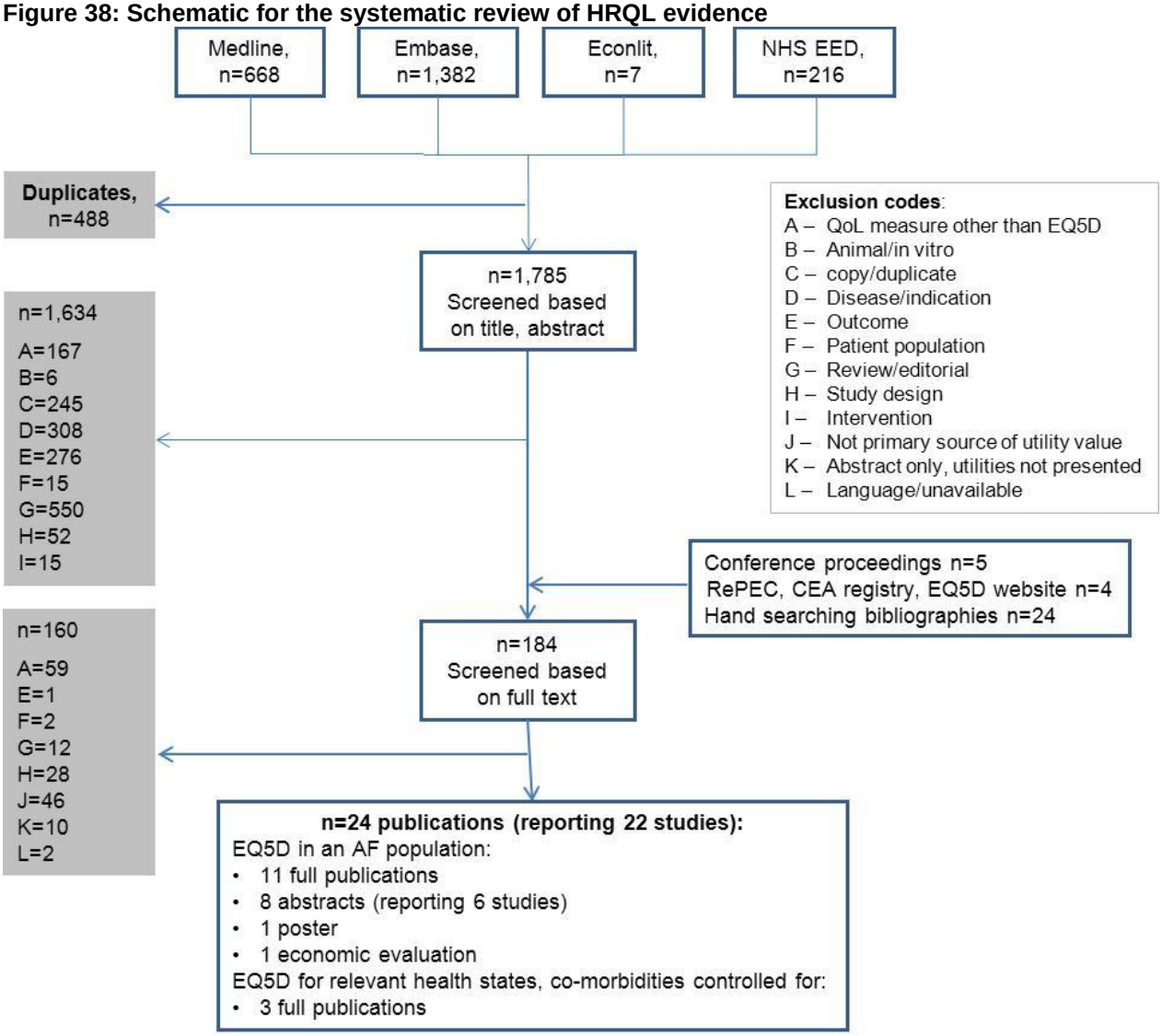
For health states not populated using the above criteria studies included at first pass were screened again and were included if they:

- Reported utility values for the relevant health states, elicited by methods other than EQ-5D
- Considered an AF population aged 18 or over

10.12.7 The data abstraction strategy.

Identified studies were independently assessed by a reviewer in order to ascertain whether they met the refined inclusion and exclusion criteria. Any uncertainties around inclusion were resolved by discussion with a second reviewer. Relevant data were extracted.

Figure 38: Schematic for the systematic review of HRQL evidence



10.12.8 Full list of studies identified

Bach et al, 2001 (123)

Berg et al, 2010 (124)

Dagres et al, 2007 (125)

Dorman et al, 2000 (126)

Gulizia et al, 2006 (127)

Gulizia et al, 2009 (128)

Khan et al, 2004 (112)

Meinertz et al, 2011 (129)

Radholm et al, 2011 (130)

Steg et al, 2012 (131)

van Wijk et al, 2007 (132)

Doyle et al, 2009 (133)

Aves et al, 2010 (134)

Bulkova et al, 2011 (135)

Dorian et al, 2009 (136)

Fiala et al, 2011 (137)

Fiala et al, 2011 (138)

Fiala et al, 2011 (139)

Fiala et al, 2011 (140)

Fiala et al, 2011 (141)

Lamotte et al, 2007 (142)

Sullivan et al, 2006 (143)

Sullivan et al, 2006 (144)

Sullivan et al, 2011 (145)

Adams et al, 2011 (146)

Das et al, 2009 (147)

Das et al, 2007 (148)

Gage et al, 1995 (97)

Gage et al, 1996 (149)

Hohmann et al, 2009 (150)

Robinson et al, 2001 (151)

Thomson et al, 2000 (152)

Lacey et al, 2003 (153)

Table 109: Studies reporting utility values for health states used in the economic model

Study	Country	Population	Sample size	Elicitation method	Health states	Utility score
Identified via original systematic review						
Aves 2010 (134)	N/R	Recently diagnosed AF	4,501	EQ-5D	AF – baseline:	
					Overall	0.783 (SD 0.225)
					AFSS ≥15:	0.679 (SD 0.256)
					Control of AF	0.79 (SD 0.22)
					No control of AF	0.77 (SD 0.23)
					AF – 12 months:	
					Overall	0.821 (SD 0.213)
					AFSS ≥15	0.749 (SD 0.245)
Berg, 2010 (124)	35 European countries	AF	Baseline 5,050 1 year follow-up 3,045	EQ-5D	AF – baseline	0.751 (SD 0.269)
					AF – Follow-up	0.779 (SD 0.253)
Dagres 2007 (125)	35 countries	AF: first detected, paroxysmal, persistent and permanent	5,333	EQ-5D	AF – baseline	F=0.73 IQR (0.59–0.85) M=0.85 IQR (0.69–1.00)
					AF – 12months	Reported as change from baseline: F=0.00 [−0.10 to 0.15] M=0.00 [−0.07 to 0.11]
Dorian 2009 (136)	Canada	Individuals with recently diagnosed AF (within 1y)	5,604 (no detail on response rate)	EQ-5D	AF –$CHADS_2$=0:	0.79 (SD 0.04)
					AF – $CHADS_2$=1:	0.76 (SD 0.03)
					AF – $CHADS_2$≥2:	0.72 (SD 0.03)
					AF – Male:	0.79 (SD 0.03)
					AF – Female:	0.73 (SD 0.03)
Dorman 2000 (126)	UK	Sample was derived from the UK hospitals participating in the International Stroke Trial	1,743 from the International Stroke Register, 867 patients completed the EQ-5D.	EQ-5D	Dependent after stroke	0.31 (0.29-0.34)
					Independent after stroke with problems	0.71 (0.68-0.74)
					Recovered from stroke (independent without persisting problems)	0.88 (0.84-0.92)
Khan 2004 (112)	UK	Patients with AF with target INR range of 2-	125	EQ-5D	AF – baseline	
					Education:	0.74 (SD 0.27)

Study	Country	Population	Sample size	Elicitation method	Health states	Utility score
		3, taking warfarin for at least 12 months, INR SD ≥ 0.5 over the previous 6 months and aged ≥ 65 years			Education and self-monitoring	0.82 (SD 0.02)
					AF – Week 24	
					Education	0.70 (SD 0.29)
					Education and self-monitoring	0.75 (SD 0.27)
Meinertz 2011 (129)	Germany	3,667 patients in 730 primary care practices. Paroxysmal, persistent (including LSPAF)	EQ-5D completed by 3,460 patients	EQ-5D	Baseline – AF	0.86 (SD 0.19)
Radholm 2011 (130)	Sweden	AF, aged 85 years	53/336 with AF	EQ-5D	Baseline – AF	Median 0.73 (IQR 0.62-0.81)
Steg 2012 (131)	International 26 countries	Patients with any history of AF in the previous year seen at >800 sites (outpatients (69.9%))	10,523	EQ-5D	Controlled AF	median 0.78, range (-0.59-1.00)
					Uncontrolled AF	median 0.73 , range (-0.59-1.00)
Sullivan 2006 (144) CEA	US	CEA	CEA	EQ-5D	AF	0.81
					Decrement for age	0.00029
					Decrement for haemorrhagic stroke	0.1385
					Decrement for ischaemic stroke	0.1385
					Decrement for MI	0.1247
					Decrement for MBs	0.1814
					Decrement for system embolic event	0.1199
					Decrement for subdural haematoma	0.1814
					Decrement for TIA	0.10322
Sullivan 2011 (145) *default setting on online catalogue	US dataset, valued with UK preferences	Default calculation.	–	EQ-5D	Acute MI	0.9192
					Old MI	0.9472
					Arterial embolism	0.9438
					Transient cerebral ischemia	0.9489
					Other aneurysm	0.8838

Study	Country	Population	Sample size	Elicitation method	Health states	Utility score
Van Wijk 2007 (132)	The Netherlands	Survivors of the DTT and EAFT trials (patients who had a TIA or MIS).	198 patients, EQ-5D completed by post	EQ-5D	15.6 years following event	0.72 (SD 0.26)
Identified via secondary search of studies included at first pass						
Gage 1995 (97)	USA	AF	69 completed interviews	Standard gamble and TTO	Mild neurological event	0.75
					Moderate-to-severe neurological event	0.39
					Recurrent neurological event	0.12
Gage 1996 (149)	USA	AF	70 completed interviews	Standard gamble and TTO	Mild stroke	0.76
					Moderate stroke	0.39
					Major stroke	0.11
Robinson 2001 (151)	UK	AF	57 completed interviews	Standard gamble	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 2000 (152)	UK	AF	57 completed interviews	Standard gamble	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)
Bach 2011 (123)	Germany	2,181 with MI, 783 with stroke and 145 with both	55,518 patients (response rate 93.5%)	EQ-5D or EQ-5D VAS for the AF population (not clear)	No MI or Stroke (AF n=1,504)	0.67 (0.18)
					MI (AF n=218)	0.6 (0.21)
					Stroke (AF n=113)	0.59 (0.22)
					MI and stroke (AF n=25)	0.47 (0.26)
Identified via search of rivaroxaban and dabigatran STA submissions						
Lacey 2003 (153)	UK	Patients discharged from hospital following	229	EQ-5D	MI (at 6 weeks)	0.683 (0.23)

Study	Country	Population	Sample size	Elicitation method	Health states	Utility score
		acute MI				

Abbreviations: AF, atrial fibrillation; AFSS, atrial fibrillation severity score; CEA, cost-effectiveness analysis; INR, International normalised ratio; IQR, inter-quartile range; LSPAF, long-standing atrial fibrillation; MI, myocardial infarction; N/R, not reported; SD, standard deviation; TIA, transient ischaemic attack; TTO, time trade-off; VAS, visual analogue scale;

10.13 Appendix 13: Search strategy for Section 7.5

10.13.1 Databases searched

A systematic review was not conducted to identify resource data from the published literature. Resource use was identified via existing technology apprisals for AF and studies identified in the cost-effectiveness and quality of life systematic reviews.

10.13.2 Date on which the search was conducted

N/A

10.13.3 Date span of the search

N/A

10.13.4 Search strategy

N/A

10.13.5 Additional searches

N/A

10.13.6 The inclusion and exclusion criteria.

N/A

10.13.7 The data abstraction strategy.

N/A

10.14 Appendix 14: Network meta-analysis

10.14.1 Probability of experiencing an outcome calculation

The probability of experiencing an outcome at the median follow-up point was calculated by dividing the number of first events by the number of patients randomised and converting this probability into an annual rate as: *rate = -ln(1-probability)/median follow-up*. This approximation accurately predicted the event rate for studies where both the rate and number of patients with events were reported.

10.14.2 The WinBugs code for the fixed effects model

```
wqw# Poisson likelihood, log link
# Random effects model for multi-arm trials

model{                          # *** PROGRAM STARTS

for(i in 1:NS){                  # LOOP THROUGH STUDIES
Temp1[i]<-Study[i]

w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0               # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {          # LOOP THROUGH ARMS
      r[i,k] ~ dpois(theta[i,k])   # Poisson likelihood
      theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
      log(lambda[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor

#Deviance contribution
      dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))  }

#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {          # LOOP THROUGH ARMS


# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])

# mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]

# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k

# adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
sumdev <- sum(resdev[])          #Total Residual Deviance
```

```
d[1]<-0       # treatment effect is zero for reference treatment


# vague priors for treatment effects
for (k in 2:NT){  d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

# Provide estimates of treatment effects T[k] on the natural (rate) scale


# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
# meanA and precA come from external RE model on ref treatment risk

A ~ dnorm(meanmA,precmA)
for (k in 1:NT) { log(T[k]) <- A + d[k]  }


# pairwise HRs and LHRs for all possible pair-wise comparisons, if NT>2
for (c in 1:(NT-1)) {
          for (k in (c+1):NT) {
                              lhr[c,k] <- (d[k]-d[c])
                              log(hr[c,k]) <- lhr[c,k]

                                                  }
                    }

# ranking on relative scale
for (k in 1:NT) {
#rk[k] <- NT+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
                                                  }

#proportion of patients that have an event: in years

for (k in 1:NT) { p6mths[k] <- 1-exp(-T[k]*0.5)
                    p12mths[k] <- 1-exp(-T[k])
                    p24mths[k] <- 1-exp(-T[k]*2)
                    }


}                                 # *** PROGRAM ENDS
```

Table 110: Data used in the base case NMAs

Study	Treatment arm	Stroke or SE				Total stroke				Systemic embolism				Haemorrhagic stroke			
		N	n	Event rate (%/yr)	Pop	N	n	Event rate	Pop	N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop
RELY 2009	Dabi 110 mg	6015	182	1.53	ITT	6015	171	1.44	ITT	6015	15	0.12[†]	ITT	6015	14	0.12	ITT
	Warfarin	6022	199	1.69	ITT	6022	185	1.57	ITT	6022	21	0.17[†]	ITT	6022	45	0.38	ITT
	Dabi 150 mg	6076	134	1.11	ITT	6076	122	1.01	ITT	6076	13	0.11[†]	ITT	6076	12	0.1	ITT
ROCKET-AF	Riva	7081	269	2.12	ITT	7081	253	1.99	ITT	7081	22[†]	0.16	ITT	7081	35	0.26	ITT
	Warfarin	7090	306	2.42	ITT	7090	281	2.22	ITT	7090	28[†]	0.21	ITT	7090	60	0.44	ITT
ARISTOTLE	Apixaban	9120	212	1.27	ITT	9120	199	1.19	ITT	9120	15	0.09	ITT	9120	40	0.24	ITT
	Warfarin	9081	265	1.60	ITT	9081	250	1.51	ITT	9081	17	0.10	ITT	9081	78	0.47	ITT
AVERROES	Apixaban	2808	51	1.60	ITT	2808	49	1.60	ITT	2808	2	0.10	ITT	2808	6	0.20	ITT
	Aspirin	2791	113	3.70	ITT	2791	105	3.40	ITT	2791	13	0.40	ITT	2791	9	0.30	ITT

Study	Treatment arm	Ischaemic stroke				Myocardial infarction				All-cause mortality				Fatal stroke			
		N	n	Event rate (%/yr)	Pop	N	n	Event rate	Pop	N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop
RELY 2009	Dabi 110 mg	6015	152	1.28	ITT	6015	86	0.72	ITT	6015	446	3.75	ITT	6015	30	0.25[†]	ITT
	Warfarin	6022	134	1.14	ITT	6022	63	0.53	ITT	6022	487	4.13	ITT	6022	44	0.37[†]	ITT
	Dabi 150 mg	6076	103	0.86	ITT	6076	89	0.74	ITT	6076	438	3.64	ITT	6076	23	0.19[†]	ITT
ROCKET-AF	Riva	7081	218[†]	1.62	ITT	7081	138[†]	1.02	ITT	7081	582	4.52	ITT	7061	47	0.42	OT
	Warfarin	7090	221[†]	1.64	ITT	7090	150[†]	1.11	ITT	7090	632	4.91	ITT	7082	67	0.59	OT
ARISTOTLE	Apixaban	9120	149	0.92[†]	ITT	9120	90	0.53	ITT	9120	603	3.52	ITT	9120	42	0.26[†]	ITT
	Warfarin	9081	155	0.96[†]	ITT	9081	102	0.61	ITT	9081	669	3.94	ITT	9081	67	0.41[†]	ITT
AVERROES	Apixaban	2808	35	1.10	ITT	2808	24	0.80	ITT	2808	111	3.50	ITT	2808	13[§]	0.41[§]	ITT
	Aspirin	2791	93	3.00	ITT	2791	28	0.90	ITT	2791	140	4.40	ITT	2791	16[§]	0.50[§]	ITT

Study	Treatment arm	Disabling stroke				Non-disabling stroke				Intracranial haemorrhage				Major bleeding			
		N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop
RELY 2009	Dabi 110 mg	6015	82	0.69[†]	ITT	6015	60	0.5	ITT	6015	27	0.23	ITT	6015	322	2.71	ITT
	Warfarin	6022	74	0.62[†]	ITT	6022	69	0.58	ITT	6022	87	0.74	ITT	6022	397	3.36	ITT
	Dabi 150 mg	6076	57	0.47[†]	ITT	6076	44	0.37	ITT	6076	36	0.30	ITT	6076	375	3.11	ITT
ROCKET-AF	Riva	7061	43	0.39	OT	7061	88	0.79	OT	7061	55	0.50	OT	7061	395	3.60	OT
	Warfarin	7082	57	0.50	OT	7082	87	0.77	OT	7082	84	0.70	OT	7082	386	3.45	OT
ARISTOTLE	Apixaban	9120	42	0.26[†]	ITT	9120	115	0.69[†]	ITT	9088	52	0.33	OT	9088	327	2.13	OT
	Warfarin	9081	50	0.31[†]	ITT	9081	133	0.80[†]	ITT	9052	122	0.80	OT	9052	462	3.09	OT
AVERROES	Apixaban	2808	18[†,§]	0.58[†,§]	ITT	2808	18[§]	0.57[§]	ITT	2798	11[§]	0.34[§]	OT	2798	45[§]	1.41[§]	OT
	Aspirin	2791	56[†,§]	1.84[†,§]	ITT	2791	35[§]	1.11[§]	ITT	2780	11[§]	0.35[§]	OT	2780	29[§]	0.92[§]	OT

Study	Treatment arm	Gastrointestinal bleeding				CRNM bleeding				Any bleeding				Discontinuations			
		N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop	N	n	Event rate (%/yr)	Pop
RELY 2009	Dabi 110 mg	6015	133	1.12	ITT	NR	NR	NR	NR	6015	1740	14.62	ITT	6015	1161	10.72[†]	ITT
	Warfarin	6022	120	1.02	ITT	NR	NR	NR	NR	6022	2142	18.15	ITT	6022	902	8.11[†]	ITT
	Dabi 150 mg	6076	182	1.51	ITT	NR	NR	NR	NR	6076	1977	16.42	ITT	6076	1211	11.11[†]	ITT
ROCKET-AF	Riva	7061	224	2.00[†]	OT	7061	1185	11.80[†]	OT	7061	1733	17.26	OT	7131	1691	14.02[†]	R
	Warfarin	7082	154	1.37[†]	OT	7082	1151	11.40[†]	OT	7082	1675	16.55	OT	7133	1584	13.01[†]	R
ARISTOTLE	Apixaban	9088	105	0.76	OT	9088	318	2.08[†]	OT	9088	2356	18.10	OT	9120	2310	16.23[†]	ITT
	Warfarin	9052	119	0.86	OT	9053	444	3.00[†]	OT	9052	3060	25.80	OT	9081	2493	17.83[†]	ITT
AVERROES	Apixaban	2798	9[§]	0.29[†§]	OT	2798	98[§]	3.11[†§]	OT	2798	325[§]	10.85[§]	OT	2808	558	20.14[†]	ITT
	Aspirin	2780	10[§]	0.32[†§]	OT	2780	74[§]	2.37[†§]	OT	2780	250[§]	8.32[§]	OT	2791	649	24.06[†]	ITT

†Calculated; §Data from CSR (68); Abbreviations: CRNM, clinically relevant non-major; dabi, dabigatran; riva, rivaroxaban; N, population number; n, number with event; NMA, network meta analysis; Pop, population analysed; ITT, intention-to-treat; OT, on-treatment; R, randomised; NR, not reported

Table 110 continued (Data used in the base case NMAs)

Study	Treatment arm	Other major bleed			
		N	n	Event rate (%/yr)	Pop
RELY 2009	Dabi 110 mg	6015	295	2.51†	ITT
	Warfarin	6022	310	2.64†	ITT
	Dabi 150 mg	6076	339	2.87†	ITT
ROCKET-AF	Riva	7061	340	3.07†	OT
	Warfarin	7082	302	2.71†	OT
ARISTOTLE	Apixaban	9088	275	1.79	OT
	Warfarin	9052	340	2.27	OT
AVERROES	Apixaban	2798	34§	1.11†§	OT§
	Aspirin	2780	18§	0.59†§	OT§

†Calculated; §Data from CSR (68)

10.14.3 Trial data used in sensitivity analyses

Table 111: Trial data used in NMA sensitivity analyses (RE-LY 2010, ROCKET on-treatment and AVERROES ITT data)

Study	Treatment arm	Stroke or SE				Total stroke				Systemic embolism				Haemorrhagic stroke			
		N	n	Event rate	Pop	N	n	Event rate	Pop	N	n	Event rate	Pop	N	n	Event rate	Pop
RELY 2010	Dabi 110 mg	6015	183	1.54	ITT	6015	171	1.44	ITT	NR	NR	NR	NR	NR	NR	NR	NR
	Warfarin	6022	202	1.71	ITT	6022	186	1.58	ITT	NR	NR	NR	NR	NR	NR	NR	NR
	Dabi 150 mg	6076	134	1.11	ITT	6076	122	1.01	ITT	NR	NR	NR	NR	NR	NR	NR	NR
ROCKET-AF	Riva	7061	189	1.7	OT	7061	184	1.65	OT	7061	5	0.04	OT	7061	29	0.26	OT
	Warfarin	7082	243	2.15	OT	7082	221	1.96	OT	7082	22	0.19	OT	7082	50	0.44	OT
Study	**Treatment arm**	**Ischaemic stroke**				**Myocardial infarction**				**All-cause mortality**				**Fatal stroke**			
		N	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**
RELY 2010	Dabi 110 mg	NR	NR	NR	NR	6015	98	0.82	ITT	NR	NR	NR	NR	NR	NR	NR	NR
	Warfarin	NR	NR	NR	NR	6022	75	0.64	ITT	NR	NR	NR	NR	NR	NR	NR	NR
	Dabi 150 mg	NR	NR	NR	NR	6076	97	0.81	ITT	NR	NR	NR	NR	NR	NR	NR	NR
ROCKET-AF	Riva	7061	149	1.34	OT	7061	101	0.91	OT	7061	208	1.87	OT	Data used in base case analysis			
	Warfarin	7082	161	1.42	OT	7082	126	1.12	OT	7082	250	2.21	OT				
Study	**Treatment arm**	**Disabling stroke**				**Non-disabling stroke**				**Intracranial haemorrhage**				**Major bleeding**			
		N	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**
RELY 2010	Dabi 110 mg	NR	NR	NR	NR	NR	NR	NR	NR	6015	27	0.23	ITT	6015	342	2.87	ITT
	Warfarin	NR	NR	NR	NR	NR	NR	NR	NR	6022	90	0.76	ITT	6022	421	3.57	ITT
	Dabi 150 mg	NR	NR	NR	NR	NR	NR	NR	NR	6076	38	0.32	ITT	6076	399	3.32	ITT
ROCKET-AF	Riva	NR	NR	NR	NR	Data used in base case analysis				Data used in base case analysis				Data used in base case analysis			
	Warfarin	NR	NR	NR	NR												
Study	**Treatment arm**	**Gastrointestinal bleeding**				**CRNM bleeding**				**Any bleeding**				**Other major bleed**			
		N	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**	**N**	**n**	**Event rate**	**Pop**
RELY 2010	Dabi 110 mg	NR	NR	NR	NR	NR	NR	NR	NR	6015	1754	14.74	ITT	6015	315	2.69	ITT
	Warfarin	NR	NR	NR	NR	NR	NR	NR	NR	6022	2166	18.37	ITT	6022	331	2.83	ITT
	Dabi 150 mg	NR	NR	NR	NR	NR	NR	NR	NR	6076	1993	16.56	ITT	6076	361	3.06	ITT
AVERROES	Apixaban	2808	12	0.4	ITT	2808	96	3.1[†]	ITT	NR	NR	NR	NR	NA	NA	NA	NA

ITT	Aspirin	2791	14	0.4	ITT	2791	84	2.7[†]	ITT	NR	NR	NR	NR	NA	NA	NA	NA

Abbreviations: ITT, intention-to-treat; NR, not reported; OT, on-treatment; SE, systemic embolism. No additional analyses were conducted for discontinuations.

10.14.4 Results of NMA sensitivity analyses

NMA 1

The results of the sensitivity analyses support the base case conclusions, except for the MI outcome in sensitivity analysis 1, where the RE-LY 2010 data was substituted for the RE-LY 2009 data. In this sensitivity analysis, there were no statistically significant differences between apixaban and both doses of dabigatran for the MI outcome.

Table 112: NMA 1 sensitivity analysis 1 (RELY 2010 and ROCKET ITT data)

	Hazard ratio [95% CrI]			
	Apixaban vs dabi 150 mg	**Apixaban vs dabi 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]
SE	NR	NR	NR	NR
Haemorrhagic stroke	NR	NR	NR	NR
Ischaemic stroke	NR	NR	NR	NR
MI	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	NR	NR	NR	NR
Fatal stroke	NR	NR	NR	NR
Disabling stroke	NR	NR	NR	NR
Non-disabling stroke	NR	NR	NR	NR
ICH[†]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding[†]	[redacted]	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	NR	NR
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	NR	NR	NR	NR

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.
[†]RELY 2010 and ROCKET OT data

Table 113: NMA 1 sensitivity analysis 2 (RELY 2009 and ROCKET OT data)

	Hazard ratio [95% CrI]			
	Apixaban vs dabi 150 mg	**Apixaban vs dabi 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]
Total stroke	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	NR	NR	NR	NR
Disabling stroke	NR	NR	NR	NR
Non-disabling stroke	NR	NR	NR	NR
ICH[†]	NR	NR	NR	NR
Major bleeding	NR	NR	NR	NR
GI bleeding	NR	NR	NR	NR
CRNM bleeding	NR	NR	[redacted]	[redacted]
Any bleeding	NR	NR	NR	NR
Discontinuations	NR	NR	NR	NR

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.
[†]data included in NMA 1 sensitivity analysis 1

NMA 2

The results of the sensitivity analyses support the base case conclusions, except for the MI outcome in sensitivity analysis 1, where the RE-LY 2010 data was substituted for the RE-LY 2009 data. In this sensitivity analysis, there were no statistically significant differences between apixaban and both doses of dabigatran for the MI outcome.

