Bayer plc response to the Appraisal Consultation Document

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

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Executive Summary

The Appraisal Committee recognised that rivaroxaban offers potential benefits as an alternative to warfarin for people with atrial fibrillation but requested additional analyses which Bayer have provided below.

These analyses have been conducted on the licensed population and two sub groups presented in the manufacturer's original submission:

- Those patients who are currently poorly controlled on warfarin
- Those patients for whom warfarin is not suitable:
    - Those patients who have discontinued warfarin for reasons other than bleeding complications and currently receive aspirin
    - Those patients who have never been initiated on warfarin due to concerns about suitability

Bayer can accept the first three recommendations of the Appraisal Committee and these have been reflected in an updated model:

A. The characteristics of the cohort in the model should represent people with atrial fibrillation in the UK

B. Clinical effectiveness data from the safety on treatment (SOT) population of the ROCKET AF study should be used considering all point estimates

C. The effect of low TTR on warfarin in the ROCKET AF study should be accounted for

However, Bayer believes that the final recommendation **(D)** of incorporating a fixed annual warfarin INR monitoring cost of £242 per person is not warranted.

Furthermore, as outlined in section 4.2 and page 26 of the ACD, the Appraisal Committee acknowledge a drop in health related quality of life for those on warfarin – for example "anxiety about the difficulty of keeping the INR within the satisfactory therapeutic range". This was not previously reflected in the modelling but has now been incorporated by applying the reported disutility figures for a GP led clinic and a hospital led clinic[1] and weighting these by the UK distribution of primary and secondary care anticoagulation management[2].

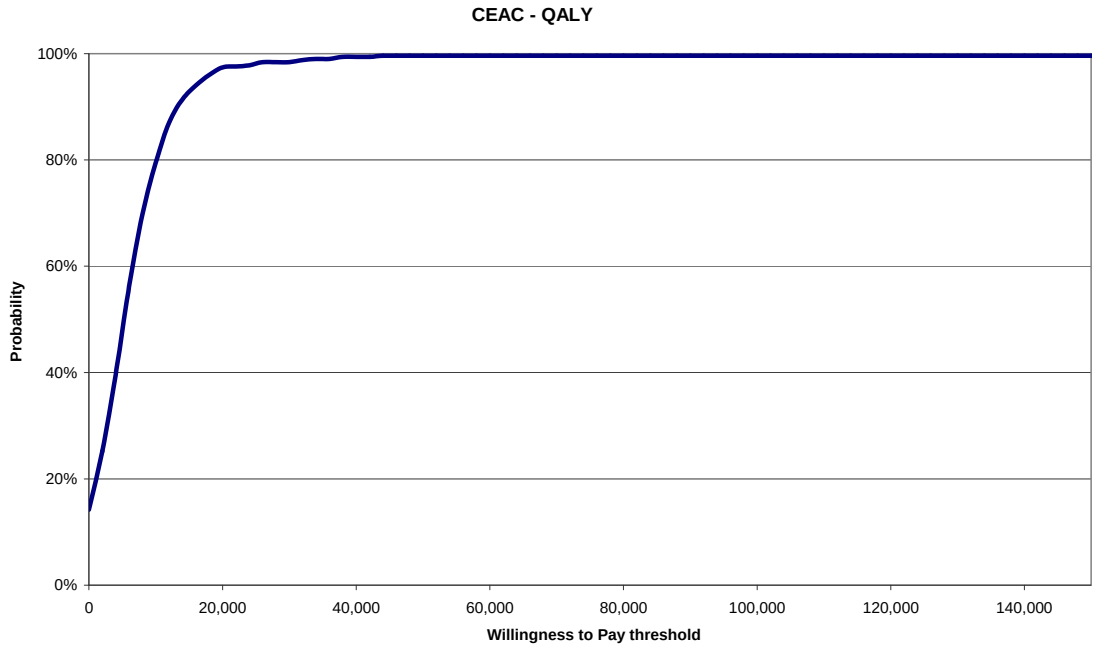
Results of analyses applying Appraisal Committee recommendations (A-C)

Applying recommendations **A-C** (where for C, an adjustment is made using the results for Western Europe), and taking account of the disutility associated with warfarin, gives the following ICERs:

Licensed population

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£6,210	9.3529	6.9953				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£705	0.0821	0.2459	£2,869

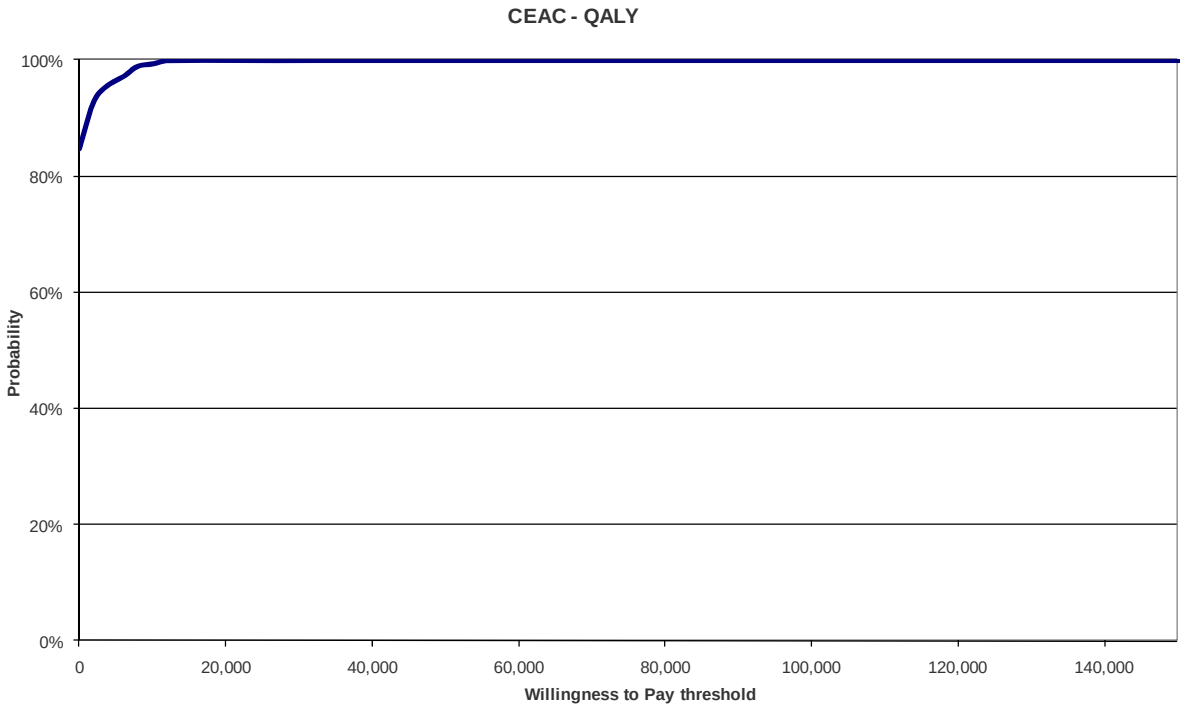
The probability of being cost effective in this population at a threshold of £20k is 97%



Patients poorly controlled on warfarin

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412				
Warfarin based on the ROCKET AF trial SoT data	£8,377	9.3472	6.9865	£1,461	-0.0877	-0.2547	Rivaroxaban dominates