Table 114: NMA 2 sensitivity analysis 1 (RELY 2010 and ROCKET ITT data)

	Hazard ratio [95% CrI]				
	Apixaban vs dabi 150 mg	**Apixaban vs dabi 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**	**Apixaban vs aspirin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	NR	NR	NR	NR	NR
Haemorrhagic stroke	NR	NR	NR	NR	NR
Ischaemic stroke	NR	NR	NR	NR	NR
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	NR	NR	NR	NR	NR
Fatal stroke	NR	NR	NR	NR	NR
Disabling stroke	NR	NR	NR	NR	NR
Non-disabling stroke	NR	NR	NR	NR	NR
ICH[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GI bleeding[‡]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	NR	NR	NR
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	NR	NR	NR	NR	NR

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.
[†]RELY 2010 and ROCKET OT data. [‡]Includes AVERROES OT data

Table 115: NMA 2 sensitivity analysis 2 (RELY 2009 and ROCKET OT data)

	Hazard ratio [95% CrI]				
	Apixaban vs dabi 150 mg	**Apixaban vs dabi 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**	**Apixaban vs aspirin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]				
	Apixaban vs dabi 150 mg	**Apixaban vs dabi 110 mg**	**Apixaban vs rivaroxaban**	**Apixaban vs warfarin**	**Apixaban vs aspirin**
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	NR	NR	NR	NR	NR
Disabling stroke	NR	NR	NR	NR	NR
Non-disabling stroke	NR	NR	NR	NR	NR
ICH[†]	NR	NR	NR	NR	NR
Major bleeding	NR	NR	NR	NR	NR
GI bleeding[‡]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	NR	NR	NR
Any bleeding	NR	NR	NR	NR	NR
Discontinuations	NR	NR	NR	NR	NR

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.
[†]data included in NMA 2 sensitivity analysis 1. [‡]Includes AVERROES OT data

10.14.5 Base case NMA results for rivaroxaban and dabigatran versus comparators

Table 116: NMA 1 base case results: rivaroxaban versus comparators

	Hazard ratio [95% CrI]		
	Rivaroxaban vs dabi 150 mg	**Rivaroxaban vs dabi 110 mg**	**Rivaroxaban vs warfarin**
Stroke + SE	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	[redacted]
Any bleeding	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.

Table 117: NMA 1 base case results: dabigatran 150 mg versus comparators

	Hazard ratio [95% CrI]		
	Dabi 150 mg vs dabi 110 mg	**Dabi 150 mg vs rivaroxaban**	**Dabi 150 mg vs warfarin**
Stroke + SE	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]		
	Dabi 150 mg vs dabi 110 mg	**Dabi 150 mg vs rivaroxaban**	**Dabi 150 mg vs warfarin**
Any stroke	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	NR
Any bleeding	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.

Table 118: NMA 1 base case results: dabigatran 110 mg versus comparators

	Hazard ratio [95% CrI]		
	Dabi 110 mg vs dabi 150 mg	**Dabi 110 mg vs rivaroxaban**	**Dabi 110 mg vs warfarin**
Stroke + SE	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]		
	Dabi 110 mg vs dabi 150 mg	**Dabi 110 mg vs rivaroxaban**	**Dabi 110 mg vs warfarin**
MI	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	NR
Any bleeding	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.

Table 119: NMA 2 base case results: rivaroxaban versus comparators

	Hazard ratio [95% CrI]			
	Rivaroxaban vs dabi 150 mg	**Rivaroxaban vs dabi 110 mg**	**Rivaroxaban vs warfarin**	**Rivaroxaban vs aspirin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]			
	Rivaroxaban vs dabi 150 mg	**Rivaroxaban vs dabi 110 mg**	**Rivaroxaban vs warfarin**	**Rivaroxaban vs aspirin**
Disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	[redacted]	[redacted]
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]

Table 120: NMA 2 base case results: dabigatran 150 mg versus comparators

	Hazard ratio [95% CrI]			
	Dabi 150 mg vs dabi 110 mg	**Dabi 150 mg vs rivaroxaban**	**Dabi 150 mg vs warfarin**	**Dabi 150 mg vs aspirin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]			
	Dabi 150 mg vs dabi 110 mg	**Dabi 150 mg vs rivaroxaban**	**Dabi 150 mg vs warfarin**	**Dabi 150 mg vs aspirin**
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	NR	NR
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.

Table 121: NMA 2 base case results: dabigatran 110 mg versus comparators

	Hazard ratio [95% CrI]			
	Dabi 110 mg vs dabi 150 mg	**Dabi 110 mg vs rivaroxaban**	**Dabi 110 mg vs warfarin**	**Dabi 110 mg vs aspirin**
Stroke + SE	[redacted]	[redacted]	[redacted]	[redacted]
Any stroke	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]
Fatal stroke	[redacted]	[redacted]	[redacted]	[redacted]
Disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
Non-disabling stroke	[redacted]	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
GI bleeding	[redacted]	[redacted]	[redacted]	[redacted]

	Hazard ratio [95% CrI]			
	Dabi 110 mg vs dabi 150 mg	**Dabi 110 mg vs rivaroxaban**	**Dabi 110 mg vs warfarin**	**Dabi 110 mg vs aspirin**
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	NR	NR	NR	NR
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention-to-treat; MI, myocardial infarction; SE, systemic embolism.

10.14.6 Subgroup analyses based on $CHADS_2$ score and time in therapeutic range (TTR) for primary efficacy (stroke/SE) and safety (major bleed) outcomes

The following subgroups were examined for both the primary efficacy (stroke/SE) and safety (major bleed) outcomes.

$CHADS_2$ score

- $CHADS_2$ score ≤ 1 (excludes ROCKET as all enrolled patients had $CHADS_2$ score ≥ 2)
- $CHADS_2$ score = 2
- $CHADS_2$ score ≥ 3

Analyses were conducted for both the warfarin suitable and unsuitable patient populations (including the AVERROES study).

Time in therapeutic range (TTR)

Centre TTR (cTTR) is calculated as the average[3] of individual TTRs during the study among warfarin treated patients. The cTTR is assigned as a proxy for the centres' quality of INR control for all its patients. In each trial study centres were grouped into quartiles according to the cTTR. The average TTR differed across trials, consequently the TTR quartiles defined for each trial were different:

- cTTR, lowest quartile (RELY, <57.1%; ROCKET, <50.6%; ARISTOTLE, <58.0%)
- cTTR, 2nd lowest quartile (RELY, 57.1-65.5%; ROCKET, 50.7-58.5%; ARISTOTLE, 58.0-65.7%)
- cTTR, 2nd highest quartile (RELY, 65.5-72.6%; ROCKET, 58.6-65.7%; ARISTOTLE, 65.7-72.2%)
- cTTR, highest quartile (RELY,>72.6%; ROCKET, >65.7%; ARISTOTLE, >72.2%)

Analyses were conducted for the warfarin-eligible population only (AVERROES does not have a warfarin treatment arm and therefore no TTR data are reported).

A summary of the data used in the subgroup analyses is presented in Table 122 ($CHADS_2$ score subgroups) and Table 123 (cTTR).

[3]For ARISTOTLE the average TTR was the median, for RELY and ROCKET, the average TTR was the mean

Table 122: Data used in the analysis of stroke/SE and major bleed for subgroups based on $CHADS_2$ score

Study	Treatment arm	Stroke or SE									Source of data
		$CHADS_2$ score ≤ 1			$CHADS_2$ score = 2			$CHADS_2$ score ≥ 3			
		N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	
RELY 2009	Dabi 110 mg	1958	42	1.06	2088	59	1.45	1968	82	2.12	Oldgren 2011 (189)
	Warfarin	1859	40	1.08	2230	60	1.38	1933	102	2.73	
	Dabi 150 mg	1958	26	0.65	2137	35	0.84	1981	73	1.88	
ROCKET-AF	Riva	NR[†]	NR[†]	NR[†]	924	30	1.46	6156	239	2.25	Patel, 2011 (63) FDA ACBD report (190)
	Warfarin	NR[†]	NR[†]	NR[†]	933	36	1.72	6155	270	2.56	
ARISTOTLE	Apixaban	3100	44	0.7	3262	74	12	2758	94	1.9	Granger 2011 (2)
	Warfarin	3083	51	0.9	3254	82	1.4	2744	132	2.8	
AVERROES	Apixaban	1004	10	0.9	1045	25	2.1	758	16	1.9	Connolly 2011 (3)
	Aspirin	1022	18	1.6	954	40	3.7	812	55	6.3	
Study	Treatment arm	Major bleed									Source of data
		$CHADS_2$ score ≤ 1			$CHADS_2$ score = 2			$CHADS_2$ score ≥ 3			
		N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	
RELY 2009	Dabi 110 mg	1958	74	1.86	2088	121	2.98	1968	147	3.80	Oldgren 2011 (189)
	Warfarin	1859	105	2.84	2230	144	3.30	1933	172	4.60	
	Dabi 150 mg	1958	84	2.11	2137	127	3.04	1981	188	4.85	
ROCKET-AF	Riva	NR[†]	NR[†]	NR[†]	923	58	3.37	6187	337	3.64	FDA ACBD report (190)
	Warfarin	NR[†]	NR[†]	NR[†]	932	49	2.69	6191	337	3.60	
ARISTOTLE	Apixaban	3100	76	1.4	3262	125	2.3	2758	126	2.9	Granger 2011 (2)
	Warfarin	3083	126	2.3	3254	163	3.0	2744	173	4.2	
AVERROES	Apixaban	1004	6	0.5	1045	14	1.2	758	24	2.9	Connolly 2011 (3)
	Aspirin	1022	6	0.5	954	14	1.3	812	19	2.1	

[†]All enrolled patients had $CHADS_2$ score ≥ 2

Abbreviations: Dabi, dabigatran; NR, not reported; SE, systemic embolism

Table 123: Data used in the analysis of stroke/SE and major bleed for subgroups based on TTR

Study	Treatment arm	Stroke or SE												Source of data
		TTR, lowest quartile			TTR, 2nd lowest quartile			TTR, 2nd highest quartile			TTR, highest quartile			
		N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	
RELY 2009	Dabi 110 mg	1497	55	1.91	1524	51	1.67	1474	40	1.34	1482	36	1.23	Wallentin 2010 (62)
	Warfarin	1504	54	1.92	1514	62	2.06	1487	45	1.51	1509	40	1.34	
	Dabi 150 mg	1509	32	1.1	1526	32	1.04	1484	31	1.04	1514	38	1.27	
ROCKET-AF	Riva	1735	45	1.77	1746	53	1.94	1734	54	1.90	1676	37	1.33	ACBD report (190)
	Warfarin	1689	62	2.53	1807	63	2.18	1758	62	2.14	1826	55	1.80	
ARISTOTLE	Apixaban	2266	70	1.75	2251	54	1.30	2256	51	1.21	2266	36	0.83	Wallentin 2011 (127)
	Warfarin	2252	88	2.28	2278	68	1.61	2266	65	1.55	2251	44	1.02	
Study	Treatment arm	Major bleed												Source of data
		TTR, lowest quartile			TTR, 2nd lowest quartile			TTR, 2nd highest quartile			TTR, highest quartile			
		N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	N	n	Event rate (%/yr)	
RELY 2009	Dabi 110 mg	1497	68	2.36	1524	103	3.38	1474	84	2.82	1482	82	2.81	Wallentin 2010 (62)
	Warfarin	1504	101	3.59	1514	124	4.13	1487	101	3.40	1509	93	3.11	
	Dabi 150 mg	1509	74	2.54	1526	102	3.33	1484	113	3.80	1514	108	3.60	
ROCKET-AF	Riva	1780	63	2.43	1731	80	3.05	1741	106	3.79	1689	135	4.94	ACBD report (190)
	Warfarin	1734	81	3.25	1785	84	3.00	1765	106	3.70	1839	115	3.81	
ARISTOTLE	Apixaban	NR	64	1.75	NR	61	1.60	NR	103	2.68	NR	98	2.49	Wallentin 2011 (69)
	Warfarin	NR	115	3.34	NR	102	2.68	NR	109	2.89	NR	136	3.46	

Abbreviations: Dabi, dabigatran; NR, not reported; SE, systemic embolism; TTR, time in therapeutic range

Results of subgroup analyses

NMA 1 – warfarin suitable population

Results for apixaban versus comparators are presented in Table 124. The following conclusions can be made with regards to apixaban versus the other NOACs:

Stroke or SE

- There were no statistically significant differences between apixaban and the other NOACs across $CHADS_2$ or TTR subgroups for the primary efficacy outcome (stroke or SE). This is consistent with the base case analysis.

Major bleeding

Apixaban had a significantly lower risk of major bleeding compared with rivaroxaban and dabigatran 150mg in the base case analysis.

Across the $CHADS_2$ subgroups:

- Apixaban had a significantly lower risk of major bleeding compared with rivaroxaban across all subgroups
- Apixaban had a consistently lower risk of major bleeding compared with dabigatran 150mg which was statistically significant for the $CHADS_2 \geq 3$ subgroup

Across the TTR subgroups:

- Apixaban had a consistently lower risk of major bleeding compared with rivaroxaban, which was significant for the 2nd lowest TTR quartile and the highest TTR quartile
- Apixaban had a consistently lower risk of major bleeding compared with dabigatran 150mg, which was statistically significant for the highest TTR quartile

Table 124: NMA 1 (warfarin suitable population) subgroup analyses based on $CHADS_2$ score and TTR

Subgroup	Hazard ratio [95% CrI]			
	Apixaban vs dabi 150 mg	Apixaban vs dabi 110 mg	Apixaban vs rivaroxaban	Apixaban vs warfarin
Stroke or SE				
$CHADS_2 \leq 1$	[redacted]	[redacted]	–	[redacted]
$CHADS_2 = 2$	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2 \geq 3$	[redacted]	[redacted]	[redacted]	[redacted]
TTR lowest quartile	[redacted]	[redacted]	[redacted]	[redacted]
TTR 2nd lowest quartile	[redacted]	[redacted]	[redacted]	[redacted]
TTR 2nd highest quartile	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Hazard ratio [95% CrI]			
	Apixaban vs dabi 150 mg	Apixaban vs dabi 110 mg	Apixaban vs rivaroxaban	Apixaban vs warfarin
TTR highest quartile	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding				
$CHADS_2 \leq 1$	[redacted]	[redacted]	–	[redacted]
$CHADS_2 = 2$	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2 \geq 3$	[redacted]	[redacted]	[redacted]	[redacted]
TTR lowest quartile	[redacted]	[redacted]	[redacted]	[redacted]
TTR 2nd lowest quartile	[redacted]	[redacted]	[redacted]	[redacted]
TTR 2nd highest quartile	[redacted]	[redacted]	[redacted]	[redacted]
TTR highest quartile	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; SE, systemic embolism; TTR, time in therapeutic range

NMA 2 – warfarin unsuitable population

Results for apixaban versus comparators are presented in Table 125. The following conclusions can be made with regards to apixaban versus the other NOACs:

Stroke or SE

- There were no statistically significant differences between apixaban and the other NOACs across $CHADS_2$ or TTR subgroups for the primary efficacy outcome (stroke or SE). This is consistent with the base case analysis.

Major bleeding

Across the $CHADS_2$ subgroups:

- Apixaban had a significantly lower risk of major bleeding compared with rivaroxaban across all subgroups
- Apixaban had a consistently lower risk of major bleeding compared with dabigatran 150mg which was statistically significant for the $CHADS_2 \geq 3$ subgroup

Table 125: NMA 2 (warfarin unsuitable population) subgroup analyses based on $CHADS_2$ score and TTR

Subgroup	Hazard ratio [95% CrI]				
	Apixaban vs dabi 150 mg	Apixaban vs dabi 110 mg	Apixaban vs rivaroxaban	Apixaban vs warfarin	Apixaban vs aspirin
Stroke or SE					
$CHADS_2 \leq 1$	[redacted]	[redacted]	–	[redacted]	[redacted]

Subgroup	Hazard ratio [95% CrI]				
	Apixaban vs dabi 150 mg	Apixaban vs dabi 110 mg	Apixaban vs rivaroxaban	Apixaban vs warfarin	Apixaban vs aspirin
$CHADS_2 = 2$	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2 \geq 3$	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding					
$CHADS_2 \leq 1$	[redacted]	[redacted]	–	[redacted]	[redacted]
$CHADS_2 = 2$	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$CHADS_2 \geq 3$	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; SE, systemic embolism

10.15 Appendix 15: AVERROES safety ITT population

Summary

- There was no statistically significant difference in risk of major, intracranial or GI bleeding between apixaban and aspirin
- The net-clinical benefit profile of apixaban (composite rate of stroke, SE, myocardial infarction, vascular death, and major bleeding) was favourable to that of aspirin (HR 0.74; 95% CI: 0.60–0.90, p=0.003)

- Significantly fewer patients in the apixaban group than in the aspirin group had a serious adverse event (p<0.001)

Bleeding outcomes

The risk of bleeding with apixaban was similar to that of aspirin. Among patients taking apixaban there were 44 major bleeding events (1.4% per year), compared with 39 events (1.2% per year) among those taking aspirin (Table 126 and Figure 39).

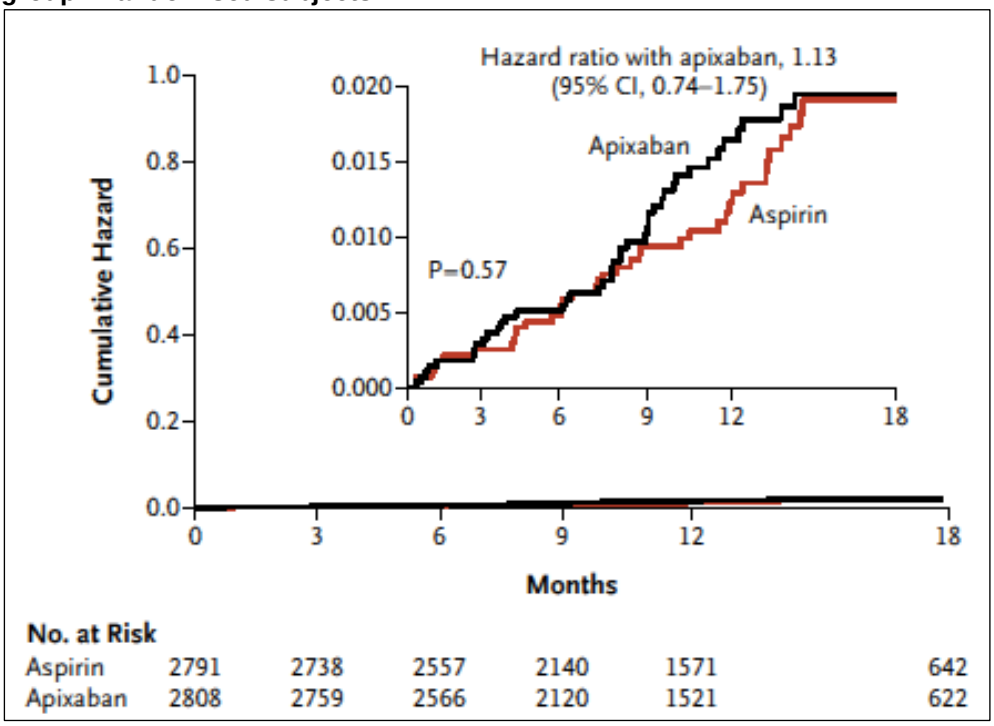
In the treated population (all subjects that received at least one dose of study drug), there were 45 major bleeding events (1.4% per year) among patients in the apixaban group, compared with 29 (0.9% per year) in the aspirin group (HR, 1.54; 95% CI: 0.96–2.45, p=0.07).

Table 126: Summary of bleeding outcomes – randomised subjects

	Apixaban N=2808		Aspirin N=2791		Hazard ratio (95% CI)	P Value
	Pts with event	Event rate[†]	Pts with event	Event rate[†]		
	no.	%/yr	no.	%/yr		
Major bleeding	44	1.4	39	1.2	1.13 (0.74–1.75)	0.57
Intracranial	11	0.4	13	0.4	0.85 (0.38–1.90)	0.69
Subdural[‡]	4	0.1	2	0.1	–	–
Other intracranial[‡,§]	1	<0.1	2	0.1	–	–
Extracranial or unclassified	33	1.1	27	0.9	1.23 (0.74–2.05)	0.42
Gastrointestinal	12	0.4	14	0.4	0.86 (0.40–1.86)	0.71
Non-gastrointestinal	20	0.6	13	0.4	1.55 (0.77–3.12)	0.22
Fatal[¶]	4	0.1	6	0.2	0.67 (0.19–2.37)	0.53
CRNM bleeding	96	3.1	84	2.7	1.15 (0.86–1.54)	0.35
Minor	188	6.3	153	5.0	1.24 (1.00–1.53)	0.05

Abbreviations: CRNM, clinically relevant non-major; Pts, patients; yr, year
[†]The percent per year is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have more than one event; [‡]Hazard ratios and p-values were not calculated for these events because there were so few events; [§]Excluding haemorrhagic stroke and subdural; [¶]Bleeding events were reported as fatal by the investigator and were confirmed at adjudication

Figure 39: Cumulative hazard rates for major bleeding, according to treatment group – randomised subjects



Net-clinical benefit

The net-clinical benefit endpoint includes both efficacy and safety events.

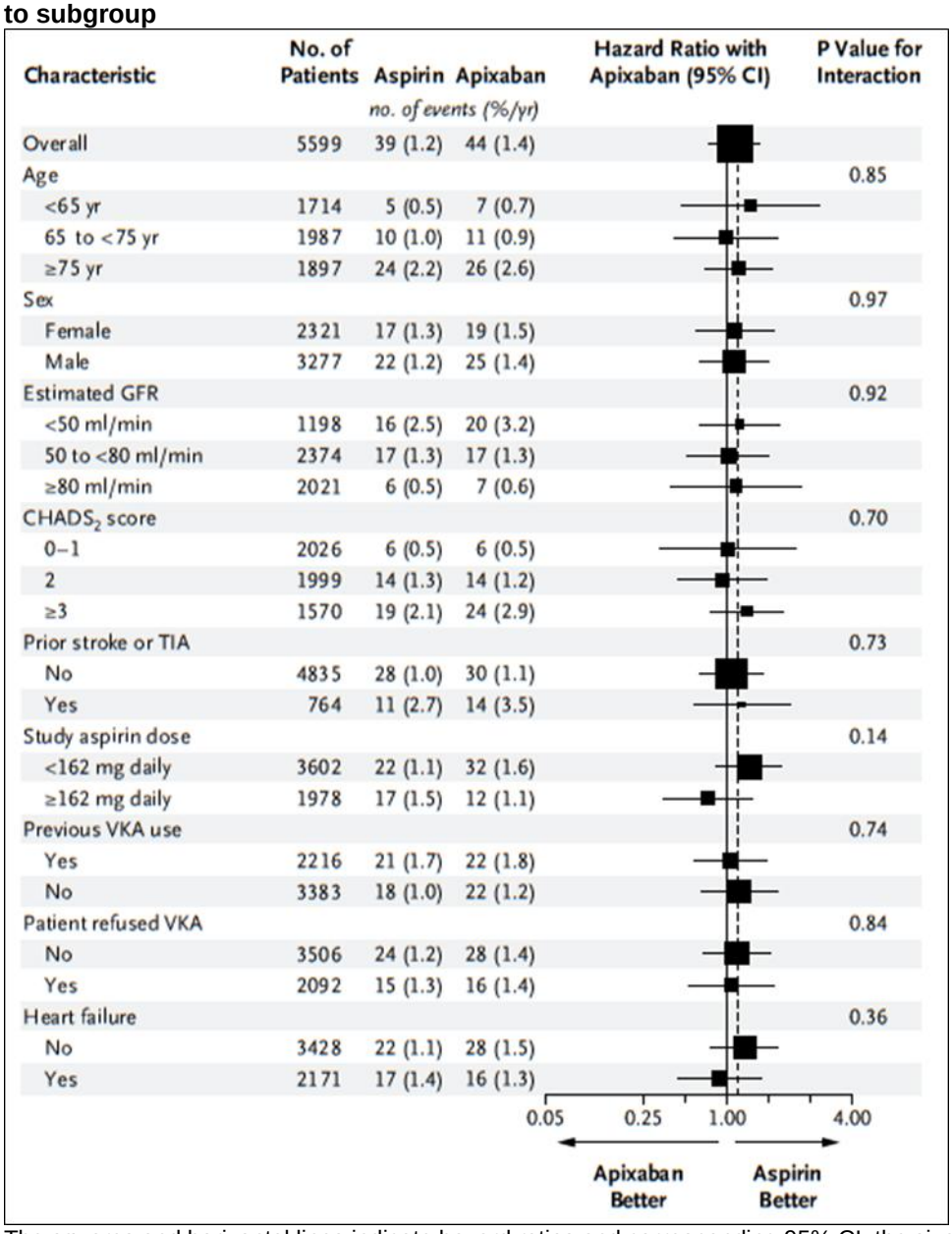
The composite rate of stroke, SE, myocardial infarction, death from vascular causes, or major bleeding was reduced with apixaban, as compared with aspirin (randomised subjects, 5.3% per year versus 7.2% per year; HR 0.74; 95% CI: 0.60–0.90, p=0.003).

Subgroup analyses for bleeding endpoints

Subgroup analyses for bleeding endpoints (major bleeding, composite of major or CRNM bleeding, all bleeding) occurring during the Double-blind Treatment Period were performed for the subgroups of clinical interest used in the subgroup analysis for the primary efficacy endpoint.

Overall, the results within subgroups were consistent with the results for the overall population. There were no significant interactions between the treatment effects and various characteristics of the patients (Figure 40).

Figure 40: Relative risks of major bleeding with apixaban compared with aspirin, according to subgroup



The squares and horizontal lines indicate hazard ratios and corresponding 95% CI; the sizes of the squares are proportional to the sizes of the subgroups. Dashed vertical lines represent the point estimates of the overall hazard ratio.

Abbreviations: GFR, glomerular filtration rate; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist; yr, year

Other safety outcomes

Significantly fewer patients in the apixaban group (22%) than in the aspirin group (27%) had a serious adverse event (p<0.001). this was primarily due to a reduced number of events related to vascular disorders of the central nervous system in the apixaban group (Table 127).

The frequency of subjects with LFT elevations (ALT, AST, and total bilirubin) was low and similar for the apixaban and aspirin treatment groups (Table 128).

Table 127: Summary of serious adverse events (>2% in either treatment arm) – randomised subjects

Number (%) subjects	Apixaban (n=2808)	Aspirin (n=2791)	P value
Cardiac disorders	316 (11.3)	338 (12.1)	0.32
Cardiac arrhythmia	120 (4.3)	126 (4.5)	0.66
Coronary artery disorder	61 (2.2)	69 (2.5)	0.46
Heart failure	121 (4.3)	130 (4.7)	0.53
Gastrointestinal disorders	68 (2.4)	78 (2.8)	0.38
General disorders and administration site conditions	68 (2.4)	78 (2.8)	0.38
Infections and infestations	117 (4.2)	148 (5.3)	0.045
Infections – pathogen unspecified	86 (3.1)	115 (4.1)	0.03
Injury, poisoning and procedural complications	61 (2.2)	61 (2.2)	0.97
Neoplasms, benign, malignant and unspecified	55 (2.0)	57 (2.0)	0.82
Nervous system disorders	85 (3.0)	183 (6.6)	<0.001
Central nervous system vascular disorders	54 (1.9)	135 (4.8)	<0.001
Respiratory, thoracic and mediastinal disorders	69 (2.5)	75 (2.7)	0.59

Table 128: Summary of liver function test abnormalities – randomised subjects

Number (%) subjects	Apixaban (n=2808)	Aspirin (n=2791)	P value
AST or ALT ≥ 3x ULN	38 (1.4)	44 (1.6)	0.49
AST or ALT ≥ 10xULN	4 (0.1)	5 (0.2)	0.73
AST or ALT ≥ 3x ULN and total bilirubin ≥ 2x ULN	6 (0.2)	10 (0.4)	0.31

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

10.16 Appendix 16: Literature search for background AF mortality

See separate document.

10.17 Appendix 17: Testing Fits for UK Lifetime Mortality Data for Men and Women

Methods

Mortality data from UK lifetables were analyzed to test the fit of commonly used parametric survival functions to identify the most appropriate choice for use in an economic modeling application. The following distributions were tested: exponential, Weibull, Gompertz, log-logisitic and log-normal.

Data for men and women were analyzed separately. Each distribution was fitted; the predicted life expectancy (LE) and predicted median lifespan were calculated to help assess the validity of the fits. The corresponding *observed* values were derived from the lifetables for comparison. In addition, the sum of squared errors between the observed and predicted survival curves was calculated as a measure of goodness of fit. Lower values indicate better fit.

Results

The table below summarizes predictions and fits of the distributions for males and females. The figures below illustrate the predicted curves with each distribution. These suggest that the Gompertz distribution provides a far superior fit, closely mimicking the shape of the observed distribution, and yields accurate estimates of LE. The fits of the other distributions fail to capture the shape from the observed survival pattern, extend out far beyond logical values for human lifespan, and produce unrealistic estimates of LE and/or median times.

Table 129: Predicted curves and fits with each distribution

	Males			Females		
Distribution	**Predicted LE (Observed=78.6)**	**Predicted Median (Observed=81.8)**	**SSE**	**Predicted LE (Observed=82.8)**	**Predicted Median (Observed=85.9)**	**SSE**
Exponential	38.5	26.7	23.69	46.0	31.9	22.30
Weibull	104.5	98.9	5.23	128.1	120.8	7.07
Gompertz	**78.1**	**80.6**	**0.035**	**82.1**	**84.6**	**0.067**
Log-Logistic	87.6	69.9	3.80	113.0	87.3	3.91
Log-Normal	60.9	56.6	7.23	66.4	61.7	6.91

Figure 41: Males Observed and Predicted Distributions

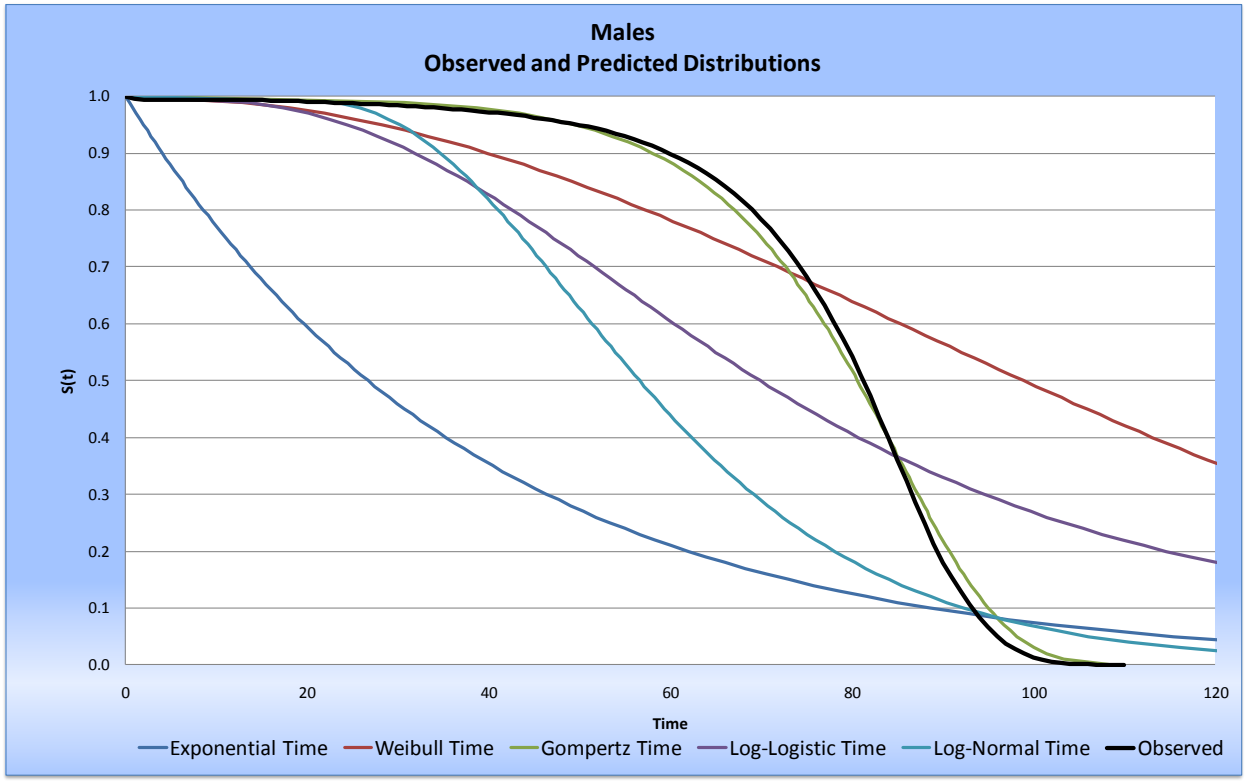
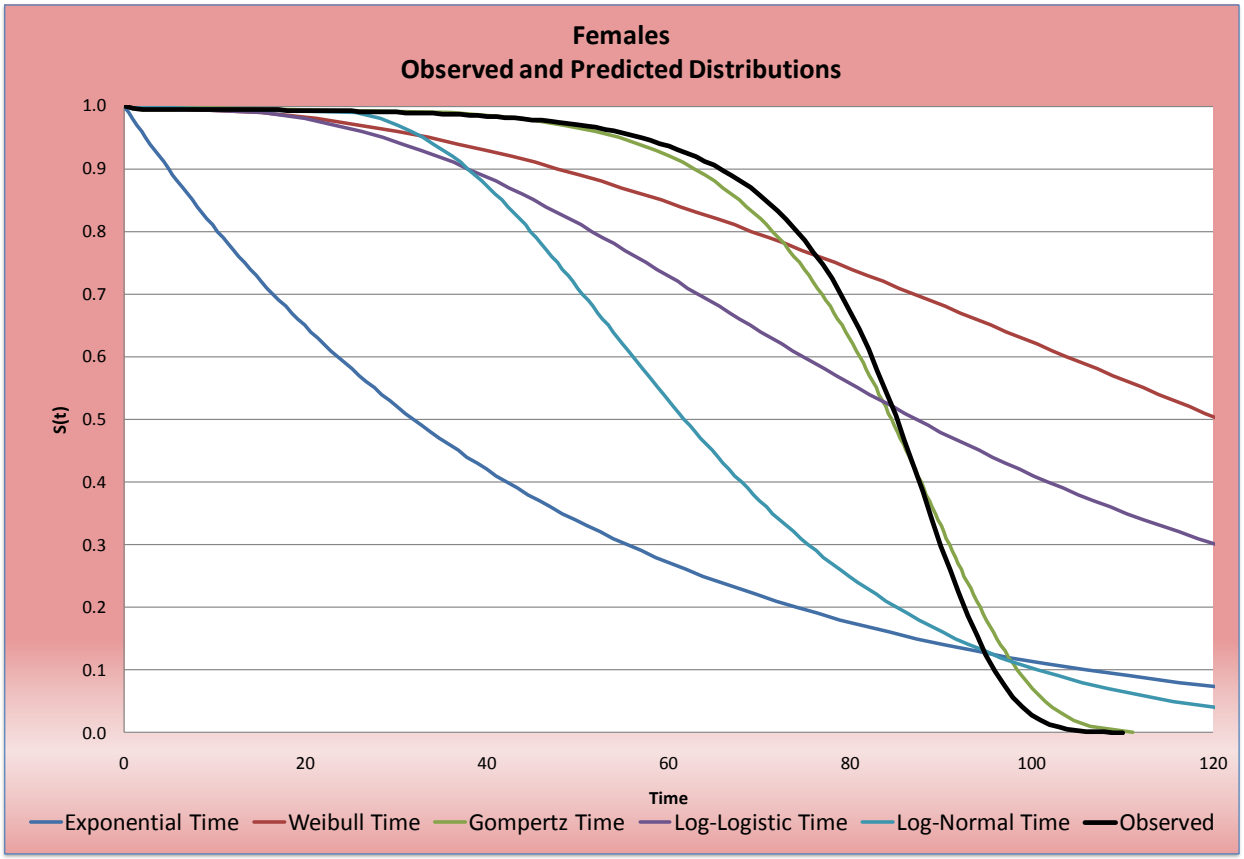


Figure 42: Females Observed and Predicted Distributions



10.18 Appendix 18: One-way sensitivity analysis variables

Table 130: One-way sensitivity analysis variables

Description	Warfarin			Dabigatran (110 mg)			Dabigatran (150 mg)			Rivaroxaban			Source of Variation	Reference
	Base	Lower	Upper	Base	Lower	Upper	Base	Lower	Upper	Base	Lower	Upper		
Gender (% Male)	0.52	0.42	0.62	0.52	0.42	0.62	0.52	0.42	0.62	0.52	0.42	0.62	±10%	(26)
Mean age for males	74.00	62.90	85.10	74.00	62.90	85.10	74.00	62.90	85.10	74.00	62.90	85.10	†	(26)
Mean age for females	74.00	62.90	85.10	74.00	62.90	85.10	74.00	62.90	85.10	74.00	62.90	85.10	†	(26)
Risk of ischemic and unspecified stroke for apixaban (Rate/100 PYs)	0.96	0.55	1.48	0.96	0.55	1.48	0.96	0.55	1.48	0.96	0.55	1.48	‡	Secondary analysis of the ARISTOTLE data
Risk of ischemic and unspecified stroke for comparator (Rate/100 PYs)	1.05	0.79	1.24	1.05	0.79	1.24	1.05	0.79	1.24	1.05	0.79	1.24	‡	Secondary analysis of the ARISTOTLE data
Risk adjustment factor for stroke per decade	1.40	0.80	2.16	1.40	0.80	2.16	1.40	0.80	2.16	1.40	0.80	2.16	†	(110)
Case fatality rate of stroke (excluding hemorrhagic strokes) for apixaban	0.18	0.11	0.26	0.18	0.11	0.26	0.18	0.11	0.26	0.18	0.11	0.26	§	Secondary analysis of the ARISTOTLE data
Case fatality rate of stroke (excluding hemorrhagic strokes) for comparator	0.15	0.09	0.22	0.27	0.21	0.34	0.35	0.28	0.42	0.27	0.21	0.34	§	Secondary analysis of the ARISTOTLE data
Risk of ICH for apixaban(Rate/100 PYs)	0.33	0.19	0.51	0.33	0.19	0.51	0.33	0.19	0.51	0.33	0.19	0.51	‡	Secondary analysis of the ARISTOTLE data
Risk of ICH for comparator (Rate/100 PYs)	0.80	-	-	0.80	-	-	0.80	-	-	0.80	-	-	‡	Secondary analysis of the ARISTOTLE data

Risk adjustment factor for ICH per decade	1.97	1.79	2.16	1.97	1.79	2.16	1.97	1.79	2.16	1.97	1.79	2.16	†	(111)
Proportion of hemorrhagic strokes among ICHs for apixaban	0.77	0.65	0.87	0.77	0.65	0.87	0.77	0.65	0.87	0.77	0.65	0.87	§	Secondary analysis of the ARISTOTLE data
Proportion of hemorrhagic strokes among ICHs for comparator	0.64	0.55	0.72	0.64	0.43	0.82	0.41	0.24	0.59	0.57	0.44	0.70	§	Secondary analysis of the ARISTOTLE data, RE;LY, Rocket
Case fatality rate of hemorrhagic stroke for apixaban	0.35	0.20	0.52	0.35	0.20	0.52	0.35	0.20	0.52	0.35	0.20	0.52	§	Secondary analysis of the ARISTOTLE data
Case fatality rate of hemorrhagic stroke for comparator	0.53	0.41	0.65	0.27	0.21	0.34	0.35	0.28	0.42	0.27	0.21	0.34	§	Secondary analysis of the ARISTOTLE data, RE;LY, Rocket
Risk of other major bleeds for apixaban (Rate/100PYs)	1.79	1.02	2.77	1.79	1.02	2.77	1.79	1.02	2.77	1.79	1.02	2.77	‡	ARISTOTLE
Risk of other major bleeds for comparator (Rate/100PYs)	2.27	1.30	3.51	2.27	1.30	3.51	2.27	1.30	3.51	2.27	1.30	3.51	‡	ARISTOTLE
Risk adjustment factor for other major bleeds per decade	1.97	1.79	2.16	1.97	1.79	2.16	1.97	1.79	2.16	1.97	1.79	2.16	†	(111)
Proportion of GI bleeds among other major bleeds for apixaban	0.38	0.32	0.44	0.38	0.32	0.44	0.38	0.32	0.44	0.38	0.32	0.44	§	ARISTOTLE Case Study Report
Proportion of GI bleeds among other major bleeds for comparator	0.35	0.30	0.40	0.41	0.36	0.46	0.49	0.44	0.54	0.45	0.40	0.50	§	Secondary analysis of the ARISTOTLE data, RELY, Rocket
Risk CRNMB for apixaban (Rate/100PYs)	2.08	1.19	3.22	2.08	1.19	3.22	2.08	1.19	3.22	2.08	1.19	3.22	‡	Secondary analysis of the ARISTOTLE data
Risk of CRNMB for comparator	3.00	2.63	3.55	3.00	2.63	3.55	3.00	2.63	3.55	3.00	2.63	3.55	‡	Secondary analysis of the

(Rate/100PYs)														ARISTOTLE data
Risk adjustment factor for CRNMB per decade	1.97	1.79	2.16	1.97	1.79	2.16	1.97	1.79	2.16	1.97	1.79	2.16	†	(111)
Case fatality rate of ICH for apixaban	0.13	0.06	0.22	0.13	0.06	0.22	0.13	0.06	0.22	0.13	0.06	0.22	§	Secondary analysis of the AVERROES data, Secondary analysis of the ARISTOTLE data
Case fatality rate of ICH for comparator	0.13	0.06	0.22	0.13	0.06	0.22	0.13	0.06	0.22	0.13	0.06	0.22	§	Secondary analysis of the AVERROES data, Secondary analysis of the ARISTOTLE data
Case fatality rate of other major bleeds for apixaban	0.02	0.01	0.03	0.02	0.01	0.03	0.02	0.01	0.03	0.02	0.01	0.03	§	Secondary analysis of the AVERROES data, Secondary analysis of the ARISTOTLE data
Case fatality rate of other major bleeds for comparator	0.02	0.01	0.03	0.02	0.01	0.03	0.02	0.01	0.03	0.02	0.01	0.03	§	Secondary analysis of the AVERROES data, Secondary analysis of the ARISTOTLE data
% switch treatment post ICH for apixaban	0.56	0.43	0.69	0.56	0.43	0.69	0.56	0.43	0.69	0.56	0.43	0.69	†	(114)
% switch treatment post ICH for comparator	0.56	0.43	0.69	0.56	0.43	0.69	0.56	0.43	0.69	0.56	0.43	0.69	¶	(114).& Warfarin = Assumption
% switch treatment post GI for apixaban	0.25	0.01	0.69	0.25	0.01	0.69	0.25	0.01	0.69	0.25	0.01	0.69	¶	(114)
% switch treatment post GI for comparator	0.25	0.01	0.69	0.25	0.01	0.69	0.25	0.01	0.69	0.25	0.01	0.69	¶	(114).& Warfarin = Assumption
Risk of MI for apixaban (Rate/100PYs)	0.53	0.30	0.82	0.53	0.30	0.82	0.53	0.30	0.82	0.53	0.30	0.82	‡	ARISTOTLE
Risk of MI for comparator (Rate/100PYs)	0.61	0.45	0.81	0.61	0.45	0.81	0.61	0.45	0.81	0.61	0.45	0.81	‡	ARISTOTLE
Risk of CV hospitalization for apixaban (Rate/100 PYs)	10.46	5.98	16.17	10.46	5.98	16.17	10.46	5.98	16.17	10.46	5.98	16.17	‡	A (rate for apixaban taken from the AVERROES, assume same rate for warfarin)
Risk of CV hospitalization for comparator	10.46	5.98	16.17	10.46	5.98	16.17	10.46	5.98	16.17	10.46	5.98	16.17	‡	A (rate for apixaban taken from the AVERROES, assume same rate for warfarin)

(Rate/100 PYs)														
Risk of other treatment discontinuations for apixaban (Rate/100 PYs)	13.42	7.67	20.74	13.42	7.67	20.74	13.42	7.67	20.74	13.42	7.67	20.74	‡	Secondary analysis of the ARISTOTLE data
Risk of other treatment discontinuations for comparator (Rate/100 PYs)	14.54	8.31	22.49	14.54	8.31	22.49	14.54	8.31	22.49	14.54	8.31	22.49	‡	Secondary analysis of the ARISTOTLE data
Risk of ischemic and unspecified strokes for aspirin 2nd line (Rate/100 PYs)	3.45	1.97	5.34	3.45	1.97	5.34	3.45	1.97	5.34	3.45	1.97	5.34	‡	Secondary analysis of the AVERROES data
Risk of ICH for aspirin 2nd line (Rate/100 PYs)	0.32	0.18	0.50	0.32	0.18	0.50	0.32	0.18	0.50	0.32	0.18	0.50	‡	Secondary analysis of the AVERROES data
Risk of other major bleeds for aspirin 2nd line (Rate/100 PYs)	0.89	0.51	1.37	0.89	0.51	1.37	0.89	0.51	1.37	0.89	0.51	1.37	‡	Secondary analysis of the AVERROES data
Risk of CRNMB for aspirin 2nd line (Rate/100 PYs)	2.94	1.68	4.54	2.94	1.68	4.54	2.94	1.68	4.54	2.94	1.68	4.54	‡	Secondary analysis of the AVERROES data
Risk of MI for aspirin 2nd line (Rate/100 PYs)	1.11	0.63	1.72	1.11	0.63	1.72	1.11	0.63	1.72	1.11	0.63	1.72	‡	Secondary analysis of the AVERROES data
Risk of CV hospitalization for aspirin 2nd line (Rate/100 PYs)	13.57	7.76	20.98	13.57	7.76	20.98	13.57	7.76	20.98	13.57	7.76	20.98	‡	Secondary analysis of the AVERROES data
Case fatality rate of stroke (excluding hemorrhagic strokes)for aspirin 2nd line	0.11	-	-	0.11	-	-	0.11	-	-	0.11	-	-	§	Secondary analysis of the AVERROES data
Utility AF	0.78	0.70	0.86	0.78	0.70	0.86	0.78	0.70	0.86	0.78	0.70	0.86	†	(112)
Utility stroke mild	0.76	0.70	0.82	0.76	0.70	0.82	0.76	0.70	0.82	0.76	0.70	0.82	†	(149)

Utility stroke moderate	0.39	0.33	0.45	0.39	0.33	0.45	0.39	0.33	0.45	0.39	0.33	0.45	†	(149)
Utility stroke severe	0.11	0.06	0.17	0.11	0.06	0.17	0.11	0.06	0.17	0.11	0.06	0.17	†	(149)
Utility hemorrhagic stroke mild	0.76	0.70	0.82	0.76	0.70	0.82	0.76	0.70	0.82	0.76	0.70	0.82	†	(149)
Utility hemorrhagic stroke moderate	0.39	0.33	0.45	0.39	0.33	0.45	0.39	0.33	0.45	0.39	0.33	0.45	†	(149)
Utility hemorrhagic stroke severe	0.11	0.06	0.17	0.11	0.06	0.17	0.11	0.06	0.17	0.11	0.06	0.17	†	(149)
Utility decrement: ICH	0.11	0.04	0.20	0.11	0.04	0.20	0.11	0.04	0.20	0.11	0.04	0.20	†	(152)
Utility decrement: other major bleed	0.11	0.04	0.20	0.11	0.04	0.20	0.11	0.04	0.20	0.11	0.04	0.20	†	(152)
Utility decrement: CRNMB	0.06	0.03	0.10	0.06	0.03	0.10	0.06	0.03	0.10	0.06	0.03	0.10	†	(145)
Utility decrement: MI	0.68	0.64	0.72	0.68	0.64	0.72	0.68	0.64	0.72	0.68	0.64	0.72	†	(153)
Utility decrement: Other CV hospitalization	0.10	0.05	0.15	0.10	0.05	0.15	0.10	0.05	0.15	0.10	0.05	0.15	†	(153)
Utility decrement: aspirin 2nd line	0.00	-	0.004	0.00	-	0.004	0.00	-	0.004	0.00	-	0.004	2* mean	(149)
Utility decrement: comparator	0.01	-	0.026	0.01	-	0.026	0.01	-	0.026	0.01	-	0.026	2* mean	(149)
Hazard Ratio for long-term mortality post ischemic & unspecified stroke mild	3.18	1.42	4.94	3.18	1.42	4.94	3.18	1.42	4.94	3.18	1.42	4.94	‡	(120)
Hazard Ratio for long-term mortality post ischemic & unspecified stroke moderate	5.84	4.08	7.60	5.84	4.08	7.60	5.84	4.08	7.60	5.84	4.08	7.60	‡	(118-120)

Hazard Ratio for long-term mortality post ischemic & unspecified stroke severe	15.75	13.99	17.51	15.75	13.99	17.51	15.75	13.99	17.51	15.75	13.99	17.51	‡	(118-120)
Hazard Ratio for long-term mortality post hemorrhagic stroke mild	3.18	1.82	4.92	3.18	1.82	4.92	3.18	1.82	4.92	3.18	1.82	4.92	‡	(118-120)
Hazard Ratio for long-term mortality post hemorrhagic stroke moderate	5.84	3.34	9.03	5.84	3.34	9.03	5.84	3.34	9.03	5.84	3.34	9.03	‡	(118-120)
Hazard Ratio for long-term mortality post hemorrhagic stroke severe	15.75	9.00	24.35	15.75	9.00	24.35	15.75	9.00	24.35	15.75	9.00	24.35	‡	(118-120)
Monitoring visit cost	13.79	6.56	17.24	13.79	6.56	17.24	13.79	6.56	17.24	13.79	6.56	17.24	†	(102)
Routine care cost	-	-	113.00	-	-	113.00	-	-	113.00	-	-	113.00	20% deviation for lower bound, upper bound cardiology visit cost	National Schedule of Reference Costs: '2009-10' - NHS Trusts and PCTs combined 2010, DoH.
Acute care stroke costs mild	3,515.64	1,495.45	5,535.83	3,515.64	1,495.45	5,535.83	3,515.64	1,495.45	5,535.83	3,515.64	1,495.45	5,535.83	†	(157)
Long-term follow-upstroke costs mild	183.91	107.54	260.29	183.91	107.54	260.29	183.91	107.54	260.29	183.91	107.54	260.29	†	(157)
Acute care stroke costs moderate	18,341.08	13,375.11	23,307.04	18,341.08	13,375.11	23,307.04	18,341.08	13,375.11	23,307.04	18,341.08	13,375.11	23,307.04	†	(157)
Long-term follow-upstroke costs moderate	358.78	188.79	528.78	358.78	188.79	528.78	358.78	188.79	528.78	358.78	188.79	528.78	†	(157)
Acute care stroke costs severe	25,050.88	17,055.07	33,046.68	25,050.88	17,055.07	33,046.68	25,050.88	17,055.07	33,046.68	25,050.88	17,055.07	33,046.68	†	(157)
Long-term follow-upstroke	544.76	-	1,270.87	544.76	-	1,270.87	544.76	-	1,270.87	544.76	-	1,270.87	†	(157)

costs severe														
Acute care hemorrhagic stroke costs mild	10,236.81	6,150.44	14,323.18	10,236.81	6,150.44	14,323.18	10,236.81	6,150.44	14,323.18	10,236.81	6,150.44	14,323.18	†	(157)
Long-term follow-up hemorrhagic stroke costs mild	183.91	107.54	260.29	183.91	107.54	260.29	183.91	107.54	260.29	183.91	107.54	260.29	†	(157)
Acute care hemorrhagic stroke costs moderate	26,299.60	15,029.26	37,569.94	26,299.6	15,029.26	37,569.94	26,299.6	15,029.26	37,569.94	26,299.6	15,029.26	37,569.94	†	(157)
Long-term follow-up hemorrhagic stroke costs moderate	358.78	188.79	528.78	358.78	188.79	528.78	358.78	188.79	528.78	358.78	188.79	528.78	†	(157)
Acute care hemorrhagic stroke costs severe	44,486.65	22,688.59	66,284.71	44,486.65	22,688.59	66,284.71	44,486.65	22,688.59	66,284.71	44,486.65	22,688.59	66,284.71	†	(157)
Long-term follow-up hemorrhagic stroke costs severe	544.76	-	1,270.87	544.76	-	1,270.87	544.76	-	1,270.87	544.76	-	1,270.87	†	(157)
Other ICH cost	3,010.00	2,329.00	3,908.00	3,010.00	2,329.00	3,908.00	3,010.00	2,329.00	3,908.00	3,010.00	2,329.00	3,908.00	†	National Schedule of Reference Costs: '2009-10'; NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data
Cost of GI	1,493.68	1,136.00	1,923.00	1,493.68	1,136.00	1,923.00	1,493.68	1,136.00	1,923.00	1,493.68	1,136.00	1,923.00	†	National Schedule of Reference Costs: '2009-10'; NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data
Non ICH and non GI Major bleed cost	3,947.92	2,461.00	5,527.00	3,947.92	2,461.00	5,527.00	3,947.92	2,461.00	5,527.00	3,947.92	2,461.00	5,527.00	†	National Schedule of Reference Costs: '2009-10'; NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data
CRNM bleeds cost	1,133.93	621.00	1,612.00	1,133.93	621.00	1,612.00	1,133.93	621.00	1,612.00	1,133.93	621.00	1,612.00	†	National Schedule of Reference Costs '2009-10'; NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data
MI Acute care cost	2,018.84	1,514.13	2,523.55	2,018.84	1,514.13	2,523.55	2,018.84	1,514.13	2,523.55	2,018.84	1,514.13	2,523.55	†	National Schedule of Reference Costs: '2009-10'; NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data

MI long-term follow-up cost	6.65	3.80	10.28	6.65	3.80	10.28	6.65	3.80	10.28	6.65	3.80	10.28	†	(158)
CV hospitalization cost	1,570.89	965.00	2,160.00	1,570.89	965.00	2,160.00	1,570.89	965.00	2,160.00	1,570.89	965.00	2,160.00	†	National Schedule of Reference Costs: '2009-10'; NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data
Stroke Hazard ratio for comparator	1.04	0.82	1.30	1.17	0.84	1.62	0.79	0.55	1.10	1.02	0.76	1.37	†	Network meta analysis 1
ICH Hazard ratio for comparator	2.43	1.77	3.41	0.75	0.43	1.27	0.98	0.58	1.64	1.73	1.08	2.79	†	Network meta analysis 1
MI Hazard ratio for comparator	1.15	0.86	1.53	1.58	1.01	2.42	1.62	1.04	2.49	1.06	0.72	1.52	†	Network meta analysis 1
Cardiovascular hospitalization Hazard ratio for comparator	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	†	Network meta analysis 1
Major Bleed Hazard ratio for comparator	1.27	1.08	1.49	1.21	0.96	1.51	1.38	1.10	1.73	1.43	1.15	1.79	†	Network meta analysis 1
CRNM Hazard ratio for comparator	1.47	1.26	1.71	1.00	1.00	1.00	1.00	1.00	1.00	1.52	1.28	1.80	†	Network meta analysis 1
Treatment discontinuation Hazard ratio for comparator	1.10	1.04	1.16	1.45	1.31	1.61	1.51	1.36	1.67	1.18	1.08	1.29	†	Network meta analysis 1
Risk of recurrent IS	0.04	0.03	0.05	0.04	0.03	0.05	0.04	0.03	0.05	0.04	0.03	0.05	†	(109)
Risk of recurrent HS	0.03	0.02	0.04	0.03	0.02	0.04	0.03	0.02	0.04	0.03	0.02	0.04	†	(109)
Risk of SE for apixaban (Rate/100PYs)	0.09	0.05	0.14	0.09	0.05	0.14	0.09	0.05	0.14	0.09	0.05	0.14	†	ARISTOTLE
Risk of SyE for comparator (Rate/100PYs)	0.10	0.06	0.15	0.10	0.06	0.15	0.10	0.06	0.15	0.10	0.06	0.15	†	ARISTOTLE
Utility: SyE	0.68	0.64	0.72	0.68	0.64	0.72	0.68	0.64	0.72	0.68	0.64	0.72	†	(145)
Case fatality rate of SyE for apixaban	0.09	0.02	0.21	0.09	0.02	0.21	0.09	0.02	0.21	0.09	0.02	0.21	§	ARISTOTLE Case Study Report
Case fatality rate of SyE for comparator	0.09	0.02	0.21	0.09	0.02	0.21	0.09	0.02	0.21	0.09	0.02	0.21	§	ARISTOTLE Case Study Report

Hazard Ratio for long-term mortality post systemic embolism	1.34	1.00	3.18	1.34	1.00	3.18	1.34	1.00	3.18	1.34	1.00	3.18	Assumption based on RR for mild stroke	Assumption, (12)
Hazard Ratio for long-term mortality post MI females	4.16	3.44	5.03	4.16	3.44	5.03	4.16	3.44	5.03	4.16	3.44	5.03	Upper bound based on highest RR observed in publication over 15 year period	(121)
Hazard Ratio for long-term mortality post MI males	2.56	2.27	2.88	2.56	2.27	2.88	2.56	2.27	2.88	2.56	2.27	2.88	Upper bound based on highest RR observed in publication over 15 year period	(121)
Case fatality rate of MI females	0.16	0.09	0.24	0.16	0.09	0.24	0.16	0.09	0.24	0.16	0.09	0.24	§	(117)
Case fatality rate of MI females	0.11	0.06	0.17	0.11	0.06	0.17	0.11	0.06	0.17	0.11	0.06	0.17	§	(117)
Acute care SyE costs	4,077.98	2,193.11	5,962.85	4,077.98	2,193.11	5,962.85	4,077.98	2,193.11	5,962.85	4,077.98	2,193.11	5,962.85	‡	(157)
Long-term follow-up SyE cost	183.91	107.54	260.29	183.91	107.54	260.29	183.91	107.54	260.29	183.91	107.54	260.29	‡	(157)
Management cost of apixaban	0.04	0.02	0.06	0.04	0.02	0.06	0.04	0.02	0.06	0.04	0.02	0.06	‡	ARISTOTLE Case Study Report; Electronic Drug Tariff, November 2011, Department of Health by the NHS Business Services Authority, NHS Prescription Services , http://www.ppa.org.uk/ppa/edt_intro.htm
Management of comparator	0.04	0.02	0.06	0.13	0.08	0.21	0.13	0.07	0.20	0.04	0.02	0.06	‡	AVERROES Case Study Report; ARISTOTLE Case Study Report; RE-LY, Electronic Drug Tariff, November 2011, Department of Health by the NHS Business Services Authority, NHS Prescription

														Services , http://www.ppa.org.uk/ppa/edt_intro.htm; National Schedule of Reference Costs Year : '2009-10' - NHS Trusts and PCTs combined Consultant Led
SyE Hazard ratio for comparator	1.12	0.55	2.26	0.78	0.29	2.07	0.72	0.26	1.95	0.84	0.34	2.07	†	Network meta analysis 1
Rate of death apixaban trial period	3.08	2.50	3.72	3.08	2.50	3.72	3.08	2.50	3.72	3.08	2.50	3.72	Calculated from patient numbers	Secondary analysis of the ARISTOTLE data
Rate of death comparator trial period	3.34	2.97	3.76	3.34	2.97	3.76	3.34	2.97	3.76	3.34	2.97	3.76	Calculated from patient numbers	Secondary analysis of the ARISTOTLE data
HR mortality trial period comparator	1.08	0.96	1.22	1.00	0.90	1.10	1.00	0.90	1.10	1.00	0.90	1.10	†	Network meta analysis 1
HR mortality AF	1.34	1.00	1.90	1.34	1.00	1.90	1.34	1.00	1.90	1.34	1.00	1.90	†	(12)
Cost discount rate	0.035	-	0.06	0.035	-	0.06	0.035	-	0.06	0.035	-	0.06		(164)
Utility discount rate	0.035	-	0.06	0.035	-	0.06	0.035	-	0.06	0.035	-	0.06		(164)
Fatal cost of stroke	3,162.11	-	4,277.84	3,162.11	-	4,277.84	3,162.11	-	4,277.84	3,162.11	-	4,277.84		(164)
Fatal cost of hemorrhagic stroke	1,645.66	-	2,996.62	1,645.66	-	2,996.62	1,645.66	-	2,996.62	1,645.66	-	2,996.62		(164)

VKA unsuitable parameters that differ to the VKA suitable by intervention

	Aspirin			**Dabigatran (110 mg)**			**Dabigatran (150 mg)**			**Rivaroxaban**			**Source of Variation**	**Reference**
	Base	**Lower**	**Upper**	**Base**	**Lower**	**Upper**	**Base**	**Lower**	**Upper**	**Base**	**Lower**	**Upper**		
Risk of ischemic and unspecified stroke for apixaban (Rate/100 PYs)	1.38	0.79	2.13	1.38	0.79	2.13	1.38	0.79	2.13	1.38	0.79	2.13	‡	Secondary analysis of the AVERROES data
Risk of ischemic and unspecified stroke for comparator (Rate/100 PYs)	3.14	2.62	5.64	3.14	2.62	5.64	3.14	2.62	5.64	3.14	2.62	5.64	‡	Secondary analysis of the AVERROES data

Case fatality rate of stroke (excluding hemorrhagic strokes) for apixaban	0.20	0.10	0.32	1.40	0.80	2.16	0.20	0.10	0.32	0.20	0.10	0.32	§	Secondary analysis of the AVERROES data
Case fatality rate of stroke (excluding hemorrhagic strokes) for comparator	0.11	0.06	0.17	0.20	0.10	0.32	0.34	0.20	0.53	0.34	0.20	0.53	§	Secondary analysis of the AVERROES data
Risk of ICH for apixaban(Rate/100 PYs)	0.34	0.20	0.53	0.34	0.20	0.53	0.35	0.15	0.54	0.35	0.15	0.54	‡	Secondary analysis of the AVERROES data
Risk of ICH for comparator (Rate/100 PYs)	0.35	0.15	0.54	0.35	0.15	0.54	0.55	0.40	0.70	0.55	0.40	0.70	‡	Secondary analysis of the AVERROES data
Proportion of hemorrhagic strokes among ICHs for apixaban	0.55	0.40	0.70	0.55	0.40	0.70	0.46	0.38	0.54	0.46	0.38	0.54	§	Secondary analysis of the AVERROES data
Proportion of hemorrhagic strokes among ICHs for comparator	0.55	0.40	0.70	0.46	0.38	0.54	1.07	0.61	1.65	1.07	0.61	1.65	§	Secondary analysis of the AVERROES data, RE;LY, Rocket
Case fatality rate of hemorrhagic stroke for apixaban	0.46	0.38	0.54	1.07	0.61	1.65	0.57	0.32	0.99	0.57	0.32	0.99	§	Secondary analysis of the AVERROES data
Case fatality rate of hemorrhagic stroke for comparator	0.46	0.38	0.54	0.57	0.32	0.99	0.35	0.22	0.49	0.35	0.22	0.49	§	Secondary analysis of the AVERROES data, RE;LY, Rocket
Risk of other major bleeds for apixaban (Rate/100PYs)	1.07	0.61	1.65	0.35	0.22	0.49	3.11	1.78	4.81	3.11	1.78	4.81	‡	AVERROES
Risk of other major bleeds for comparator (Rate/100PYs)	0.57	0.32	0.99	3.11	1.78	4.81	2.37	2.03	3.62	2.37	2.03	3.62	‡	AVERROES
Proportion of GI bleeds among other major bleeds for	0.35	0.22	0.49	2.37	2.03	3.62	0.76	0.43	1.18	0.76	0.43	1.18	§	AVERROES Case Study Report

apixaban														
Proportion of GI bleeds among other major bleeds for comparator	0.39	0.22	0.57	0.76	0.43	1.18	0.89	0.50	1.51	0.89	0.50	1.51	§	Secondary analysis of the AVERROES data, RELY, Rocket
Risk of CRNMB for apixaban (Rate/100PYs)	3.11	1.78	4.81	0.89	0.50	1.51	12.09	10.38	14.07	12.09	10.38	14.07	‡	Secondary analysis of the AVERROES data
Risk of CRNMB for comparator (Rate/100PYs)	2.37	2.03	3.62	12.09	10.38	14.07	17.66	10.09	27.31	17.66	10.09	27.31	‡	Secondary analysis of the AVERROES data
% switch treatment post ICH for comparator	-	1.00	1.00	17.66	10.09	27.31	19.65	18.84	23.63	19.65	18.84	23.63	¶	(114).& Aspirin = Assumption
% switch treatment post GI for comparator	-	1.00	1.00	19.65	18.84	23.63	0.79	0.56	1.10	1.03	0.77	1.38	¶	(114)
Risk of MI for apixaban (Rate/100PYs)	0.76	0.43	1.18	1.57	1.01	2.41	0.98	0.59	1.63	1.73	1.07	2.80	‡	AVERROES
Risk of MI for comparator (Rate/100PYs)	0.89	0.50	1.51	0.06	0.03	0.09	1.61	1.06	2.47	1.05	0.73	1.53	‡	AVERROES
Risk of CV hospitalization for comparator (Rate/100 PYs)	12.09	10.38	14.07	0.41	0.23	0.63	1.50	1.36	1.67	1.43	1.14	1.80	‡	Secondary analysis of the AVERROES data
Risk of other treatment discontinuations for apixaban (Rate/100 PYs)	17.66	10.09	27.31	0.77	0.29	2.06	0.06	0.03	0.09	1.53	1.29	1.81	‡	Secondary analysis of the AVERROES data
Risk of other treatment discontinuations for comparator (Rate/100 PYs)	19.65	18.84	23.63	2.97	2.59	3.37	0.41	0.23	0.63	1.18	1.08	1.30	‡	Secondary analysis of the AVERROES data
Stroke Hazard ratio for comparator	2.75	1.90	4.09	3.59	2.74	4.73	0.70	0.26	1.93	0.06	0.03	0.09	†	Network meta analysis 2
ICH Hazard ratio for comparator	1.04	0.45	2.46	0.75	0.42	1.28	2.97	2.59	3.37	0.41	0.23	0.63	†	Network meta analysis 2
MI Hazard ratio	1.13	0.66	1.98										†	Network meta analysis 2

for comparator				1.57	1.01	2.41	3.59	2.74	4.73	0.83	0.34	2.12		
Cardiovascular hospitalization Hazard ratio for comparator	1.16	0.99	1.35	1.00	1.00	1.00	1.00	1.00	1.00	2.97	2.59	3.37	†	Network meta analysis 2
Major Bleed Hazard ratio for comparator	0.53	0.30	0.93	1.21	0.96	1.51	1.38	1.10	1.72	3.59	2.74	4.73	†	Network meta analysis 2
CRNM Hazard ratio for comparator	0.87	0.65	1.16	1.00	1.00	1.00	1.00	1.00	1.00	1.53	1.29	1.81	†	Network meta analysis 2
Treatment discontinuation Hazard ratio for comparator	1.20	1.07	1.34	1.45	1.30	1.61	1.50	1.36	1.67	1.18	1.08	1.30	†	Network meta analysis 2
Risk of SE for apixaban (Rate/100PYs)	0.06	0.03	0.09	0.06	0.03	0.09	0.06	0.03	0.09	0.06	0.03	0.09	†	(3)
Risk of SE for comparator (Rate/100PYs)	0.41	0.23	0.63	0.41	0.23	0.63	0.41	0.23	0.63	0.41	0.23	0.63	†	(3)
Management of comparator	0.04	0.02	0.06	0.13	0.08	0.21	0.13	0.07	0.20	0.04	0.02	0.06	†	AVERROES Case Study Report; Electronic Drug Tariff, November 2011, Department of Health by the NHS Business Services Authority, NHS Prescription Services , http://www.ppa.org.uk/ppa/edt_intro.htm
SE Hazard ratio for comparator	4.72	1.22	35.06	0.77	0.29	2.06	0.70	0.26	1.93	0.83	0.34	2.12	†	Network meta analysis 2
Rate of death apixaban trial period	2.97	2.59	3.37	2.97	2.59	3.37	2.97	2.59	3.37	2.97	2.59	3.37	Calculated from patient numbers	Secondary analysis of the AVERROES data
Rate of death comparator trial period	3.59	2.74	4.73	3.59	2.74	4.73	3.59	2.74	4.73	3.59	2.74	4.73	Calculated from patient numbers	Secondary analysis of the AVERROES data
HR mortality trial period comparator	1.21	0.92	1.59	1.00	0.90	1.10	1.00	0.90	1.10	1.00	0.90	1.10	†	Network meta analysis 2

†95% CIs from source. ‡Assumed 25% SE of the mean – Gamma Distribution. §Patient numbers –Beta distribution. ¶ Assumed 25% SE of the mean – β- distribution.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CRNMB, clinically relevant non-major bleed; CV, cardiovascular; GI, gastrointestinal; HR, hazard ratio; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction; PY, patient years; SE, standard error; SyE, systemic embolism.

10.19 Appendix 19: PSA variables

Table 131: PSA variables

Input	Mean	Distribution	SE	Shape	Scale	Reference
CHADS = 0	9.80%	Dirichlet	0.002	3,302	3,340	(42)
CHADS = 1	30.10%	Dirichlet	0.002	12,508	12,585	(42)
CHADS = 2	29.60%	Dirichlet	0.002	12,157	12,038	(42)
CHADS = 3	17.90%	Dirichlet	0.002	8,706	8,858	(42)
CHADS = 4	8.50%	Dirichlet	0.001	3,704	3,711	(42)
CHADS = 5	4.10%	Dirichlet	0.001	2,465	2,358	(42)
CHADS = 6	0.00%	Dirichlet	0.001	0	0.0000027	(42). As 0% shape and scale are assumptions
CHADS = 0	9.80%	Dirichlet	0.002	3,302	3,405	(42)
CHADS = 1	30.10%	Dirichlet	0.002	12,508	12,609	(42)
CHADS = 2	29.60%	Dirichlet	0.002	12,157	12,240	(42)
CHADS = 3	17.90%	Dirichlet	0.002	8,706	8,775	(42)
CHADS = 4	8.50%	Dirichlet	0.001	3,704	3,783	(42)
CHADS = 5	4.10%	Dirichlet	0.001	2,465	2,513	(42)
CHADS = 6	0.00%	Dirichlet	0.001	0	0.0000027	(42). As 0% shape and scale are assumptions
Stroke						
Apixaban stroke risk by CHADS for VKA unsuitable						
CHADS = 0	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES
CHADS = 1	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 2	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 3	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 4	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 5	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 6	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Aspirin stroke risk by CHADS for VKA unsuitable						
CHADS = 0	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary Analysis of AVERROES
CHADS = 1	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 2	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 3	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 4	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 5	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 6	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Apixaban stroke risk by CHADS for VKA suitable						
CHADS = 0	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary Analysis of ARISTOTLE
CHADS = 1	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 2	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 3	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	

CHADS = 4	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 5	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 6	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Warfarin stroke risk by CHADS for VKA suitable						
CHADS = 0	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary Analysis of ARISTOTLE
CHADS = 1	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 2	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 3	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 4	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 5	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CHADS = 6	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Hazard ratio for stroke for VKA unsuitable						
Aspirin (1st line)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 2
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for stroke for VKA suitable						
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 1
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for stroke by cTTR apixaban						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for stroke by cTTR warfarin						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
Stroke risk adjustment factor						
VKA unsuitable	1.4	Gamma	0.4	16.0	0.1	(110)
VKA suitable	1.4	Gamma	0.4	16.0	0.1	(110)
Stroke mild proportion for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Dabigatran (110mg)	35.0%	Dirichlet	60.00	51.03		(58)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	75.78		(58)
Rivaroxaban	49.0%	Dirichlet	88.00	92.72		(63)
Stroke mild proportion for VKA suitable						

Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (using the distribution observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	35.0%	Dirichlet	60.00	67.43		(58)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	67.86		(58)
Rivaroxaban	49.0%	Dirichlet	88.00	103.07		(63)
Stroke moderate proportion for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Dabigatran (110mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Dabigatran (150mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Rivaroxaban	[redacted]	Dirichlet	[redacted]	[redacted]		(63) calculation see 7.3.6
Stroke moderate proportion for VKA suitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (using the distribution observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Dabigatran (150mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Rivaroxaban	[redacted]	Dirichlet	[redacted]	[redacted]		(63) calculation see 7.3.6
Stroke severe proportion for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Dabigatran (110mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Dabigatran (150mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Rivaroxaban	[redacted]	Dirichlet	[redacted]	[redacted]		(63) calculation see 7.3.6
Stroke severe proportion for VKA suitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data

Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (using the distribution observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Dabigatran (150mg)	[redacted]	Dirichlet	[redacted]	[redacted]		(58) calculation see 7.3.6
Rivaroxaban	[redacted]	Dirichlet	[redacted]	[redacted]		(63) calculation see 7.3.6
Stroke case fatality rate for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Dabigatran (110mg)	27.0%	Dirichlet	46.00	36.56		(108)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	69.57		(108)
Rivaroxaban	[redacted]	Dirichlet	[redacted]	[redacted]		(63)
Stroke case fatality rate for VKA suitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (using the distribution observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		Assume same distribution as aspirin (1st line)
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	27.0%	Dirichlet	46.00	40.17		(108)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	52.35		(108)}
Rivaroxaban	[redacted]	Dirichlet	[redacted]	[redacted]		(63)
Recurrent stroke annual rate VKA unsuitable	0.041	Gamma	0.0038	118.15	0.00	(109)
Recurrent stroke annual rate VKA suitable	0.041	Gamma	0.0038	118.15	0.00	(109)
Bleeding						
ICH risk for VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
ICH risk for VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for ICH for VKA unsuitable						

Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 3
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for ICH for VKA suitable						
Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		NMA 1
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for ICH by cTTR apixaban						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for ICH by cTTR warfarin						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
ICH type distribution for VKA unsuitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (110mg)	64.0%	Beta	21.9	14.0	7.9	(58)
Dabigatran (150mg)	41.0%	Beta	29.3	12.0	17.3	(58)
Rivaroxaban	57.0%	Beta	55.0	31.4	23.7	(63)
ICH type distribution for VKA suitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Assumption same distribution as observed in AVERROES)
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	64.0%	Beta	21.9	14.0	7.9	(58)
Dabigatran (150mg)	41.0%	Beta	29.3	12.0	17.3	(58)
Rivaroxaban	57.0%	Beta	55.0	31.4	23.7	(63)
Haemorrhagic stroke mild proportion for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Dabigatran (110mg)	35.0%	Dirichlet	60.00	62.68		(58)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	52.81		(58)
Rivaroxaban	49.0%	Dirichlet	77.00	78.94		(63)

Haemorrhagic stroke mild proportion for VKA suitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (same distribution as observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	35.0%	Dirichlet	60.00	61.97		(58)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	65.47		(58)
Rivaroxaban	49.0%	Dirichlet	77.00	78.88		(63)
Haemorrhagic stroke moderate proportion for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Dabigatran (110mg)	28.0%	Dirichlet	48.00	36.69		(58)
Dabigatran (150mg)	22.0%	Dirichlet	41.00	37.69		(58)
Rivaroxaban	18.0%	Dirichlet	39.00	32.68		(63)
Haemorrhagic stroke moderate proportion for VKA suitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (same distribution as observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	28.0%	Dirichlet	48.00	43.34		(58)
Dabigatran (150mg)	22.0%	Dirichlet	41.00	43.66		(58)
Rivaroxaban	18.0%	Dirichlet	39.00	53.02		(63)
Haemorrhagic stroke severe proportion for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Dabigatran (110mg)	10.0%	Dirichlet	17.00	23.34		(58)
Dabigatran (150mg)	8.0%	Dirichlet	15.00	12.09		(58)
Rivaroxaban	6.0%	Dirichlet	14.00	17.47		(63)
Haemorrhagic stroke severe proportion for VKA suitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (same distribution as observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data

Dabigatran (110mg)	10.0%	Dirichlet	17.00	15.45		(58)
Dabigatran (150mg)	8.0%	Dirichlet	15.00	10.25		(58)
Rivaroxaban	6.0%	Dirichlet	14.00	17.04		(63)
Haemorrhagic stroke Case fatality rate for VKA unsuitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Dabigatran (110mg)	27.0%	Dirichlet	46.00	46.78		(58)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	75.69		(58)
Rivaroxaban	27.0%	Dirichlet	48.00	34.19		(63)
Haemorrhagic stroke case fatality rate for VKA suitable						
Apixaban	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Aspirin	[redacted]	Dirichlet	[redacted]	[redacted]		Assumption (same distribution as observed in AVERROES)
Aspirin (2nd line)	[redacted]	Dirichlet	[redacted]	[redacted]		
Warfarin	[redacted]	Dirichlet	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
Dabigatran (110mg)	27.0%	Dirichlet	46.00	36.05		(58)
Dabigatran (150mg)	35.0%	Dirichlet	65.00	64.48		(58)
Rivaroxaban	27.0%	Dirichlet	48.00	54.22		(63)
Recurrent stroke annual rate VKA unsuitable	0.030	Gamma	0.0060	25.00	0.00	(109)
Recurrent stroke annual rate VKA suitable	0.030	Gamma	0.0060	25.00	0.00	(109)
Other major bleeding risk for VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other major bleeding risk for VKA suitable						
Apixaban	1.8	Gamma	0.4	16.0	0.1	(2)
Warfarin	2.3	Gamma	0.6	16.0	0.1	
Hazard ratio for other major bleed for VKA unsuitable						
Aspirin (1st line)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 2
Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for other major bleed for VKA suitable						
Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		NMA 1
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		

Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard Ratio for Other Major Bleed by cTTR apixaban						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for other major bleed by cTTR warfarin						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
Other major bleed type distribution for VKA unsuitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	(68)
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (110mg)	41.0%	Beta	322.0	132.0	190.0	(58)
Dabigatran (150mg)	49.0%	Beta	375.0	183.8	191.3	(58)
Rivaroxaban	45.0%	Beta	395.0	177.8	217.3	(63)
Other major bleed type distribution for VKA suitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	(67)
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Assumption (same distribution as observed in AVERROES)
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE
Dabigatran (110mg)	41.0%	Beta	322.0	132.0	190.0	(58)
Dabigatran (150mg)	49.0%	Beta	375.0	183.8	191.3	(58)
Rivaroxaban	45.0%	Beta	395.0	177.8	217.3	(63)
CRNM bleeding risk for VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CRNM bleeding risk for VKA suitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data
Warfarin	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Aspirin (1st line)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 2
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Hazard ratio for CRNM bleed by cTTR apixaban						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		

Hazard ratio for CRNM bleed by cTTR warfarin						
cTTR < 58%	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of ARISTOTLE data
65.7% ≤ cTTR < 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
cTTR ≥ 72.2%	[redacted]	Lognormal	[redacted]	[redacted]		
ICH risk adjustment factor						
VKA Unsuitable	2.0	Gamma	0.5	16.0	0.1	(111)
VKA Suitable	2.0	Gamma	0.5	16.0	0.1	
Other major bleed risk adjustment factor						
VKA Unsuitable	2.0	Gamma	0.5	16.0	0.1	(111)
VKA Suitable	2.0	Gamma	0.5	16.0	0.1	
CRNM bleed risk adjustment factor						
VKA Unsuitable	2.0	Gamma	0.5	16.0	0.1	(111)
VKA Suitable	2.0	Gamma	0.5	16.0	0.1	
Other ICH case fatality for VKA unsuitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES and ARISTOTLE data
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (110mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Assumption, Secondary analysis of AVERROES and ARISTOTLE data
Dabigatran (150mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Rivaroxaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Other major bleed case fatality for VKA unsuitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES and ARISTOTLE data
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (110mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Assumption, Secondary analysis of AVERROES and ARISTOTLE data
Dabigatran (150mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Rivaroxaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Other ICH case fatality for VKA suitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES and ARISTOTLE data
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Assumption, Secondary analysis of AVERROES and ARISTOTLE data
Dabigatran (110mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (150mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Rivaroxaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Other major bleed case fatality for VKA suitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES and ARISTOTLE data
Aspirin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	

Dabigatran (110mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	Assumption, Secondary analysis of AVERROES and ARISTOTLE data
Dabigatran (150mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Rivaroxaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Other ICH treatment interruption proportion for VKA unsuitable						
Apixaban	44.0%	Beta	52.3	23.0	29.3	(114)
Dabigatran (110mg)	44.0%	Beta	52.3	23.0	29.3	
Dabigatran (150mg)	44.0%	Beta	52.3	23.0	29.3	
Rivaroxaban	44.0%	Beta	52.3	23.0	29.3	
Other ICH treatment interruption proportion for VKA suitable						
Apixaban	44.0%	Beta	52.3	23.0	29.3	(114)
Warfarin	44.0%	Beta	52.3	23.0	29.3	
Dabigatran (110mg)	44.0%	Beta	52.3	23.0	29.3	
Dabigatran (150mg)	44.0%	Beta	52.3	23.0	29.3	
Rivaroxaban	44.0%	Beta	52.3	23.0	29.3	
GI bleed no treatment change proportion for VKA unsuitable						
Apixaban	75.0%	Beta	0.2	3.3	1.1	(113)
Dabigatran (110mg)	75.0%	Beta	0.2	3.3	1.1	
Dabigatran (150mg)	75.0%	Beta	0.2	3.3	1.1	
Rivaroxaban	75.0%	Beta	0.2	3.3	1.1	
GI bleed no treatment change proportion for VKA suitable						
Apixaban	75.0%	Beta	0.2	3.3	1.1	(113)
Warfarin	75.0%	Beta	0.2	3.3	1.1	
Dabigatran (110mg)	75.0%	Beta	0.2	3.3	1.1	
Dabigatran (150mg)	75.0%	Beta	0.2	3.3	1.1	
Rivaroxaban	75.0%	Beta	0.2	3.3	1.1	
Non GI bleed no treatment change proportion for VKA unsuitable						
Apixaban	75.0%	Beta	0.2	3.3	1.1	(113)
Dabigatran (110mg)	75.0%	Beta	0.2	3.3	1.1	
Dabigatran (150mg)	75.0%	Beta	0.2	3.3	1.1	
Rivaroxaban	75.0%	Beta	0.2	3.3	1.1	
Non GI bleed no treatment change proportion for VKA suitable						
Apixaban	75.0%	Beta	0.2	3.3	1.1	(113)
Warfarin	75.0%	Beta	0.2	3.3	1.1	
Dabigatran (110mg)	75.0%	Beta	0.2	3.3	1.1	
Dabigatran (150mg)	75.0%	Beta	0.2	3.3	1.1	
Rivaroxaban	75.0%	Beta	0.2	3.3	1.1	
Other events						
MI risk for VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	(68)
Aspirin (1st line)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
MI bleeding risk for VKA suitable						

Apixaban	0.5	Gamma	0.1	16.0	0.0	(2)
Warfarin	0.6	Gamma	0.2	16.0	0.0	
MI HR for VKA unsuitable						
Aspirin (1st line)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 2
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
MI HR for VKA suitable						
Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		NMA 1
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
MI case fatality rate VKA unsuitable						
Males	0.1	Beta	0.0	14.2	117.0	(117)
Females	0.2	Beta	0.0	13.3	72.2	
MI case fatality rate VKA suitable						
Males	0.1	Beta	0.0	14.2	117.0	(117)
Females	0.2	Beta	0.0	13.3	72.2	
MI risk adjustment factor						
VKA Unsuitable	1.3	Gamma	0.3	16.0	0.1	(112)
VKA Suitable	1.3	Gamma	0.3	16.0	0.1	
Other CV hospitalisation risk for VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other CV hospitalisation risk for VKA suitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Warfarin	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other CV hospitalisation HR for VKA unsuitable						
Aspirin (1st line)	[redacted]	Lognormal	[redacted]	[redacted]		Secondary analysis of AVERROES data
Other treatment discontinuation rate for VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Aspirin (1st line)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other treatment discontinuation rate for VKA suitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data
Warfarin	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other treatment discontinuation rate for VKA unsuitable						
Aspirin (1st line)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 2
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		

Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Systemic embolism risk for VKA unsuitable						
Apixaban	0.1	Gamma	0.0	16.0	0.0	(3)
Aspirin (1st line)	0.4	Gamma	0.1	16.0	0.0	
Systemic embolism risk for VKA suitable						
Apixaban	0.1	Gamma	0.0	16.0	0.0	(2)
Warfarin	0.1	Gamma	0.0	16.0	0.0	
Systemic embolism hazard ratio for VKA unsuitable						
Aspirin (1st line)	[redacted]	Lognormal	[redacted]	[redacted]		NMA 2
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Warfarin	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (110mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Dabigatran (150mg)	[redacted]	Lognormal	[redacted]	[redacted]		
Rivaroxaban	[redacted]	Lognormal	[redacted]	[redacted]		
Systemic embolism case fatality rate VKA unsuitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	(67)
Aspirin (1st line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (110mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (150mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Rivaroxaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
No Treatment	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Systemic embolism case fatality rate VKA suitable						
Apixaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	(67)
Aspirin (1st line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Aspirin (2nd line)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Warfarin	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (110mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Dabigatran (150mg)	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Rivaroxaban	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
No Treatment	[redacted]	Beta	[redacted]	[redacted]	[redacted]	
Subsequent treatment						
Event risk aspirin (2nd line)						
Stroke (excluding haemorrhagic stroke)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVERROES data

ICH	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other major bleeds	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
CRNM bleeds	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
MI	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other CV hospitalisation	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
SE	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Assumption (68)
AF baseline death HR	[redacted]	Uniform		[redacted]	[redacted]	
Other death risk trial period VKA unsuitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of AVEREROES data
Aspirin (1st line)	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Other death risk trial period VKA suitable						
Apixaban	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	Secondary analysis of ARISTOTLE data
Warfarin	[redacted]	Gamma	[redacted]	[redacted]	[redacted]	
Stroke death HR mild	3.2	Gamma	0.8	16.0	0.2	(120)
Stroke death HR moderate	5.8	Gamma	1.5	16.0	0.4	
Stroke death HR severe	15.8	Gamma	3.9	16.0	1.0	
Haemorrhagic stroke death HR mild	3.2	Gamma	0.8	16.0	0.2	
Haemorrhagic stroke death HR moderate	5.8	Gamma	1.5	16.0	0.4	
Haemorrhagic stroke death HR severe	15.8	Gamma	3.9	16.0	1.0	
MI death HR males	2.6	Gamma	0.6	16.0	0.2	
MI death HR females	4.2	Gamma	1.0	16.0	0.3	
SE death HR	1.3	Gamma	0.3	16.0	0.1	
Dyspepsia management monthly cost/ Anticoagulant Management Monthly Cost						
Apixaban	0.04	Gamma	0.01	16.0	0.00	Assumption (58, 67, 68); National Schedule of Reference Costs Year : '2009-10' - NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data, National Schedule of Reference Costs Year : '2009-10' - NHS Trusts and PCTs combined Consultant Led, Electronic Drug Tariff, November 2011, Department of Health by the NHS Business Services Authority, NHS Prescription
Aspirin (1st line)	0.04	Gamma	0.01	16.0	0.00	
Aspirin (2nd line)	0.04	Gamma	0.01	16.0	0.00	
Warfarin	0.04	Gamma	0.01	16.0	0.00	
Dabigatran (110mg)	0.13	Gamma	0.03	16.0	0.01	
Dabigatran (150mg)	0.13	Gamma	0.03	16.0	0.01	

Rivaroxaban	0.04	Gamma	0.01	16.0	0.00	Services , http://www.ppa.org.uk/ppa/edt_intro.htm
Mild ischaemic stroke acute care (per episode)	£3,515.64	Gamma	1030.7	11.6	302.2	(157)
Mild ischaemic stroke maintenance care (per month)	£ 183.91	Gamma	39.0	22.3	8.3	
Moderate ischaemic stroke acute care (per episode)	£18,341.08	Gamma	2533.7	52.4	350.0	
Moderate ischaemic stroke maintenance care (per month)	£ 358.78	Gamma	86.7	17.1	21.0	
Severe ischaemic stroke acute care (per episode)	£25,050.88	Gamma	4079.6	37.7	664.4	
Severe ischaemic stroke maintenance care (per month)	£ 544.76	Gamma	370.5	2.2	251.9	
Fatal ischaemic stroke cost (per episode)	£3,162.11	Gamma	569.3	30.9	102.5	
Mild haemorrhagic stroke acute care (per episode)	£10,236.81	Gamma	2084.9	24.1	424.6	
Mild haemorrhagic stroke maintenance care (per month)	£ 183.91	Gamma	39.0	22.3	8.3	
Moderate haemorrhagic stroke acute care (per episode)	£26,299.60	Gamma	5750.3	20.9	1257.3	
Moderate haemorrhagic stroke maintanence care (per month)	£ 358.78	Gamma	86.7	17.1	21.0	
Severe haemorrhagic stroke acute care (per episode)	£44,486.65	Gamma	11121.7	16.0	2780.4	
Severe haemorrhagic stroke maintanence care (per month)	£ 544.76	Gamma	370.5	2.2	251.9	
Fatal haemorrhagic stroke cost (per episode)	£1,645.66	Gamma	689.3	5.7	288.7	
Systemic embolism acute care cost (per episode)	£4,077.98	Gamma	961.7	18.0	226.8	

Systemic embolism acute care cost (per month)	£183.91	Gamma	39.0	22.3	8.3	
Other ICH (excluding haemorrhagic stroke)	£3,010.00	Lognormal	0.0	8.0		National Schedule of Reference Costs Year : '2009-10' - NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data
Other major bleed GI (excluding ICH)	£1,493.68	Lognormal	0.0	7.3		
Other major bleed non-GI (excluding ICH)	£3,947.92	Lognormal	0.0	8.3		
CRNM bleed	£1,133.93	Lognormal	0.0	7.0		
MI acute care (per episode)	£2,018.84	Gamma	504.7	16.0	126.2	
MI maintanence care (per month)	£ 6.65	Gamma	1.7	16.0	0.4	Electronic Drug Tariff, November 2011, Department of Health by the NHS Business Services Authority, NHS Prescription Services , http://www.ppa.org.uk/ppa/edt_intro.htm
Other CV hospitalisation	£1,570.89	Lognormal	0.0	7.4		National Schedule of Reference Costs Year : '2009-10' - NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data
Utility Value						
AF baseline	0.8	Beta	0.0427	72.7	20.5	(112)
Mild ischaemic stroke	0.8	Beta	0.0299	154.3	48.7	(149)
Moderate ischaemic stroke	0.4	Beta	0.0299	103.4	161.7	
Severe ischaemic stroke	0.1	Beta	0.0299	11.9	96.6	
Mild haemorrhagic stroke	0.8	Beta	0.0299	154.3	48.7	
Moderate haemorrhagic stroke	0.4	Beta	0.0299	103.4	161.7	
Severe haemorrhagic stroke	0.1	Beta	0.0299	11.9	96.6	
Systemic embolism	0.7	Beta	0.0191	406.1	191.5	(145)
Utility decrement						
Other ICH	0.107	Beta	0.040	6.2	52.1	(152)
Other major Bleed	0.107	Beta	0.040	6.2	52.1	
CRNM bleed	0.1	Beta	0.017	10.6	170.9	(145)
MI	0.7	Beta	0.019	397.4	184.5	(153)
Other CV	0.1	Beta	0.026	12.5	116.8	

hospitalisation						
Apixaban	0.002	Beta	0.00102	3.8	1912.1	(149) Lower 95% CI (0) and upper 95% CI (2* mean) estimated
Dabigatran	0.002	Beta	0.00102	3.8	1912.1	(149) Lower 95% CI (0) and upper 95% CI (2* mean) estimated
Rivaroxaban	0.002	Beta	0.00102	3.8	1912.1	(149) Lower 95% CI (0) and upper 95% CI (2* mean) estimated
Aspirin	0.002	Beta	0.00102	3.8	1912.1	(149) Lower 95% CI (0) and upper 95% CI (2* mean) estimated
Warfarin	0.013	Beta	0.00663	3.8	286.9	(149) Lower 95% CI (0) and upper 95% CI (2* mean) estimated

10.20 Appendix 20: Markov traces

Markov traces showing proportions of the model cohort in each state are presented in tables below.

Table 132: Markov trace, apixaban, VKA suitable

Month	NVAF	Ischaemic stroke	Haemorrhagic stroke	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	97.9%	0.1%	0.0%	0.0%	0.1%	1.6%	0.4%
2.76	95.7%	0.2%	0.0%	0.0%	0.1%	3.1%	0.8%
4.14	93.7%	0.3%	0.1%	0.0%	0.2%	4.6%	1.2%
5.52	91.7%	0.4%	0.1%	0.0%	0.2%	6.0%	1.6%
6.90	89.7%	0.5%	0.1%	0.0%	0.3%	7.4%	2.0%
8.28	87.8%	0.6%	0.1%	0.1%	0.3%	8.8%	2.4%
9.66	85.9%	0.7%	0.1%	0.1%	0.4%	10.1%	2.8%
11.04	84.0%	0.8%	0.2%	0.1%	0.4%	11.3%	3.2%
12.42	82.2%	0.9%	0.2%	0.1%	0.5%	12.6%	3.6%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 133: Markov trace, warfarin, VKA suitable

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	97.3%	0.1%	0.0%	0.0%	0.1%	2.0%	0.4%
2.76	94.7%	0.3%	0.0%	0.0%	0.2%	4.0%	0.8%

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
4.14	92.2%	0.4%	0.0%	0.0%	0.2%	5.9%	1.2%
5.52	89.8%	0.5%	0.1%	0.0%	0.3%	7.7%	1.6%
6.90	87.4%	0.7%	0.1%	0.0%	0.4%	9.5%	2.0%
8.28	85.0%	0.8%	0.1%	0.0%	0.5%	11.2%	2.4%
9.66	82.8%	0.9%	0.1%	0.0%	0.5%	12.8%	2.8%
11.04	80.6%	1.1%	0.1%	0.0%	0.6%	14.4%	3.2%
12.42	78.4%	1.2%	0.1%	0.0%	0.7%	15.9%	3.6%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 134: Markov trace, dabigatran 110mg & 150mg, VKA suitable

Month	NVAF	Ischaemic stroke	Haemorrhagic stroke	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	97.3%	0.1%	0.0%	0.0%	0.1%	2.0%	0.4%
2.76	94.7%	0.3%	0.0%	0.0%	0.2%	4.0%	0.8%
4.14	92.2%	0.4%	0.0%	0.0%	0.2%	5.9%	1.2%
5.52	89.8%	0.5%	0.1%	0.0%	0.3%	7.7%	1.6%
6.90	87.4%	0.7%	0.1%	0.0%	0.4%	9.5%	2.0%
8.28	85.0%	0.8%	0.1%	0.0%	0.5%	11.2%	2.4%
9.66	82.8%	0.9%	0.1%	0.0%	0.5%	12.8%	2.8%
11.04	80.6%	1.1%	0.1%	0.0%	0.6%	14.4%	3.2%
12.42	78.4%	1.2%	0.1%	0.0%	0.7%	15.9%	3.6%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 135: Markov trace, dabigatran 110mg, VKA suitable

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	97.3%	0.1%	0.0%	0.0%	0.1%	2.0%	0.4%
2.76	94.7%	0.3%	0.0%	0.0%	0.2%	4.0%	0.8%
4.14	92.2%	0.4%	0.0%	0.0%	0.2%	5.9%	1.2%
5.52	89.8%	0.5%	0.1%	0.0%	0.3%	7.7%	1.6%
6.90	87.4%	0.7%	0.1%	0.0%	0.4%	9.5%	2.0%
8.28	85.0%	0.8%	0.1%	0.0%	0.5%	11.2%	2.4%
9.66	82.8%	0.9%	0.1%	0.0%	0.5%	12.8%	2.8%
11.04	80.6%	1.1%	0.1%	0.0%	0.6%	14.4%	3.2%
12.42	78.4%	1.2%	0.1%	0.0%	0.7%	15.9%	3.6%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 136: Markov trace, rivaroxaban, VKA suitable

Month	NVAF	Ischaemic stroke	Haemorrhagic stroke	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	97.3%	0.1%	0.0%	0.0%	0.1%	2.0%	0.4%
2.76	94.7%	0.3%	0.0%	0.0%	0.2%	4.0%	0.8%
4.14	92.2%	0.4%	0.0%	0.0%	0.2%	5.9%	1.2%
5.52	89.8%	0.5%	0.1%	0.0%	0.3%	7.7%	1.6%
6.90	87.4%	0.7%	0.1%	0.0%	0.4%	9.5%	2.0%
8.28	85.0%	0.8%	0.1%	0.0%	0.5%	11.2%	2.4%
9.66	82.8%	0.9%	0.1%	0.0%	0.5%	12.8%	2.8%
11.04	80.6%	1.1%	0.1%	0.0%	0.6%	14.4%	3.2%
12.42	78.4%	1.2%	0.1%	0.0%	0.7%	15.9%	3.6%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 137: Markov trace, apixaban, VKA unsuitable

Month	NVAF	Ischaemic stroke	Haemorrhagic stroke	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	97.3%	0.1%	0.0%	0.0%	0.1%	2.0%	0.4%
2.76	94.7%	0.3%	0.0%	0.0%	0.2%	4.0%	0.8%
4.14	92.2%	0.4%	0.0%	0.0%	0.2%	5.9%	1.2%
5.52	89.8%	0.5%	0.1%	0.0%	0.3%	7.7%	1.6%
6.90	87.4%	0.7%	0.1%	0.0%	0.4%	9.5%	2.0%
8.28	85.0%	0.8%	0.1%	0.0%	0.5%	11.2%	2.4%
9.66	82.8%	0.9%	0.1%	0.0%	0.5%	12.8%	2.8%
11.04	80.6%	1.1%	0.1%	0.0%	0.6%	14.4%	3.2%
12.42	78.4%	1.2%	0.1%	0.0%	0.7%	15.9%	3.6%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 138: Markov trace, aspirin, VKA unsuitable

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	96.6%	0.4%	0.0%	0.0%	0.1%	2.4%	0.5%
2.76	93.3%	0.8%	0.0%	0.1%	0.2%	4.7%	1.0%

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
4.14	90.2%	1.1%	0.0%	0.1%	0.3%	6.9%	1.5%
5.52	87.1%	1.5%	0.1%	0.1%	0.3%	8.9%	2.0%
6.90	84.1%	1.8%	0.1%	0.1%	0.4%	10.9%	2.5%
8.28	81.3%	2.2%	0.1%	0.2%	0.5%	12.8%	3.0%
9.66	78.5%	2.5%	0.1%	0.2%	0.6%	14.6%	3.5%
11.04	75.8%	2.8%	0.1%	0.2%	0.7%	16.4%	4.0%
12.42	73.3%	3.2%	0.1%	0.2%	0.7%	18.0%	4.5%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant.

Table 139: Markov trace, dabigatran 110mg & 150mg, VKA unsuitable

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	96.3%	0.1%	0.0%	0.0%	0.1%	3.0%	0.4%
2.76	92.8%	0.2%	0.0%	0.0%	0.2%	6.0%	0.8%
4.14	89.4%	0.3%	0.0%	0.0%	0.4%	8.7%	1.2%
5.52	86.1%	0.4%	0.0%	0.0%	0.5%	11.4%	1.7%
6.90	82.9%	0.5%	0.1%	0.0%	0.6%	13.9%	2.1%
8.28	79.8%	0.6%	0.1%	0.0%	0.7%	16.3%	2.5%
9.66	76.9%	0.7%	0.1%	0.0%	0.8%	18.6%	2.9%
11.04	74.0%	0.8%	0.1%	0.0%	0.9%	20.8%	3.3%
12.42	71.3%	0.9%	0.1%	0.0%	1.0%	22.8%	3.7%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 140: Markov trace, dabigatran 110mg, VKA unsuitable

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	96.4%	0.1%	0.0%	0.0%	0.1%	2.9%	0.4%
2.76	92.9%	0.3%	0.0%	0.0%	0.2%	5.7%	0.8%
4.14	89.5%	0.4%	0.0%	0.0%	0.4%	8.4%	1.3%
5.52	86.3%	0.6%	0.1%	0.0%	0.5%	11.0%	1.7%
6.90	83.1%	0.7%	0.1%	0.0%	0.6%	13.4%	2.1%
8.28	80.1%	0.9%	0.1%	0.0%	0.7%	15.7%	2.5%
9.66	77.2%	1.0%	0.1%	0.0%	0.8%	17.9%	2.9%
11.04	74.4%	1.2%	0.1%	0.0%	0.9%	20.0%	3.4%
12.42	71.7%	1.3%	0.2%	0.0%	1.0%	22.0%	3.8%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Table 141: Markov trace, rivaroxaban, VKA unsuitable

Month	NVAF	Ischaemic stroke	Haemorrhagic	Systemic embolism	MI	NVAF W/O original AC	Death
0.00	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1.38	96.9%	0.1%	0.0%	0.0%	0.1%	2.4%	0.4%
2.76	94.0%	0.2%	0.1%	0.0%	0.2%	4.7%	0.8%
4.14	91.1%	0.4%	0.1%	0.0%	0.2%	7.0%	1.2%
5.52	88.3%	0.5%	0.1%	0.0%	0.3%	9.1%	1.7%
6.90	85.6%	0.6%	0.1%	0.0%	0.4%	11.2%	2.1%
8.28	82.9%	0.8%	0.2%	0.0%	0.5%	13.1%	2.5%
9.66	80.4%	0.9%	0.2%	0.0%	0.6%	15.0%	2.9%
11.04	77.9%	1.0%	0.2%	0.0%	0.6%	16.8%	3.3%
12.42	75.5%	1.2%	0.3%	0.0%	0.7%	18.6%	3.7%

Abbreviations: NVAF, non-valvular atrial fibrillation; MI, myocardial infarction; W/O, without; AC, anticoagulant

Markov traces showing QALYs accrued over time are presented in the tables below.

Table 142: Markov trace, apixaban, VKA suitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13292	0.00016	0.00003	0.00002	0.00000	-0.00001	0.00000	0.00004	-0.00003	0.13312
2.76	0.08793	0.00019	0.00003	0.00002	0.00000	-0.00001	0.00000	0.00008	-0.00002	0.08822
4.14	0.08741	0.00026	0.00004	0.00003	0.00000	-0.00001	0.00000	0.00012	-0.00002	0.08783
5.52	0.08689	0.00032	0.00005	0.00004	0.00000	-0.00001	0.00000	0.00017	-0.00002	0.08744
6.90	0.08637	0.00039	0.00006	0.00005	0.00000	-0.00001	0.00000	0.00021	-0.00002	0.08704
8.28	0.08584	0.00046	0.00007	0.00006	0.00000	-0.00001	0.00000	0.00025	-0.00002	0.08665
9.66	0.08531	0.00053	0.00008	0.00007	0.00000	-0.00001	0.00000	0.00029	-0.00002	0.08625
11.04	0.08478	0.00060	0.00009	0.00008	0.00000	-0.00001	0.00000	0.00034	-0.00002	0.08585
12.42	0.08140	0.00065	0.00009	0.00008	0.00000	-0.00001	0.00000	0.00037	-0.00002	0.08256

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 143: Markov trace, warfarin, VKA suitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13092	0.00016	0.00004	0.00002	0.00000	-0.00001	0.00000	0.00005	-0.00003	0.13113
2.76	0.08654	0.00019	0.00004	0.00002	0.00000	-0.00001	0.00000	0.00009	-0.00002	0.08686
4.14	0.08599	0.00026	0.00006	0.00003	0.00000	-0.00001	0.00000	0.00014	-0.00002	0.08644
5.52	0.08543	0.00032	0.00007	0.00004	0.00000	-0.00001	0.00000	0.00019	-0.00002	0.08602

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
6.90	0.08487	0.00039	0.00009	0.00005	0.00000	-0.00001	0.00000	0.00024	-0.00002	0.08560
8.28	0.08430	0.00046	0.00010	0.00006	0.00000	-0.00001	0.00000	0.00029	-0.00002	0.08518
9.66	0.08374	0.00053	0.00011	0.00007	0.00000	-0.00001	0.00000	0.00033	-0.00002	0.08475
11.04	0.08317	0.00060	0.00012	0.00008	0.00000	-0.00001	0.00000	0.00038	-0.00002	0.08432
12.42	0.07981	0.00065	0.00013	0.00009	0.00000	-0.00001	0.00000	0.00041	-0.00002	0.08106

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 144: Markov trace, dabigatran 110mg & 150mg, VKA suitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13291	0.00009	0.00002	0.00001	0.00000	-0.00002	0.00000	0.00007	-0.00003	0.13305
2.76	0.08792	0.00012	0.00002	0.00002	0.00000	-0.00001	0.00000	0.00013	-0.00002	0.08817
4.14	0.08739	0.00016	0.00002	0.00002	0.00000	-0.00001	0.00000	0.00020	-0.00002	0.08777
5.52	0.08686	0.00021	0.00003	0.00003	0.00000	-0.00001	0.00000	0.00027	-0.00002	0.08736
6.90	0.08633	0.00026	0.00004	0.00004	0.00000	-0.00001	0.00000	0.00033	-0.00002	0.08696
8.28	0.08579	0.00031	0.00004	0.00005	0.00000	-0.00001	0.00000	0.00040	-0.00002	0.08655
9.66	0.08524	0.00037	0.00005	0.00006	0.00000	-0.00001	0.00000	0.00046	-0.00002	0.08614
11.04	0.08470	0.00042	0.00005	0.00007	0.00000	-0.00001	0.00000	0.00053	-0.00002	0.08573
12.42	0.08130	0.00047	0.00006	0.00007	0.00000	-0.00001	0.00000	0.00057	-0.00002	0.08244

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 145: Markov trace, dabigatran 110 mg, VKA suitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13282	0.00014	0.00002	0.00001	0.00000	-0.00001	0.00000	0.00006	-0.00003	0.13302
2.76	0.08781	0.00018	0.00002	0.00002	0.00000	-0.00001	0.00000	0.00013	-0.00002	0.08813
4.14	0.08725	0.00024	0.00003	0.00003	0.00000	-0.00001	0.00000	0.00019	-0.00002	0.08771
5.52	0.08669	0.00031	0.00004	0.00003	0.00000	-0.00001	0.00000	0.00026	-0.00002	0.08730
6.90	0.08613	0.00037	0.00005	0.00004	0.00000	-0.00001	0.00000	0.00032	-0.00002	0.08688
8.28	0.08556	0.00044	0.00005	0.00005	0.00000	-0.00001	0.00000	0.00039	-0.00002	0.08646
9.66	0.08499	0.00051	0.00006	0.00006	0.00000	-0.00001	0.00000	0.00045	-0.00002	0.08604
11.04	0.08442	0.00058	0.00007	0.00007	0.00000	-0.00001	0.00000	0.00051	-0.00002	0.08562
12.42	0.08101	0.00063	0.00007	0.00008	0.00000	-0.00001	0.00000	0.00055	-0.00002	0.08231

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 146: Markov trace, rivaroxaban, VKA suitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13288	0.00015	0.00005	0.00002	0.00000	-0.00002	0.00000	0.00004	-0.00003	0.13308
2.76	0.08788	0.00018	0.00006	0.00002	0.00000	-0.00001	0.00000	0.00009	-0.00002	0.08819
4.14	0.08734	0.00024	0.00007	0.00003	0.00000	-0.00001	0.00000	0.00013	-0.00002	0.08778
5.52	0.08681	0.00031	0.00009	0.00003	0.00000	-0.00001	0.00000	0.00018	-0.00002	0.08738
6.90	0.08627	0.00037	0.00011	0.00004	0.00000	-0.00001	0.00000	0.00022	-0.00002	0.08698

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
8.28	0.08572	0.00044	0.00013	0.00005	0.00000	-0.00001	0.00000	0.00027	-0.00002	0.08657
9.66	0.08518	0.00051	0.00014	0.00006	0.00000	-0.00001	0.00000	0.00031	-0.00002	0.08616
11.04	0.08463	0.00058	0.00016	0.00007	0.00000	-0.00001	0.00000	0.00036	-0.00002	0.08575
12.42	0.08124	0.00063	0.00017	0.00008	0.00000	-0.00001	0.00000	0.00039	-0.00002	0.08246

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 147: Markov trace, apixaban, VKA unsuitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13281	0.00019	0.00001	0.00001	0.00000	-0.00001	0.00000	0.00006	-0.00003	0.13304
2.76	0.08779	0.00024	0.00001	0.00002	0.00000	0.00000	0.00000	0.00012	-0.00002	0.08815
4.14	0.08723	0.00032	0.00002	0.00002	0.00000	0.00000	0.00000	0.00018	-0.00002	0.08773
5.52	0.08666	0.00040	0.00002	0.00003	0.00000	0.00000	0.00000	0.00024	-0.00002	0.08732
6.90	0.08610	0.00048	0.00002	0.00004	0.00000	0.00000	0.00000	0.00029	-0.00002	0.08690
8.28	0.08553	0.00056	0.00003	0.00004	0.00000	0.00000	0.00000	0.00035	-0.00002	0.08649
9.66	0.08496	0.00065	0.00003	0.00005	0.00000	0.00000	0.00000	0.00041	-0.00002	0.08607
11.04	0.08438	0.00073	0.00003	0.00006	0.00000	0.00000	0.00000	0.00047	-0.00002	0.08565
12.42	0.08098	0.00079	0.00004	0.00007	0.00000	0.00000	0.00000	0.00051	-0.00002	0.08235

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 148: Markov trace, aspirin, VKA unsuitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13196	0.00053	0.00001	0.00006	0.00000	0.00000	0.00000	0.00007	-0.00003	0.13258
2.76	0.08679	0.00063	0.00001	0.00007	0.00000	0.00000	0.00000	0.00013	-0.00002	0.08760
4.14	0.08592	0.00083	0.00002	0.00009	0.00000	0.00000	0.00000	0.00020	-0.00002	0.08702
5.52	0.08505	0.00102	0.00002	0.00011	0.00000	0.00000	0.00000	0.00026	-0.00002	0.08644
6.90	0.08419	0.00121	0.00002	0.00013	0.00000	0.00000	0.00000	0.00033	-0.00002	0.08586
8.28	0.08333	0.00140	0.00003	0.00016	0.00000	0.00000	0.00000	0.00039	-0.00002	0.08528
9.66	0.08249	0.00158	0.00003	0.00018	0.00000	0.00000	0.00000	0.00045	-0.00002	0.08471
11.04	0.08165	0.00176	0.00003	0.00020	0.00000	0.00000	0.00000	0.00052	-0.00002	0.08413
12.42	0.07808	0.00187	0.00004	0.00021	0.00000	0.00000	0.00000	0.00056	-0.00002	0.08074

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 149: Markov trace, dabigatran 110 mg & 150 mg, VKA unsuitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13277	0.00013	0.00002	0.00001	0.00000	-0.00001	0.00000	0.00009	-0.00003	0.13298
2.76	0.08775	0.00016	0.00002	0.00001	0.00000	-0.00001	0.00000	0.00019	-0.00002	0.08811
4.14	0.08717	0.00023	0.00003	0.00002	0.00000	-0.00001	0.00000	0.00028	-0.00002	0.08769
5.52	0.08658	0.00029	0.00003	0.00002	0.00000	-0.00001	0.00000	0.00037	-0.00002	0.08727

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
6.90	0.08600	0.00036	0.00004	0.00003	0.00000	-0.00001	0.00000	0.00046	-0.00002	0.08686
8.28	0.08540	0.00043	0.00004	0.00004	0.00000	-0.00001	0.00000	0.00055	-0.00002	0.08644
9.66	0.08481	0.00050	0.00005	0.00005	0.00000	-0.00001	0.00000	0.00064	-0.00002	0.08601
11.04	0.08421	0.00057	0.00005	0.00006	0.00000	-0.00001	0.00000	0.00072	-0.00002	0.08559
12.42	0.08078	0.00063	0.00006	0.00006	0.00000	-0.00001	0.00000	0.00078	-0.00002	0.08228

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 150: Markov trace, dabigatran 110 mg, VKA unsuitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13264	0.00021	0.00002	0.00001	0.00000	-0.00001	0.00000	0.00009	-0.00003	0.13293
2.76	0.08760	0.00025	0.00002	0.00001	0.00000	-0.00001	0.00000	0.00018	-0.00002	0.08805
4.14	0.08697	0.00034	0.00003	0.00002	0.00000	-0.00001	0.00000	0.00027	-0.00002	0.08761
5.52	0.08634	0.00043	0.00004	0.00003	0.00000	-0.00001	0.00000	0.00036	-0.00002	0.08717
6.90	0.08571	0.00052	0.00005	0.00003	0.00000	-0.00001	0.00000	0.00045	-0.00002	0.08674
8.28	0.08508	0.00061	0.00005	0.00004	0.00000	-0.00001	0.00000	0.00054	-0.00002	0.08630
9.66	0.08445	0.00070	0.00006	0.00005	0.00000	-0.00001	0.00000	0.00062	-0.00002	0.08586
11.04	0.08382	0.00080	0.00007	0.00006	0.00000	-0.00001	0.00000	0.00071	-0.00002	0.08542
12.42	0.08037	0.00086	0.00007	0.00007	0.00000	-0.00001	0.00000	0.00076	-0.00002	0.08210

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

Table 151: Markov trace, rivaroxaban, VKA unsuitable discounted QALYs

Months	NVAF	Ischaemic Stroke	Haemorrhagic Stroke	Systemic Embolism	ICH	Major Bleeds	CRNM Bleeds	MI	Other CV hospitalisation	Sum
0.00										
1.38	0.13274	0.00021	0.00005	0.00001	0.00000	-0.00001	0.00000	0.00006	-0.00003	0.13303
2.76	0.08772	0.00026	0.00006	0.00001	0.00000	-0.00001	0.00000	0.00012	-0.00002	0.08814
4.14	0.08713	0.00034	0.00008	0.00002	0.00000	-0.00001	0.00000	0.00019	-0.00002	0.08772
5.52	0.08654	0.00043	0.00009	0.00003	0.00000	-0.00001	0.00000	0.00025	-0.00002	0.08731
6.90	0.08594	0.00052	0.00011	0.00003	0.00000	-0.00001	0.00000	0.00031	-0.00002	0.08689
8.28	0.08535	0.00061	0.00013	0.00004	0.00000	-0.00001	0.00000	0.00037	-0.00002	0.08647
9.66	0.08475	0.00071	0.00014	0.00005	0.00000	-0.00001	0.00000	0.00043	-0.00002	0.08605
11.04	0.08415	0.00080	0.00016	0.00006	0.00000	-0.00001	0.00000	0.00049	-0.00002	0.08563
12.42	0.08073	0.00086	0.00017	0.00006	0.00000	-0.00001	0.00000	0.00053	-0.00002	0.08233

Abbreviations: CRNM, clinically relevant non-major; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation

10.21 Appendix 21: Number of Events (Total Population)

Table 152: Summary of QALY gain by health state in VKA suitable population

Health state	Total QALYs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% Absolute increment			
	Apix	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi		Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
NVAF	5.458	5.282	5.388	5.363	5.317	0.176	0.070	0.095	0.140	0.176	0.070	0.095	0.140	108%	139%	133%	135%
Ischaemic Stroke																	
Mild	0.151	0.143	0.151	0.136	0.146	0.007	0.000	0.015	0.005	0.007	0.000	0.015	0.005	4%	1%	20%	5%
Moderate	0.040	0.045	0.041	0.045	0.049	-0.005	-0.002	-0.005	-0.009	0.005	0.002	0.005	0.009	3%	3%	8%	9%
Severe	0.002	0.002	0.002	0.002	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Recurrent Ischaemic Stroke																	
Mild	0.011	0.010	0.011	0.010	0.010	0.001	0.000	0.001	0.000	0.001	0.000	0.001	0.000	0%	0%	2%	0%
Moderate	0.004	0.004	0.004	0.004	0.005	0.000	0.000	0.000	-0.001	0.000	0.000	0.000	0.001	0%	0%	0%	1%
Severe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Haemorrhagic Stroke																	
Mild	0.010	0.015	0.023	0.007	0.008	-0.005	-0.013	0.003	0.002	0.005	0.013	0.003	0.002	3%	26%	4%	2%
Moderate	0.005	0.005	0.004	0.002	0.003	0.000	0.001	0.003	0.002	0.000	0.001	0.003	0.002	0%	3%	4%	2%
Severe	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Recurrent Haemorrhagic Stroke																	
Mild	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	1%	0%	0%
Moderate	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Severe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%

Health state	Total QALYs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% Absolute increment			
	Apix	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi		Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
Other events																	
SE	0.059	0.061	0.060	0.063	0.063	-0.002	-0.001	-0.004	-0.004	0.002	0.001	0.004	0.004	2%	2%	6%	4%
Other ICH	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Other major bleed	0.000	-0.001	-0.001	-0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
CRNM bleed	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
MI	0.122	0.129	0.127	0.157	0.154	-0.007	-0.005	-0.035	-0.032	0.007	0.005	0.035	0.032	5%	10%	49%	31%
CV hospitalisation	-0.001	-0.001	-0.001	-0.001	-0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
TOTAL QALYs	**5.860**	**5.696**	**5.809**	**5.788**	**5.756**	**0.163**	**0.050**	**0.072**	**0.104**	**0.163**	**0.050**	**0.072**	**0.104**	**100%**	**100%**	**100%**	**100%**

Abbreviations: Apix, apixaban; CRNM, clinically relevant non-major; CV, cardiovascular; Dabi, dabigatran; ICH, intracranial haemorrhage; MI, myocardial infarction QALY, quality-adjusted life year; Riva, rivaroxaban; SE, systemic embolism; Warf, warfarin

Table 153: Summary of QALY gain by health state in VKA unsuitable population

Health state	Total QALYs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% Absolute increment			
	Apix	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi		Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
NVAF	5.253	4.792	5.106	5.165	5.106	0.461	0.147	0.088	0.147	0.461	0.147	0.088	0.147	140%	162%	184%	162%
Ischemic Stroke																	
Mild	0.158	0.223	0.164	0.152	0.164	-0.066	-0.007	0.005	-0.007	0.066	0.007	0.005	0.007	20%	8%	11%	8%
Moderate	0.050	0.081	0.055	0.050	0.055	-0.032	-0.006	0.000	-0.006	0.032	0.006	0.000	0.006	10%	6%	1%	6%
Severe	0.003	0.004	0.003	0.002	0.003	-0.001	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0%	0%	0%	0%
Recurrent Ischemic Stroke																	
Mild	0.009	0.013	0.009	0.008	0.009	-0.004	0.000	0.000	0.000	0.004	0.000	0.000	0.000	1%	0%	1%	0%
Moderate	0.005	0.008	0.006	0.005	0.006	-0.003	0.000	0.000	0.000	0.003	0.000	0.000	0.000	1%	1%	0%	1%
Severe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Haemorrhagic Stroke																	

Health state	Total QALYs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% Absolute increment			
	Apix	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi		Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
Mild	0.003	0.002	0.007	0.006	0.007	0.000	-0.004	-0.003	-0.004	0.000	0.004	0.003	0.004	0%	5%	7%	5%
Moderate	0.003	0.002	0.003	0.002	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	1%	0%
Severe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Recurrent Haemorrhagic Stroke																	
Mild	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Moderate	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Severe	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Other events																	
SE	0.058	0.086	0.063	0.064	0.063	-0.028	-0.005	-0.006	-0.005	0.028	0.005	0.006	0.005	8%	6%	13%	6%
Other ICH	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
Other major bleed	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
CRNM bleed	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
MI	0.144	0.142	0.177	0.181	0.177	0.002	-0.033	-0.037	-0.033	0.002	0.033	0.037	0.033	1%	36%	77%	36%
CV hospitalisation	-0.001	-0.001	-0.001	-0.001	-0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0%	0%	0%	0%
TOTAL QALYs	**5.683**	**5.354**	**5.592**	**5.635**	**5.592**	**0.329**	**0.091**	**0.048**	**0.091**	**0.329**	**0.091**	**0.048**	**0.091**	**100%**	**100%**	**100%**	**100%**

Abbreviations: Apix, apixaban; CRNM, clinically relevant non-major; CV, cardiovascular; Dabi, dabigatran; ICH, intracranial haemorrhage; MI, myocardial infarction QALY, quality-adjusted life year; Riva, rivaroxaban; SE, systemic embolism; Warf, warfarin

Table 154: Number of Events (Total Population) VKA suitable population

Number of Events (Total Population)	Apixaban	Warfarin	Rivaroxaban	Dabigatran 150mg & Dabigatran 110mg	Dabigatran (110mg)
Ischemic Stroke					
Non-fatal Mild	75	72	75	71	73
Non-fatal Moderate	62	68	65	70	74
Non-fatal Severe	24	26	25	27	29
Fatal	24	23	28	29	30

TOTAL	186	188	193	197	205
Recurrent Ischemic Stroke					
Non-fatal Mild	9	9	9	9	10
Non-fatal Moderate	4	4	4	4	4
Non-fatal Severe	1	1	1	1	1
Fatal	3	3	3	3	3
TOTAL	17	17	18	17	18
Hemorrhagic Stroke					
Non-fatal Mild	4	6	9	3	3
Non-fatal Moderate	6	6	5	3	4
Non-fatal Severe	3	5	3	3	3
Fatal	9	18	8	6	6
TOTAL	22	35	25	15	15
Recurrent Hemorrhagic Stroke					
Non-fatal Mild	0	0	0	0	0
Non-fatal Moderate	0	0	0	0	0
Non-fatal Severe	0	0	0	0	0
Fatal	0	0	1	0	0
TOTAL	1	1	2	1	1
Systemic Embolism					
Non-fatal	18	19	18	19	19
Fatal	2	2	2	2	2
TOTAL	20	21	20	21	21
Other ICH					
Non-fatal	9	19	17	13	9
Fatal	1	3	2	2	1

TOTAL	10	21	19	14	11
Other Major Bleeds					
Non-fatal GI Bleeds	53	56	73	65	55
Non-fatal Non ICH or Non GI Related Major Bleeds	86	99	95	80	81
Fatal	3	3	3	3	3
TOTAL	142	158	171	148	138
Clinically Relevant Non-Major Bleeds	241	284	291	232	230
MI					
Non-fatal	61	63	63	74	73
Fatal	9	10	10	11	11
TOTAL	70	73	73	85	84
Other CV Hospitalization	1,009	989	1,007	1,016	1,005
Other Treatment Discontinuation	592	597	626	690	679
Deaths					
Event Related (acute)	49	60	56	54	54
Event related (death due to stroke, HS, MI, SE)	254	264	262	270	277
Other	696	676	682	676	669
TOTAL	1,000	1,000	1,000	1,000	1,000

Table 155: Number of Events (Total Population) VKA unsuitable population

Number of Events (Total Population)	Apixaban	Aspirin	Rivaroxaban	Dabigatran (150mg) & Dabigatran (110mg)	Dabigatran (110mg)

Ischemic Stroke					
Non-fatal Mild	77	99	84	76	80
Non-fatal Moderate	73	105	71	75	80
Non-fatal Severe	30	41	27	29	31
Fatal	28	30	32	31	33
TOTAL	208	276	213	212	223
Recurrent Ischemic Stroke					
Non-fatal Mild	8	11	8	8	8
Non-fatal Moderate	5	8	6	5	6
Non-fatal Severe	2	3	2	2	2
Fatal	4	6	4	4	4
TOTAL	19	28	20	19	20
Hemorrhagic Stroke					
Non-fatal Mild	1	1	7	2	3
Non-fatal Moderate	3	3	4	3	3
Non-fatal Severe	5	4	3	3	3
Fatal	8	7	8	6	6
TOTAL	17	15	22	14	15
Recurrent Hemorrhagic Stroke					
Non-fatal Mild	0	0	0	0	0
Non-fatal Moderate	0	0	0	0	0
Non-fatal Severe	0	0	0	0	0
Fatal	0	0	1	0	0
TOTAL	1	0	1	1	1
Systemic Embolism					
Non-fatal	18	23	18	20	19

Fatal	2	2	2	2	2
TOTAL	20	26	20	22	21
Other ICH					
Non-fatal	12	11	15	12	9
Fatal	2	2	2	2	1
TOTAL	14	12	17	14	10
Other Major Bleeds					
Non-fatal GI Bleeds	32	23	44	41	35
Non-fatal Non ICH or Non GI Related Major Bleeds	56	35	59	52	52
Fatal	2	1	2	2	2
TOTAL	90	59	105	95	89
Clinically Relevant Non-Major Bleeds	277	228	333	257	255
MI					
Non-fatal	69	66	70	81	80
Fatal	11	10	11	12	12
TOTAL	79	76	80	94	92
Other CV Hospitalization	985	953	982	992	978
Other Treatment Discontinuation	650	637	681	737	722
Deaths					
Event Related (acute)	54	56	59	57	58
Event related (death due to stroke, HS, MI, SE)	275	342	283	289	297
Other	671	602	658	654	645

TOTAL	1,000	1,000	1,000	1,000	1,000

Table 156: Summary of costs by health state for VKA suitable population

Health states		Total Costs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% absolute increment			
		Apix	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
Anticoagulants		£3,347	£252	£2,891	£2,657	£2,716	£3,095	£456	£690	£631	£3,095	£456	£690	£631	172%	223%	126%	211%
Routine care		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	0%	0%	0%	0%
Monitoring		£72	£977	£80	£90	£88	-£905	-£8	-£18	-£16	£905	£8	£18	£16	50%	4%	3%	5%
Ischaemic stroke																		
Mild	Event related	£214	£204	£214	£198	£208	£10	£0	£16	£6	£10	£0	£16	£6	1%	0%	3%	2%
	Long-term care	£437	£416	£438	£396	£423	£21	-£1	£41	£14	£21	£1	£41	£14	1%	1%	8%	5%
Mod-erate	Event related	£901	£991	£936	£1,021	£1,082	-£90	-£35	-£119	-£180	£90	£35	£119	£180	5%	17%	22%	60%
	Long-term care	£440	£496	£458	£501	£545	-£55	-£18	-£61	-£105	£55	£18	£61	£105	3%	9%	11%	35%
Severe	Event related	£483	£515	£494	£545	£573	-£33	-£11	-£62	-£90	£33	£11	£62	£90	2%	5%	11%	30%
	Long-term care	£122	£133	£124	£138	£149	-£11	-£2	-£16	-£27	£11	£2	£16	£27	1%	1%	3%	9%
Fatal		£61	£58	£74	£75	£78	£4	-£13	-£14	-£17	£4	£13	£14	£17	0%	6%	3%	6%
Recurrent ischaemic stroke																		
Mild	Event related	£25	£25	£25	£24	£26	£0	£0	£0	-£2	£0	£0	£0	£2	0%	0%	0%	1%
	Long-term care	£31	£30	£31	£28	£30	£2	£0	£4	£1	£2	£0	£4	£1	0%	0%	1%	0%
Mod-erate	Event related	£51	£52	£52	£51	£54	-£1	-£1	£0	-£4	£1	£1	£0	£4	0%	0%	0%	1%
	Long-term care	£44	£48	£46	£47	£52	-£3	-£1	-£2	-£7	£3	£1	£2	£7	0%	1%	0%	2%
Severe	Event related	£26	£27	£27	£26	£28	£0	£0	£0	-£2	£0	£0	£0	£2	0%	0%	0%	1%
	Long-term care	£10	£11	£11	£11	£12	-£1	£0	£0	-£2	£1	£0	£0	£2	0%	0%	0%	1%
Fatal		£8	£8	£8	£7	£8	£0	£0	£0	-£1	£0	£0	£0	£1	0%	0%	0%	0%
Haemorrhagic stroke																		
Mild	Event related	£35	£54	£79	£24	£27	-£19	-£44	£11	£8	£19	£44	£11	£8	1%	21%	2%	3%
	Long-term care	£28	£44	£65	£20	£22	-£16	-£37	£8	£5	£16	£37	£8	£5	1%	18%	1%	2%
Mod-erate	Event related	£139	£125	£102	£68	£81	£14	£38	£71	£59	£14	£38	£71	£59	1%	18%	13%	20%
	Long-term care	£56	£50	£41	£26	£32	£5	£15	£30	£24	£5	£15	£30	£24	0%	7%	5%	8%
Severe	Event related	£124	£197	£111	£100	£106	-£73	£13	£24	£18	£73	£13	£24	£18	4%	6%	4%	6%
	Long-term care	£19	£33	£17	£15	£16	-£14	£2	£4	£3	£14	£2	£4	£3	1%	1%	1%	1%
Fatal		£12	£25	£11	£8	£8	-£14	£1	£4	£4	£14	£1	£4	£4	1%	0%	1%	1%

Health states		Total Costs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% absolute increment			
		Apix	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Warf	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
Recurrent Haemorrhagic stroke																		
Mild	Event related	£2	£3	£3	£1	£1	-£1	-£1	£1	£1	£1	£1	£1	£1	0%	0%	0%	0%
	Long-term care	£1	£1	£2	£0	£1	£0	-£1	£0	£0	£0	£1	£0	£0	0%	0%	0%	0%
Mod-erate	Event related	£7	£9	£11	£4	£5	-£2	-£3	£3	£2	£2	£3	£3	£2	0%	2%	1%	1%
	Long-term care	£3	£4	£4	£2	£2	-£1	-£1	£2	£1	£1	£1	£2	£1	0%	1%	0%	0%
Severe	Event related	£4	£5	£6	£2	£3	-£1	-£2	£2	£1	£1	£2	£2	£1	0%	1%	0%	0%
	Long-term care	£1	£1	£1	£1	£1	£0	£0	£0	£0	£0	£0	£0	£0	0%	0%	0%	0%
Fatal		£1	£1	£1	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	0%	0%	0%	0%
Systemic embolism																		
Event related		£58	£61	£60	£63	£62	-£2	-£1	-£5	-£4	£2	£1	£5	£4	0%	1%	1%	1%
Long-term care		£193	£202	£197	£208	£206	-£9	-£3	-£15	-£13	£9	£3	£15	£13	0%	2%	3%	4%
Other ICH		£22	£48	£42	£32	£23	-£26	-£20	-£10	-£1	£26	£20	£10	£1	1%	10%	2%	0%
Other major bleeds																		
GI bleeds		£67	£71	£94	£85	£70	-£4	-£27	-£18	-£3	£4	£27	£18	£3	0%	13%	3%	1%
Non ICH or non GI related major bleeds		£287	£335	£320	£271	£273	-£49	-£33	£16	£13	£49	£33	£16	£13	3%	16%	3%	4%
CRNM bleeds		£224	£269	£275	£218	£216	-£45	-£51	£7	£9	£45	£51	£7	£9	2%	25%	1%	3%
MI																		
Event related		£100	£105	£104	£124	£122	-£5	-£4	-£24	-£22	£5	£4	£24	£22	0%	2%	4%	7%
Long-term care		£14	£15	£15	£18	£18	-£1	-£1	-£4	-£4	£1	£1	£4	£4	0%	0%	1%	1%
CV Hospitalisation		£1,309	£1,287	£1,309	£1,323	£1,309	£23	£0	-£13	£1	£23	£0	£13	£1	1%	0%	2%	0%
Management costs		£3	£3	£3	£7	£7	£0	£0	-£3	-£4	£0	£0	£3	£4	0%	0%	1%	1%
TOTAL COST		£8,983	£7,188	£8,778	£8,437	£8,684	£1,795	£205	£547	£299	£1,795	£205	£547	£299	100%	100%	100%	100%

Table 157: Summary of costs by health state for VKA unsuitable population

Health states		Total Costs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% absolute increment			
		Apix	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
Anticoagulants		£2,876	£189	£2,474	£2,226	£2,283	£2,686	£401	£649	£592	£2,686	£401	£649	£592	281%	153%	101%	175%
Routine care		£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	0%	0%	0%	0%
Monitoring		£81	£181	£88	£99	£96	-£100	-£7	-£18	-£15	£100	£7	£18	£15	10%	3%	3%	4%
Ischaemic stroke																		
Mild	Event related	£221	£295	£241	£216	£229	-£74	-£20	£5	-£8	£74	£20	£5	£8	8%	8%	1%	2%
	Long-term care	£458	£652	£507	£443	£478	-£195	-£50	£15	-£21	£195	£50	£15	£21	20%	19%	2%	6%
Mod-erate	Event related	£1,083	£1,627	£1,036	£1,107	£1,186	-£544	£47	-£24	-£103	£544	£47	£24	£103	57%	18%	4%	30%
	Long-term care	£551	£915	£520	£558	£615	-£364	£31	-£7	-£64	£364	£31	£7	£64	38%	12%	1%	19%
Severe	Event related	£596	£877	£545	£591	£627	-£281	£51	£5	-£31	£281	£51	£5	£31	29%	19%	1%	9%
	Long-term care	£159	£263	£141	£154	£169	-£104	£18	£5	-£10	£104	£18	£5	£10	11%	7%	1%	3%
Fatal		£74	£81	£84	£83	£87	-£8	-£11	-£10	-£14	£8	£11	£10	£14	1%	4%	2%	4%
Recurrent ischaemic stroke																		
Mild	Event related	£21	£32	£22	£21	£22	-£11	-£1	£0	-£1	£11	£1	£0	£1	1%	0%	0%	0%
	Long-term care	£25	£37	£28	£24	£26	-£12	-£3	£1	-£1	£12	£3	£1	£1	1%	1%	0%	0%
Mod-erate	Event related	£77	£117	£79	£75	£82	-£40	-£3	£1	-£5	£40	£3	£1	£5	4%	1%	0%	2%
	Long-term care	£56	£94	£57	£55	£62	-£38	£0	£1	-£6	£38	£0	£1	£6	4%	0%	0%	2%
Severe	Event related	£45	£68	£46	£44	£48	-£23	-£2	£1	-£3	£23	£2	£1	£3	2%	1%	0%	1%
	Long-term care	£16	£27	£16	£16	£17	-£11	£0	£1	-£1	£11	£0	£1	£1	1%	0%	0%	0%
Fatal		£9	£14	£10	£9	£10	-£5	£0	£0	-£1	£5	£0	£0	£1	1%	0%	0%	0%
Haemorrhagic stroke																		
Mild	Event related	£10	£9	£68	£21	£24	£1	-£58	-£11	-£14	£1	£58	£11	£14	0%	22%	2%	4%
	Long-term care	£8	£7	£58	£17	£20	£1	-£50	-£10	-£12	£1	£50	£10	£12	0%	19%	2%	4%
Mod-erate	Event related	£74	£67	£94	£64	£75	£7	-£20	£10	-£1	£7	£20	£10	£1	1%	8%	2%	0%
	Long-term care	£29	£27	£38	£25	£30	£2	-£9	£4	-£1	£2	£9	£4	£1	0%	4%	1%	0%
Severe	Event related	£169	£153	£112	£102	£107	£16	£57	£67	£62	£16	£57	£67	£62	2%	22%	10%	18%
	Long-term care	£28	£26	£17	£15	£17	£2	£11	£13	£11	£2	£11	£13	£11	0%	4%	2%	3%
Fatal		£11	£10	£11	£8	£8	£1	£0	£3	£3	£1	£0	£3	£3	0%	0%	0%	1%

Health states		Total Costs					Increment: Apixaban vs. comparator				Absolute Increment: Apixaban vs. comparator				% absolute increment			
		Apix	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)	Asp	Riva	Dabi (110mg/ 150mg)	Dabi (110mg)
Recurrent Haemorrhagic stroke																		
Mild	Event related	£0	£0	£1	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	0%	0%	0%	0%
	Long-term care	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	£0	0%	0%	0%	0%
Mod-erate	Event related	£2	£2	£6	£3	£3	£0	-£4	£0	-£1	£0	£4	£0	£1	0%	1%	0%	0%
	Long-term care	£1	£1	£2	£1	£1	£0	-£2	£0	£0	£0	£2	£0	£0	0%	1%	0%	0%
Severe	Event related	£5	£5	£14	£6	£7	£0	-£8	-£1	-£1	£0	£8	£1	£1	0%	3%	0%	0%
	Long-term care	£1	£1	£2	£1	£1	£0	-£1	£0	£0	£0	£1	£0	£0	0%	0%	0%	0%
Fatal		£0	£0	£1	£0	£0	£0	-£1	£0	£0	£0	£1	£0	£0	0%	0%	0%	0%
Systemic embolism																		
Event related		£58	£79	£60	£64	£63	-£22	-£2	-£6	-£5	£22	£2	£6	£5	2%	1%	1%	1%
Long-term care		£190	£281	£196	£211	£207	-£92	-£7	-£21	-£18	£92	£7	£21	£18	10%	3%	3%	5%
Other ICH		£30	£27	£39	£31	£23	£3	-£9	£0	£7	£3	£9	£0	£7	0%	3%	0%	2%
Other major bleeds																		
GI bleeds		£40	£28	£56	£53	£45	£12	-£16	-£12	-£4	£12	£16	£12	£4	1%	6%	2%	1%
Non ICH or non GI related major bleeds		£185	£116	£198	£176	£176	£69	-£13	£9	£9	£69	£13	£9	£9	7%	5%	1%	3%
CRNM bleeds		£263	£217	£322	£245	£243	£46	-£59	£18	£20	£46	£59	£18	£20	5%	22%	3%	6%
MI																		
Event related		£115	£111	£117	£139	£136	£4	-£2	-£24	-£21	£4	£2	£24	£21	0%	1%	4%	6%
Long-term care		£17	£17	£17	£21	£21	£0	£0	-£4	-£4	£0	£0	£4	£4	0%	0%	1%	1%
CV Hospitalisation		£1,283	£1,257	£1,281	£1,296	£1,278	£26	£2	-£13	£5	£26	£2	£13	£5	3%	1%	2%	1%
Management costs		£3	£3	£3	£6	£6	£0	£0	-£3	-£3	£0	£0	£3	£3	0%	0%	0%	1%
TOTAL COST		£8,870	£7,916	£8,608	£8,228	£8,531	£955	£262	£642	£339	£955	£262	£642	£339	100%	100%	100%	100%

10.22 Appendix 22: Output from tornado diagrams

Table 158: Output from tornado diagrams in VKa suitable population, variables ranked by size of effect on ICER

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
WarfarinUtility	£15,518	£8,529	StrokeHRComparator	£6,984	£703	StrokeRiskASA2nd	£18,263	£3,321	StrokeHRComparator	£18,065	£770
ICH_HRComparator	£14,027	£8,149	StrokeRiskASA2nd	£5,906	£1,000	StrokeHRComparator	£13,525	£4,274	ICH_HRComparator	£9,948	£893
StrokeHRComparator	£14,056	£8,518	ICH_HRComparator	£3,713	£1,833	AFtrialHROther	£12,313	£5,779	StrokeRiskASA2nd	£7,706	£1,880
AFtrialHROther	£13,854	£9,049	ICHRiskApixaban	£3,976	£2,206	StrokeRiskApixaban	£11,777	£5,363	AFtrialHROther	£8,294	£3,102
MonitoringVisitCost	£13,917	£9,620	DiscCosts	£3,876	£2,372	ICHRiskApixaban	£10,915	£5,875	%HemStrokeComparator	£5,970	£2,798
DiscUtility	£12,777	£8,659	RoutineCareCost	£4,346	£2,879	MI_HRComparator	£10,281	£5,861	OMB_HRComparator	£5,566	£2,525
ICHRiskApixaban	£13,120	£9,137	DiscUtility	£3,520	£2,104	DiscUtility	£9,473	£5,462	StrokeRiskApixaban	£5,631	£2,922
FemaleAge	£12,495	£9,506	CFRHemStrokeApixaban	£3,419	£2,234	ICH_HRComparator	£9,136	£5,852	CFRHemStrokeApixaban	£5,103	£2,791
MaleAge	£12,137	£9,573	CVRiskApixaban	£3,537	£2,360	AFDeathHR	£9,304	£6,684	DiscUtility	£5,043	£2,951
DiscCosts	£12,502	£10,175	CV_RiskASA2nd	£3,394	£2,228	DiscCosts	£9,343	£6,729	%HemStrokeApixaban	£5,165	£3,075
RoutineCareCost	£13,227	£11,008		£3,374	£2,303		£8,993	£6,552	SE_HRComparator	£4,684	£2,729

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
			OMB_HRComparator			StrokeRiskAdjustment					
AFDeathHR	£12,288	£10,118	ModStrokeFUCost	£3,389	£2,368	BaseUtilityAF	£8,908	£6,680	RoutineCareCost	£5,794	£4,090
BaseUtilityAF	£12,095	£10,099	ModStrokeAcuteCost	£3,358	£2,400	MaleAge	£7,611	£5,536	DiscCosts	£5,171	£3,535
MI_HRComparator	£11,948	£10,016	CFRStrokeComparator	£3,323	£2,423	%HemStrokeApixaban	£8,647	£6,609	MI_HRComparator	£5,060	£3,494
%HemStrokeComparator	£12,001	£10,182	%HemStrokeComparator	£3,378	£2,482	CV_RiskASA2nd	£8,510	£6,530	StrokeRiskAdjustment	£4,902	£3,426
StrokeRiskASA2nd	£11,630	£10,379	AFtrialHROther	£3,460	£2,564	%HemStrokeComparator	£8,591	£6,759	CFRStrokeApixaban	£4,632	£3,240
%HemStrokeApixaban	£11,548	£10,408	%HemStrokeApixaban	£3,300	£2,430	CVRiskApixaban	£8,644	£6,840	BaseUtilityAF	£4,811	£3,558
TmtDiscRiskApixaban	£11,448	£10,475	SE_HRComparator	£3,126	£2,258	OMB_HRComparator	£8,455	£6,678	CVRiskApixaban	£4,775	£3,551
OMB_HRComparator	£11,428	£10,520	BaseUtilityAF	£3,368	£2,514	RoutineCareCost	£9,134	£7,635	CV_RiskASA2nd	£4,627	£3,412
SE_HRComparator	£11,240	£10,548	CFRStrokeApixaban	£3,229	£2,407	TmtDiscRiskApixaban	£8,373	£6,879	CRNMB_HRComparator	£4,606	£3,471

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
TmtDiscHRComparator	£11,316	£10,701	TmtDiscHRComparator	£3,224	£2,417	FemaleAge	£7,402	£5,948	OMBRiskApixaban	£4,609	£3,511
CFR_ICH_Comparator	£11,269	£10,686	FemaleAge	£3,099	£2,346	MI_RiskASA2nd	£8,293	£6,994	CFRStrokeComparator	£4,562	£3,529
CFR_OMB_Comparator	£11,263	£10,702	SevereStrokeFUCost	£3,158	£2,506	CFRHemStrokeApixaban	£8,202	£6,936	FemaleAge	£4,540	£3,622
AFtrialRateApixaban	£11,282	£10,724	SevereStrokeAcuteCost	£3,160	£2,597	TmtDiscHRComparator	£8,366	£7,109	CRNMBCost	£4,551	£3,661
CFRHemStrokeComparator	£11,268	£10,727	ModHemStrokeAcuteCost	£3,130	£2,627	SE_HRComparator	£7,982	£6,740	AFDeathHR	£4,646	£3,764
CFR_OMB_Apixaban	£11,286	£10,801	HR_Death ModStroke	£3,051	£2,592	MIRiskApixaban	£8,236	£7,041	TmtDiscHRComparator	£4,385	£3,580
OMBRiskApixaban	£11,214	£10,756	StrokeRisk Adjustment	£3,117	£2,704	ModStroke AcuteCost	£8,085	£7,184	CRNMBRiskApixaban	£4,443	£3,642
SevereHemStrokeAcuteCost	£11,230	£10,785	MI_HRComparator	£3,086	£2,714	ModHemStrokeAcuteCost	£8,079	£7,190	MildHemStrokeAcuteCost	£4,448	£3,732
CFRHemStrokeApixaban	£11,197	£10,787	MaleAge	£2,898	£2,537	ICH_RiskASA2nd	£8,035	£7,164	MaleAge	£4,371	£3,677
ModStrokeFUCost	£11,179	£10,837	ICH_RiskASA2nd	£3,021	£2,707	ModStroke FUCost	£8,055	£7,214	CFRHemStrokeComparator	£4,419	£3,757

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
CRNMB_HRComparator	£11,146	£10,844	CRNMBRiskApixaban	£3,026	£2,763	CFR_OMB_Apixaban	£8,045	£7,350	MildHemStrokeFUCost	£4,406	£3,775
ModStrokeAcuteCost	£11,158	£10,857	%GIBleedApixaban	£3,000	£2,754	CFR_OMB_Comparator	£7,937	£7,291	ModHemStrokeAcuteCost	£4,386	£3,795
CVRiskApixaban	£11,171	£10,879	ModHemStrokeFUCost	£2,992	£2,765	SevereStrokeAcuteCost	£7,911	£7,359	%GIBleedComparator	£4,368	£3,816
ICHRiskAdjustment	£11,132	£10,885	FatalStrokeCost	£3,044	£2,820	SevereStrokeFUCost	£7,868	£7,324	OMB_Cost	£4,339	£3,826
CRNMBRiskApixaban	£11,115	£10,872	%GIBleedComparator	£2,987	£2,773	MildStrokeFUCost	£7,894	£7,375	%GIBleedApixaban	£4,342	£3,831
CRNMBCost	£11,132	£10,892	AFDeathHR	£3,002	£2,790	HR_DeathMI_females	£7,859	£7,440	CFR_OMB_Comparator	£4,315	£3,862
StrokeRiskAdjustment	£11,140	£10,907	CFRHemStrokeComparator	£2,985	£2,778	MI_Utility	£7,844	£7,430	ModStrokeAcuteCost	£4,283	£3,897
OMB_Cost	£11,120	£10,888	StrokeRiskApixaban	£2,975	£2,768	ModHemStrokeFUCost	£7,841	£7,428	ICH_RiskASA2nd	£4,262	£3,883
MIRiskApixaban	£11,108	£10,886	OMBRiskApixaban	£2,993	£2,788	CFR_ICH_Comparator	£7,819	£7,409	%SwitchTmT_GI_Comparator	£4,312	£3,942

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
%SwitchTmT_GI_Comparator	£11,084	£10,870	%SwitchTmT_GI_Apixaban	£2,949	£2,746	CRNMBRiskApixaban	£7,858	£7,459	CFR_OMB_Apixaban	£4,307	£3,948
CFRStrokeApixaban	£11,122	£10,918	SERiskApixaban	£2,992	£2,790	SERiskApixaban	£7,859	£7,460	CFR_ICH_Comparator	£4,260	£3,903
%Male	£11,110	£10,909	CRNMB_RiskASA2nd	£2,959	£2,777	ICHRiskAdjustment	£7,837	£7,444	ModStrokeFUCost	£4,267	£3,914
SevereHemStrokeFUCost	£11,094	£10,893	SevereHemStrokeAcuteCost	£2,969	£2,788	%Male	£7,828	£7,455	FatalStrokeCost	£4,346	£4,000
CFR_ICH_Apixaban	£11,104	£10,936	%SwitchTmT_GI_Comparator	£2,989	£2,814	%GIBleedApixaban	£7,811	£7,453	MI_RiskASA2nd	£4,249	£3,923
SevereStrokeFUCost	£11,078	£10,914	TmtDiscRiskApixaban	£2,839	£2,678	HR_DeathMildStroke	£7,756	£7,409	SERiskApixaban	£4,260	£3,958
MI_RiskASA2nd	£11,082	£10,919	HR_DeathMildStroke	£2,988	£2,828	SevereHemStrokeAcuteCost	£7,808	£7,461	%SwitchTmT_GI_Apixaban	£4,187	£3,899
%GIBleedComparator	£11,089	£10,929	MI_RiskASA2nd	£2,954	£2,800	HR_DeathMI_males	£7,802	£7,483	GICost	£4,220	£3,935
%SwitchTmT_GI_Apixaban	£11,111	£10,954	ICHRiskAdjustment	£2,958	£2,804	CRNMB_RiskASA2nd	£7,771	£7,462	ICHRiskApixaban	£4,232	£3,951
%GIBleedApixaban	£11,085	£10,928	OMB_RiskASA2nd	£2,945	£2,795	ASA_Utility	£7,785	£7,490	ModHemStrokeFUCost	£4,224	£3,957

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
HR_DeathMildHemStroke	£11,102	£10,946	HR_DeathModHemStroke	£2,971	£2,822	OMB_RiskASA2nd	£7,762	£7,473	SevereHemStrokeAcuteCost	£4,198	£3,983
CV_RiskASA2nd	£11,076	£10,921	MildStrokeFUCost	£2,938	£2,819	CFR_MI_females	£7,759	£7,488	OtherICHCost	£4,182	£3,970
FatalHemStrokeCost	£11,092	£10,938	MonitoringVisitCost	£2,959	£2,841	%GIBleedComparator	£7,770	£7,500	CRNMB_RiskASA2nd	£4,174	£3,984
CFR_ICH_Comparator	£11,060	£10,923	MIAcuteCost	£2,931	£2,827	CFRStrokeComparator	£7,761	£7,502	MildHemStrokeUtility	£4,172	£4,006
SevereStrokeAcuteCost	£11,072	£10,943	SEFUCost	£2,929	£2,828	FatalStrokeCost	£7,825	£7,567	OMB_RiskASA2nd	£4,162	£4,000
CFR_ICH_Apixaban	£11,083	£10,963	OMB_Cost	£2,930	£2,831	MildStrokeUtility	£7,770	£7,514	HR_DeathModHemStroke	£4,186	£4,032
CFRStrokeComparator	£11,063	£10,945	MI_Utility	£2,928	£2,830	MildStrokeAcuteCost	£7,760	£7,509	HR_DeathMildStroke	£4,194	£4,045
MildStrokeFUCost	£11,066	£10,950	HR_DeathMI_females	£2,929	£2,834	CFR_ICH_Apixaban	£7,773	£7,534	SevereStrokeAcuteCost	£4,163	£4,018
ModerateStrokeUtility	£11,064	£10,954	%Male	£2,924	£2,836	%SwitchTmT_GI_Comparator	£7,718	£7,494	HemStrokeRecurrentRate	£4,145	£4,016
CVCost	£11,060	£10,954	ModerateStrokeUtility	£2,923	£2,837	CFRStrokeApixaban	£7,726	£7,503	CFR_ICH_Apixaban	£4,164	£4,038

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
HR_DeathSE	£11,035	£10,939	MIRiskApixaban	£2,919	£2,837	CFR_MI_males	£7,733	£7,516	MonitoringVisitCost	£4,172	£4,051
MildHemStrokeAcuteCost	£11,055	£10,961	CFR_ICH_Apixaban	£2,908	£2,829	WarfarinUtility	£7,739	£7,533	HR_DeathModStroke	£4,133	£4,020
ICH_RiskASA2nd	£11,048	£10,957	SevereHemStrokeFUCost	£2,922	£2,846	MonitoringVisitCost	£7,769	£7,570	SevereStrokeFUCost	£4,137	£4,028
OtherICHCost	£11,043	£10,961	HR_DeathMI_males	£2,917	£2,844	ModerateStrokeUtility	£7,731	£7,543	MIRiskApixaban	£4,152	£4,044
MildHemStrokeFUCost	£11,049	£10,966	FatalHemStrokeCost	£2,911	£2,839	HR_DeathModStroke	£7,703	£7,520	ASA_Utility	£4,140	£4,042
MildStrokeUtility	£11,051	£10,968	CRNMBCost	£2,913	£2,842	HR_DeathSE	£7,687	£7,510	SevereHemStrokeFUCost	£4,143	£4,051
MildStrokeAcuteCost	£11,041	£10,974	CFR_OMB_Comparator	£2,909	£2,843	OMB_Cost	£7,725	£7,550	HR_DeathMildHemStroke	£4,146	£4,060
ModHemStrokeAcuteCost	£11,040	£10,975	ASA_Utility	£2,912	£2,846	SEFUCost	£7,720	£7,550	CFR_ICH_Apixaban	£4,120	£4,039
HR_DeathSevereHemStroke	£11,031	£10,966	CFR_OMB_Apixaban	£2,917	£2,851	MIAcuteCost	£7,719	£7,551	%Male	£4,128	£4,054
HR_DeathMildStroke	£11,046	£10,988	MildHemStrokeAcuteCost	£2,910	£2,847	SevereHemStrokeFUCost	£7,723	£7,568	WarfarinUtility	£4,124	£4,057
MildHemStrokeUti	£11,036	£10,977	HR_Death	£2,904	£2,848	CVCost	£7,706	£7,565	CFR_ICH_Comparat	£4,125	£4,068

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
lity			SevereStroke						or		
MI_Utility	£11,035	£10,980	CFR_MI_females	£2,902	£2,851	GICost	£7,695	£7,562	SEFUCost	£4,118	£4,062
HR_DeathMI_females	£11,036	£10,982	OMBRiskAdjustment	£2,905	£2,854	HR_DeathModHemStroke	£7,715	£7,585	HR_DeathMI_females	£4,115	£4,068
SEFUCost	£11,030	£10,985	CFR_ICH_Comparator	£2,910	£2,859	MildHemStrokeAcuteCost	£7,699	£7,570	MI_Utility	£4,113	£4,067
HR_DeathModStroke	£11,035	£10,991	ManagCostComparator	£2,900	£2,851	CFR_ICH_Apixaban	£7,707	£7,593	HR_DeathSE	£4,103	£4,060
HR_DeathMI_males	£11,030	£10,987	WarfarinUtility	£2,902	£2,856	CFRHemStrokeComparator	£7,692	£7,579	ModerateStrokeUtility	£4,112	£4,070
CFR_MI_females	£11,025	£10,987	MildHemStrokeFUCost	£2,901	£2,857	OMBRiskApixaban	£7,698	£7,585	CRNMBRiskAdjustment	£4,111	£4,069
HemStrokeRecurrentRate	£11,022	£10,988	MildStrokeAcuteCost	£2,900	£2,858	HR_DeathMildHemStroke	£7,676	£7,573	ICHRiskAdjustment	£4,112	£4,071
SERiskApixaban	£11,026	£10,993	CFR_MI_males	£2,898	£2,856	FatalHemStrokeCost	£7,679	£7,580	OMBRiskAdjustment	£4,110	£4,072
ASA_Utility	£11,024	£10,991	CRNMBRiskAdjustm	£2,897	£2,861	MildHemStrokeFUCos	£7,683	£7,586	ManagCostApixaban	£4,111	£4,074

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
			ent			t					
CFR_MI_males	£11,021	£10,991	MI_FUCost	£2,894	£2,859	ModerateHemStrokeUtility	£7,680	£7,588	HR_DeathMI_males	£4,109	£4,073
FatalStrokeCost	£11,015	£10,987	SEAcuteCost	£2,896	£2,862	%SwitchTmT_GI_Apixaban	£7,695	£7,606	MIAcuteCost	£4,108	£4,073
%SwitchTmT_ICH_Comparator	£11,022	£10,994	HR_DeathSevereHemStroke	£2,897	£2,869	OMBRiskAdjustment	£7,677	£7,594	HR_DeathSevereHemStroke	£4,112	£4,078
ModHemStrokeFUCost	£11,021	£10,994	HemStrokeRecurrentRate	£2,894	£2,868	CRNMBCost	£7,674	£7,593	ManagCostComparator	£4,105	£4,072
OMB_RiskASA2nd	£11,019	£10,994	CFR_ICH_Apixaban	£2,893	£2,868	OtherICHCost	£7,667	£7,592	ModerateHemStrokeUtility	£4,106	£4,074
CRNMB_RiskASA2nd	£11,018	£10,994	CFR_ICH_Comparator	£2,889	£2,866	HemStrokeRecurrentRate	£7,673	£7,607	CFR_MI_females	£4,103	£4,076
SE_Utility	£11,018	£10,997	MildStrokeUtility	£2,890	£2,868	CFR_ICH_Comparator	£7,658	£7,597	%SwitchTmT_ICH_Comparator	£4,102	£4,078
OMBRiskAdjustment	£11,018	£10,998	ModerateHemStrokeUtility	£2,888	£2,869	SEAcuteCost	£7,664	£7,605	SEAcuteCost	£4,101	£4,079
SevereHemStrok	£11,017	£11,000	StrokeRec	£2,887	£2,869	ManagCos	£7,660	£7,602	CFR_MI_males	£4,100	£4,078

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
eUtility			urrentRate			tComparator					
CRNMBRiskAdjustment	£11,015	£11,000	ManagCostApixaban	£2,889	£2,871	MI_FUCost	£7,659	£7,603	MildStrokeAcuteCost	£4,100	£4,080
MIAcuteCost	£11,015	£11,000	GICost	£2,886	£2,870	CRNMBRiskAdjustment	£7,662	£7,608	MildStrokeFUCost	£4,100	£4,081
SevereStrokeUtility	£11,016	£11,001	SevereStrokeUtility	£2,887	£2,872	SE_Utility	£7,661	£7,608	FatalHemStrokeCost	£4,096	£4,083
SEAcuteCost	£11,014	£11,001	SE_Utility	£2,885	£2,873	HR_Death SevereHemStroke	£7,669	£7,616	OMB_Utility	£4,096	£4,083
GICost	£11,013	£11,001	HR_Death MildHemStroke	£2,884	£2,875	MildHemStrokeUtility	£7,660	£7,612	StrokeRecurrentRate	£4,096	£4,084
ManagCostApixaban	£11,014	£11,003	MildHemStrokeUtility	£2,883	£2,875	HR_Death SevereStroke	£7,654	£7,611	MI_FUCost	£4,095	£4,084
ManagCostComparator	£11,012	£11,002	%SwitchTmT_ICH_Apixaban	£2,882	£2,875	SevereStrokeUtility	£7,653	£7,620	OtherICHUtility	£4,094	£4,085
StrokeRiskApixaban	£11,010	£10,999	CVCost	£2,882	£2,876	ManagCostApixaban	£7,649	£7,623	SE_Utility	£4,095	£4,086
OtherICHUtility	£11,012	£11,002	OtherICHCost	£2,881	£2,875	StrokeRecurrentRate	£7,647	£7,623	AFtrialRateApixaban	£4,095	£4,086

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
ModerateHemStrokeUtility	£11,012	£11,003	%SwitchTmT_ICH_Comparator	£2,881	£2,876	AFtrialRateApixaban	£7,647	£7,624	%SwitchTmT_ICH_Apixaban	£4,095	£4,086
HR_DeathSevereStroke	£11,011	£11,004	HR_DeathSE	£2,880	£2,875	%SwitchTmT_ICH_Comparator	£7,642	£7,628	HR_DeathSevereStroke	£4,094	£4,086
%SwitchTmT_ICH_Apixaban	£11,011	£11,004	SevereHemStrokeUtility	£2,880	£2,878	SevereHemStrokeUtility	£7,639	£7,629	TmtDiscRiskApixaban	£3,994	£3,987
OMB_Utility	£11,010	£11,004	AFtrialRateApixaban	£2,879	£2,879	OtherICHUtility	£7,637	£7,631	MildStrokeUtility	£4,093	£4,088
MI_FUCost	£11,010	£11,005	OtherICHUtility	£2,879	£2,879	OMB_Utility	£7,637	£7,632	CVCost	£4,093	£4,088
StrokeRecurrentRate	£11,009	£11,006	OMB_Utility	£2,879	£2,879	%SwitchTmT_ICH_Apixaban	£7,637	£7,632	SevereStrokeUtility	£4,092	£4,089
HR_DeathModHemStroke	£11,009	£11,007	CRNMB_Utility	£2,879	£2,879	CV_Utility	£7,635	£7,634	SevereHemStrokeUtility	£4,092	£4,089
CV_Utility	£11,009	£11,007	CV_Utility	£2,879	£2,879	CRNMB_Utility	£7,635	£7,635	CRNMB_Utility	£4,091	£4,090
CRNMB_Utility	£11,008	£11,007	StrokeRiskWarfarin	£2,879	£2,879	StrokeRiskWarfarin	£7,635	£7,635	CV_Utility	£4,090	£4,090
StrokeRiskWarfarin	£11,008	£11,008	ICHRiskWarfarin	£2,879	£2,879	ICHRiskWarfarin	£7,635	£7,635	StrokeRiskWarfarin	£4,090	£4,090

Warfarin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
ICHRiskWarfarin	£11,008	£11,008	OMBRisk Warfarin	£2,879	£2,879	OMBRisk Warfarin	£7,635	£7,635	ICHRiskWarfarin	£4,090	£4,090
OMBRiskWarfarin	£11,008	£11,008	CRNMBRiskWarfarin	£2,879	£2,879	CRNMBRiskWarfarin	£7,635	£7,635	OMBRiskWarfarin	£4,090	£4,090
CRNMBRiskWarfarin	£11,008	£11,008	MIRiskWarfarin	£2,879	£2,879	MIRiskWarfarin	£7,635	£7,635	CRNMBRiskWarfarin	£4,090	£4,090
MIRiskWarfarin	£11,008	£11,008	CVRiskWarfarin	£2,879	£2,879	CVRiskWarfarin	£7,635	£7,635	MIRiskWarfarin	£4,090	£4,090
CVRiskWarfarin	£11,008	£11,008	TmtDiscRiskWarfarin	£2,879	£2,879	TmtDiscRiskWarfarin	£7,635	£7,635	CVRiskWarfarin	£4,090	£4,090
TmtDiscRiskWarfarin	£11,008	£11,008	CFRStrokeASA2nd	£2,879	£2,879	CFRStrokeASA2nd	£7,635	£7,635	TmtDiscRiskWarfarin	£4,090	£4,090
CFRStrokeASA2nd	£11,008	£11,008	CV_HRComparator	£2,879	£2,879	CV_HRComparator	£7,635	£7,635	CFRStrokeASA2nd	£4,090	£4,090
CV_HRComparator	£11,008	£11,008	CRNMB_HRComparator	£2,879	£2,879	CRNMB_HRComparator	£7,635	£7,635	CV_HRComparator	£4,090	£4,090
SERiskWarfarin	£11,008	£11,008	SERiskWarfarin	£2,879	£2,879	SERiskWarfarin	£7,635	£7,635	SERiskWarfarin	£4,090	£4,090
AFtrialRateOther	£11,008	£11,008	AFtrialRateOther	£2,879	£2,879	AFtrialRateOther	£7,635	£7,635	AFtrialRateOther	£4,090	£4,090

Table 159: Output from tornado diagrams in VKA unsuitable population, variables ranked by size of effect on ICER

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
StrokeHRComparator	£7,689	£63	StrokeHRComparator	£11,665	£756	StrokeRiskASA2nd	£48,481	£5,605	StrokeHRComparator	£11,665	Apixaban dominated
StrokeRiskApixaban	£6,528	£724	StrokeRiskASA2nd	£7,455	£1,542	StrokeRiskApixaban	£46,387	£6,630	StrokeRiskASA2nd	£7,455	£1,542
FemaleAge	£3,921	£1,461	ICH_HRComparator	£4,646	£2,588	StrokeHRComparator	£44,605	£5,889	ICH_HRComparator	£4,646	£2,588
SE_HRComparator	£3,169	£817	CFRStrokeApixaban	£4,521	£2,481	MI_HRComparator	£27,567	£8,312	CFRStrokeApixaban	£4,521	£2,481
MaleAge	£3,661	£1,663	DiscUtility	£4,534	£2,754	AFtrialHROther	£21,792	£9,973	DiscUtility	£4,534	£2,754
RoutineCareCost	£4,329	£2,903	StrokeRiskApixaban	£4,573	£3,082	StrokeRiskAdjustment	£18,871	£10,017	StrokeRiskApixaban	£4,573	£3,082
StrokeRiskAdjustment	£3,653	£2,343	DiscCosts	£4,709	£3,219	ICHRiskApixaban	£18,414	£10,860	DiscCosts	£4,709	£3,219
DiscUtility	£3,453	£2,210	RoutineCareCost	£5,222	£3,732	AFDeathHR	£18,518	£11,039	RoutineCareCost	£5,222	£3,732
ICH_HRComparator	£3,316	£2,088	%HemStrokeApixaban	£4,521	£3,051	DiscUtility	£16,758	£9,583	%HemStrokeApixaban	£4,521	£3,051
ModStrokeFUCost	£3,482	£2,324	ICHRiskApixaban	£4,549	£3,204	ICH_HRComparator	£16,511	£10,015	ICHRiskApixaban	£4,549	£3,204
	£3,384	£2,422		£4,518	£3,179		£17,073	£10,807	BaseUtilityAF	£4,518	£3,179

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
ModStrokeAcuteCost			BaseUtilityAF			%HemStrokeApixaban					
BaseUtilityAF	£3,419	£2,523	CVRiskApixaban	£4,446	£3,170	MaleAge	£14,642	£8,529	CVRiskApixaban	£4,446	£3,170
SevereStrokeFUCost	£3,252	£2,438	StrokeRiskAdjustment	£4,424	£3,178	BaseUtilityAF	£16,773	£11,232	StrokeRiskAdjustment	£4,424	£3,178
CFRStrokeComparator	£3,309	£2,557	CV_RiskASA2nd	£4,273	£3,049	FemaleAge	£14,598	£9,067	CV_RiskASA2nd	£4,273	£3,049
CFRStrokeApixaban	£3,163	£2,561	CFRStrokeComparator	£4,279	£3,150	MIRiskApixaban	£15,448	£11,709	CFRStrokeComparator	£4,279	£3,150
SevereStrokeAcuteCost	£3,199	£2,608	MI_HRComparator	£4,383	£3,291	MI_RiskASA2nd	£15,397	£11,735	MI_HRComparator	£4,383	£3,291
DiscCosts	£3,277	£2,708	TmtDiscHRComparator	£4,190	£3,140	%HemStrokeComparator	£15,400	£11,759	TmtDiscHRComparator	£4,190	£3,140
AFtrialHROther	£3,184	£2,651	AFtrialHROther	£4,336	£3,342	DiscCosts	£15,716	£12,206	AFtrialHROther	£4,336	£3,342
AFDeathHR	£3,233	£2,705	%HemStrokeComparator	£4,264	£3,308	TmtDiscHRComparator	£15,391	£12,118	%HemStrokeComparator	£4,264	£3,308
MildStrokeFUCost	£3,165	£2,642	FemaleAge	£4,093	£3,275	TmtDiscRiskApixaban	£15,038	£11,877	FemaleAge	£4,093	£3,275

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
CV_HRComparator	£3,133	£2,636	AFDeathHR	£4,190	£3,466	CV_RiskASA2nd	£14,697	£11,886	AFDeathHR	£4,190	£3,466
HR_DeathModStroke	£3,077	£2,616	ModStrokeFUCost	£4,093	£3,371	CVRiskApixaban	£14,884	£12,330	ModStrokeFUCost	£4,093	£3,371
TmtDiscRiskApixaban	£3,074	£2,698	SevereHemStrokeAcuteCost	£4,058	£3,406	ICH_RiskASA2nd	£14,320	£12,468	SevereHemStrokeAcuteCost	£4,058	£3,406
%HemStrokeApixaban	£3,086	£2,723	ModStrokeAcuteCost	£4,056	£3,408	OMB_HRComparator	£14,205	£12,585	ModStrokeAcuteCost	£4,056	£3,408
%HemStrokeComparator	£3,061	£2,757	OMB_HRComparator	£4,004	£3,404	RoutineCareCost	£15,008	£13,454	OMB_HRComparator	£4,004	£3,404
MildStrokeAcuteCost	£3,052	£2,754	CFRHemStrokeApixaban	£4,017	£3,440	SevereHemStrokeAcuteCost	£14,134	£12,775	CFRHemStrokeApixaban	£4,017	£3,440
TmtDiscHRComparator	£3,041	£2,763	SE_HRComparator	£3,888	£3,323	CFR_ICH_Apixaban	£14,204	£12,944	SE_HRComparator	£3,888	£3,323
SERiskApixaban	£3,010	£2,769	MaleAge	£3,846	£3,395	SE_HRComparator	£13,769	£12,595	MaleAge	£3,846	£3,395
MonitoringVisitCost	£3,062	£2,827	CRNMBRiskApixaban	£3,958	£3,555	MI_Utility	£14,039	£12,900	CRNMBRiskApixaban	£3,958	£3,555
SEFUCost	£3,019	£2,787	ICH_RiskASA2nd	£3,902	£3,528	HR_DeathMI_females	£14,070	£12,934	ICH_RiskASA2nd	£3,902	£3,528

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
OMBRiskApixaban	£3,023	£2,808	%GIBleedApixaban	£3,889	£3,560	CFR_ICH_Comparator	£13,953	£12,858	%GIBleedApixaban	£3,889	£3,560
OMB_HRComparator	£2,982	£2,768	SevereHemStrokeFUCost	£3,899	£3,607	CFR_OMB_Apixaban	£14,066	£13,017	SevereHemStrokeFUCost	£3,899	£3,607
CRNMB_HRComparator	£2,983	£2,796	SevereStrokeFUCost	£3,855	£3,569	CFR_OMB_Comparator	£13,914	£12,917	SevereStrokeFUCost	£3,855	£3,569
OMB_Cost	£2,987	£2,824	HR_DeathModStroke	£3,839	£3,558	CFRStrokeApixaban	£14,102	£13,134	HR_DeathModStroke	£3,839	£3,558
CFRHemStrokeApixaban	£2,984	£2,821	MI_RiskASA2nd	£3,865	£3,594	HR_DeathMI_males	£13,915	£13,047	MI_RiskASA2nd	£3,865	£3,594
CFRHemStrokeComparator	£2,972	£2,835	SevereStrokeAcuteCost	£3,852	£3,612	CFRHemStrokeApixaban	£13,878	£13,015	SevereStrokeAcuteCost	£3,852	£3,612
%Male	£2,971	£2,838	FatalStrokeCost	£3,890	£3,677	%Male	£13,899	£13,047	FatalStrokeCost	£3,890	£3,677
CRNMBRiskApixaban	£2,977	£2,845	MIRiskApixaban	£3,836	£3,625	CRNMBRiskApixaban	£13,901	£13,104	MIRiskApixaban	£3,836	£3,625
MI_HRComparator	£2,953	£2,830	MildStrokeFUCost	£3,833	£3,632	CFR_MI_females	£13,820	£13,034	MildStrokeFUCost	£3,833	£3,632
CRNMBCost	£2,962	£2,840	CRNMB_RiskASA2nd	£3,817	£3,625	HR_DeathSE	£13,684	£12,923	CRNMB_RiskASA2nd	£3,817	£3,625

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
ICHRiskApixaban	£2,960	£2,857	CRNMBCost	£3,823	£3,634	ASA_Utility	£13,831	£13,098	CRNMBCost	£3,823	£3,634
ModerateStrokeUtility	£2,954	£2,856	CFRHemStrokeComparator	£3,829	£3,641	%GIBleedApixaban	£13,753	£13,127	CFRHemStrokeComparator	£3,829	£3,641
MildStrokeUtility	£2,951	£2,853	OMBRiskApixaban	£3,837	£3,649	CFR_MI_males	£13,741	£13,116	OMBRiskApixaban	£3,837	£3,649
WarfarinUtility	£2,950	£2,858	SEFUCost	£3,814	£3,650	SevereHemStrokeFUCost	£13,809	£13,189	SEFUCost	£3,814	£3,650
%GIBleedApixaban	£2,947	£2,856	OMB_RiskASA2nd	£3,804	£3,642	CFRStrokeComparator	£13,744	£13,202	OMB_RiskASA2nd	£3,804	£3,642
StrokeRecurrentRate	£2,941	£2,861	MI_Utility	£3,807	£3,658	ICHRiskAdjustment	£13,727	£13,196	MI_Utility	£3,807	£3,658
HR_DeathMildStroke	£2,926	£2,853	SERiskApixaban	£3,814	£3,668	WarfarinUtility	£13,723	£13,196	SERiskApixaban	£3,814	£3,668
HR_DeathSevereStroke	£2,932	£2,868	HR_DeathMI_females	£3,808	£3,665	HR_DeathMildStroke	£13,629	£13,123	HR_DeathMI_females	£3,808	£3,665
CVRiskApixaban	£2,938	£2,877	MonitoringVisitCost	£3,820	£3,691	OMB_RiskASA2nd	£13,664	£13,191	MonitoringVisitCost	£3,820	£3,691
SEAcuteCost	£2,934	£2,873	%Male	£3,797	£3,671	CRNMB_RiskASA2nd	£13,647	£13,210	%Male	£3,797	£3,671

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
CVCost	£2,933	£2,872	MildHemStrokeAcuteCost	£3,793	£3,671	SERiskApixaban	£13,685	£13,275	MildHemStrokeAcuteCost	£3,793	£3,671
FatalStrokeCost	£2,941	£2,890	MildStrokeAcuteCost	£3,793	£3,672	HR_DeathMildHemStroke	£13,701	£13,295	MildStrokeAcuteCost	£3,793	£3,672
SevereHemStrokeAcuteCost	£2,928	£2,878	%GIBleedComparator	£3,791	£3,675	SEFUCost	£13,641	£13,268	%GIBleedComparator	£3,791	£3,675
%GIBleedComparator	£2,929	£2,880	MIAcuteCost	£3,790	£3,675	CFR_ICH_Apixaban	£13,671	£13,328	MIAcuteCost	£3,790	£3,675
AFtrialRateApixaban	£2,924	£2,881	MildHemStrokeFUCost	£3,789	£3,676	CRNMBCost	£13,610	£13,288	MildHemStrokeFUCost	£3,789	£3,676
CFR_ICH_Comparator	£2,927	£2,888	ICHRiskAdjustment	£3,790	£3,677	MonitoringVisitCost	£13,651	£13,361	ICHRiskAdjustment	£3,790	£3,677
%SwitchTmT_GI_Apixaban	£2,915	£2,881	HR_DeathMI_males	£3,790	£3,679	%SwitchTmT_GI_Comparator	£13,556	£13,275	HR_DeathMI_males	£3,790	£3,679
HR_DeathSE	£2,926	£2,894	HR_DeathSevereHemStroke	£3,802	£3,694	MildStrokeFUCost	£13,594	£13,315	HR_DeathSevereHemStroke	£3,802	£3,694
SE_Utility	£2,917	£2,889	%SwitchTmT_GI_Apixaban	£3,770	£3,663	FatalStrokeCost	£13,657	£13,383	%SwitchTmT_GI_Apixaban	£3,770	£3,663

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
GICost	£2,914	£2,894	%SwitchTmT_GI_Comparator	£3,795	£3,697	SevereStrokeFUCost	£13,607	£13,340	%SwitchTmT_GI_Comparator	£3,795	£3,697
ModHemStrokeAcuteCost	£2,913	£2,894	CFR_ICH_Apixaban	£3,789	£3,692	ModStrokeAcuteCost	£13,586	£13,323	CFR_ICH_Apixaban	£3,789	£3,692
SevereStrokeUtility	£2,914	£2,895	ASA_Utility	£3,777	£3,688	MIAcuteCost	£13,578	£13,331	ASA_Utility	£3,777	£3,688
CV_RiskASA2nd	£2,913	£2,895	CFR_MI_females	£3,772	£3,685	MildStrokeUtility	£13,581	£13,340	CFR_MI_females	£3,772	£3,685
OMBRiskAdjustment	£2,912	£2,895	OMB_Cost	£3,773	£3,694	%GIBleedComparator	£13,558	£13,351	OMB_Cost	£3,773	£3,694
SevereHemStrokeFUCost	£2,912	£2,897	ModerateStrokeUtility	£3,772	£3,694	SE_Utility	£13,556	£13,351	ModerateStrokeUtility	£3,772	£3,694
CFR_ICH_Apixaban	£2,908	£2,894	CFR_OMB_Apixaban	£3,776	£3,699	CVCost	£13,558	£13,353	CFR_OMB_Apixaban	£3,776	£3,699
ICHRiskAdjustment	£2,910	£2,896	CFR_OMB_Comparator	£3,766	£3,692	OMBRiskApixaban	£13,562	£13,369	CFR_OMB_Comparator	£3,766	£3,692
CFR_ICH_Apixaban	£2,911	£2,897	CFR_MI_males	£3,764	£3,694	HR_DeathSevereHemStroke	£13,578	£13,386	CFR_MI_males	£3,764	£3,694
CRNMBRiskAdjustment	£2,910	£2,897	WarfarinUtility	£3,765	£3,700	MildHemStrokeAcuteCost	£13,546	£13,363	WarfarinUtility	£3,765	£3,700

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
CFR_ICH_Comparator	£2,908	£2,897	FatalHemStrokeCost	£3,759	£3,700	CFR_ICH_Comparator	£13,523	£13,344	FatalHemStrokeCost	£3,759	£3,700
CFR_OMB_Apixaban	£2,909	£2,899	HR_DeathMildStroke	£3,772	£3,717	MildHemStrokeFUCost	£13,540	£13,369	HR_DeathMildStroke	£3,772	£3,717
StrokeRiskASA2nd	£2,910	£2,903	SEAcuteCost	£3,758	£3,707	ModHemStrokeAcuteCost	£13,539	£13,370	SEAcuteCost	£3,758	£3,707
MI_RiskASA2nd	£2,907	£2,900	MildStrokeUtility	£3,756	£3,707	OMB_Cost	£13,532	£13,381	MildStrokeUtility	£3,756	£3,707
ModHemStrokeFUCost	£2,906	£2,900	CRNMBRiskAdjustment	£3,757	£3,709	MildHemStrokeUtility	£13,526	£13,378	CRNMBRiskAdjustment	£3,757	£3,709
HR_DeathSevereHemStroke	£2,907	£2,901	ManagCostComparator	£3,753	£3,706	%SwitchTmT_GI_Apixaban	£13,550	£13,405	ManagCostComparator	£3,753	£3,706
MIAcuteCost	£2,906	£2,900	CFR_ICH_Comparator	£3,752	£3,707	GICost	£13,515	£13,382	CFR_ICH_Comparator	£3,752	£3,707
FatalHemStrokeCost	£2,906	£2,900	OtherICHCost	£3,757	£3,714	MildStrokeAcuteCost	£13,517	£13,392	OtherICHCost	£3,757	£3,714
HR_DeathModHemStroke	£2,906	£2,901	MI_FUCost	£3,750	£3,709	ModStrokeFUCost	£13,514	£13,395	MI_FUCost	£3,750	£3,709
ManagCostApixa	£2,906	£2,901	StrokeRec	£3,751	£3,711	SEAcuteC	£13,514	£13,395	StrokeRecurrentRate	£3,751	£3,711

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
ban			urrentRate			ost					
OtherICHCost	£2,906	£2,901	TmtDiscRiskApixaban	£3,633	£3,593	FatalHemStrokeCost	£13,501	£13,397	TmtDiscRiskApixaban	£3,633	£3,593
CFR_OMB_Comparator	£2,905	£2,901	CVCost	£3,751	£3,713	CRNMBRiskAdjustment	£13,502	£13,408	CVCost	£3,751	£3,713
%SwitchTmT_ICH_Apixaban	£2,905	£2,901	CFR_ICH_Apixaban	£3,745	£3,712	MI_FUCost	£13,493	£13,406	CFR_ICH_Apixaban	£3,745	£3,712
ManagCostComparator	£2,905	£2,901	OMBRiskAdjustment	£3,749	£3,716	SevereStrokeAcuteCost	£13,494	£13,415	OMBRiskAdjustment	£3,749	£3,716
HR_DeathMI_females	£2,905	£2,901	MildHemStrokeUtility	£3,745	£3,718	ModHemStrokeFUCost	£13,492	£13,417	MildHemStrokeUtility	£3,745	£3,718
CRNMB_RiskASA2nd	£2,905	£2,902	HemStroke Recurrent Rate	£3,743	£3,717	ManagCostComparator	£13,487	£13,412	HemStrokeRecurrent Rate	£3,743	£3,717
MildHemStrokeAcuteCost	£2,904	£2,902	SE_Utility	£3,745	£3,720	OMBRiskAdjustment	£13,493	£13,418	SE_Utility	£3,745	£3,720
OMB_RiskASA2nd	£2,904	£2,902	GICost	£3,743	£3,719	HemStroke Recurrent Rate	£13,485	£13,413	GICost	£3,743	£3,719
MI_Utility	£2,904	£2,902	HR_Death SevereStro	£3,742	£3,720	HR_Death ModStroke	£13,499	£13,427	HR_DeathSevereStroke	£3,742	£3,720

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
			ke								
HR_DeathMI_males	£2,904	£2,902	CFR_ICH_Comparator	£3,745	£3,725	SevereHemStrokeUtility	£13,483	£13,418	CFR_ICH_Comparator	£3,745	£3,725
ICH_RiskASA2nd	£2,904	£2,902	ModHemStrokeAcuteCost	£3,742	£3,722	ModerateStrokeUtility	£13,479	£13,431	ModHemStrokeAcuteCost	£3,742	£3,722
MildHemStrokeFUCost	£2,904	£2,902	ModHemStrokeFUCost	£3,741	£3,723	StrokeRecurrentRate	£13,478	£13,433	ModHemStrokeFUCost	£3,741	£3,723
OMB_Utility	£2,904	£2,903	HR_DeathSE	£3,737	£3,720	ManagCostApixaban	£13,473	£13,440	HR_DeathSE	£3,737	£3,720
HemStrokeRecurrentRate	£2,904	£2,903	ManagCostApixaban	£3,742	£3,725	ModerateHemStrokeUtility	£13,469	£13,439	ManagCostApixaban	£3,742	£3,725
MIRiskApixaban	£2,904	£2,902	%SwitchTmT_ICH_Apixaban	£3,739	£3,725	%SwitchTmT_ICH_Comparator	£13,470	£13,440	%SwitchTmT_ICH_Apixaban	£3,739	£3,725
ASA_Utility	£2,904	£2,903	HR_DeathModHemStroke	£3,736	£3,727	SevereStrokeUtility	£13,467	£13,439	HR_DeathModHemStroke	£3,736	£3,727
MI_FUCost	£2,904	£2,903	SevereHemStrokeUtility	£3,736	£3,727	AFtrialRateApixaban	£13,467	£13,443	SevereHemStrokeUtility	£3,736	£3,727
ModerateHemStr	£2,903	£2,903	SevereStro	£3,737	£3,729	%SwitchT	£13,466	£13,442	SevereStrokeUtility	£3,737	£3,729

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
okeUtility			keUtility			mT_ICH_Apixaban					
CFR_MI_females	£2,903	£2,903	%SwitchTmT_ICH_Comparator	£3,735	£3,730	HR_DeathSevereStroke	£13,467	£13,444	%SwitchTmT_ICH_Comparator	£3,735	£3,730
HR_DeathMildHemStroke	£2,903	£2,903	ModerateHemStrokeUtility	£3,733	£3,731	CFRHemStrokeComparator	£13,462	£13,447	ModerateHemStroke Utility	£3,733	£3,731
SevereHemStrokeUtility	£2,903	£2,903	AFtrialRate Apixaban	£3,733	£3,731	OMB_Utility	£13,458	£13,449	AFtrialRateApixaban	£3,733	£3,731
CFR_MI_males	£2,903	£2,903	OtherICHUtility	£3,733	£3,731	OtherICHCost	£13,457	£13,452	OtherICHUtility	£3,733	£3,731
MildHemStrokeUtility	£2,903	£2,903	HR_Death MildHemStroke	£3,733	£3,732	HR_Death ModHemStroke	£13,456	£13,452	HR_DeathMildHemStroke	£3,733	£3,732
CV_Utility	£2,903	£2,903	CRNMB_Utility	£3,732	£3,732	CV_Utility	£13,456	£13,452	CRNMB_Utility	£3,732	£3,732
OtherICHUtility	£2,903	£2,903	CV_Utility	£3,732	£3,732	CRNMB_Utility	£13,455	£13,454	CV_Utility	£3,732	£3,732
CRNMB_Utility	£2,903	£2,903	OMB_Utility	£3,732	£3,732	OtherICHUtility	£13,455	£13,454	OMB_Utility	£3,732	£3,732
StrokeRisk Aspirin	£2,903	£2,903	StrokeRisk Aspirin	£3,732	£3,732	StrokeRisk Aspirin	£13,454	£13,454	StrokeRisk Aspirin	£3,732	£3,732
ICHRisk Aspirin	£2,903	£2,903	ICHRisk Aspirin	£3,732	£3,732	ICHRisk Aspirin	£13,454	£13,454	ICHRisk Aspirin	£3,732	£3,732

Aspirin			Dabigatran 110mg			Dabigatran 110mg & 150mg			Rivaroxaban		
Variable	ICER		Variable			Variable			Variable		
	High value	Low value		High value	Low value		High value	Low value		High value	Low value
OMBRisk Aspirin	£2,903	£2,903	OMBRisk Aspirin	£3,732	£3,732	OMBRisk Aspirin	£13,454	£13,454	OMBRisk Aspirin	£3,732	£3,732
CRNMBRisk Aspirin	£2,903	£2,903	CRNMBRisk Aspirin	£3,732	£3,732	CRNMBRisk Aspirin	£13,454	£13,454	CRNMBRisk Aspirin	£3,732	£3,732
%SwitchTmT_ICH_Comparator	£2,914	£2,914	MIRisk Aspirin	£3,732	£3,732	MIRisk Aspirin	£13,454	£13,454	MIRisk Aspirin	£3,732	£3,732
%SwitchTmT_GI_Comparator	£2,920	£2,920	CVRisk Aspirin	£3,732	£3,732	CVRisk Aspirin	£13,454	£13,454	CVRisk Aspirin	£3,732	£3,732
MIRisk Aspirin	£2,903	£2,903	TmtDiscRisk Aspirin	£3,732	£3,732	TmtDiscRisk Aspirin	£13,454	£13,454	TmtDiscRisk Aspirin	£3,732	£3,732
CVRisk Aspirin	£2,903	£2,903	CFRStrokeASA2nd	£3,732	£3,732	CFRStrokeASA2nd	£13,454	£13,454	CFRStrokeASA2nd	£3,732	£3,732
TmtDiscRisk Aspirin	£2,903	£2,903	CV_HRComparator	£3,732	£3,732	CV_HRComparator	£13,454	£13,454	CV_HRComparator	£3,732	£3,732
CFRStrokeASA2nd	£2,903	£2,903	CRNMB_HRComparator	£3,732	£3,732	CRNMB_HRComparator	£13,454	£13,454	CRNMB_HRComparator	£3,732	£3,732
SERisk Aspirin	£2,903	£2,903	SERisk Aspirin	£3,732	£3,732	SERisk Aspirin	£13,454	£13,454	SERisk Aspirin	£3,732	£3,732
AFtrialRateOther	£2,903	£2,903	AFtrialRateOther	£3,732	£3,732	AFtrialRateOther	£13,454	£13,454	AFtrialRateOther	£3,732	£3,732

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the

specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of

any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).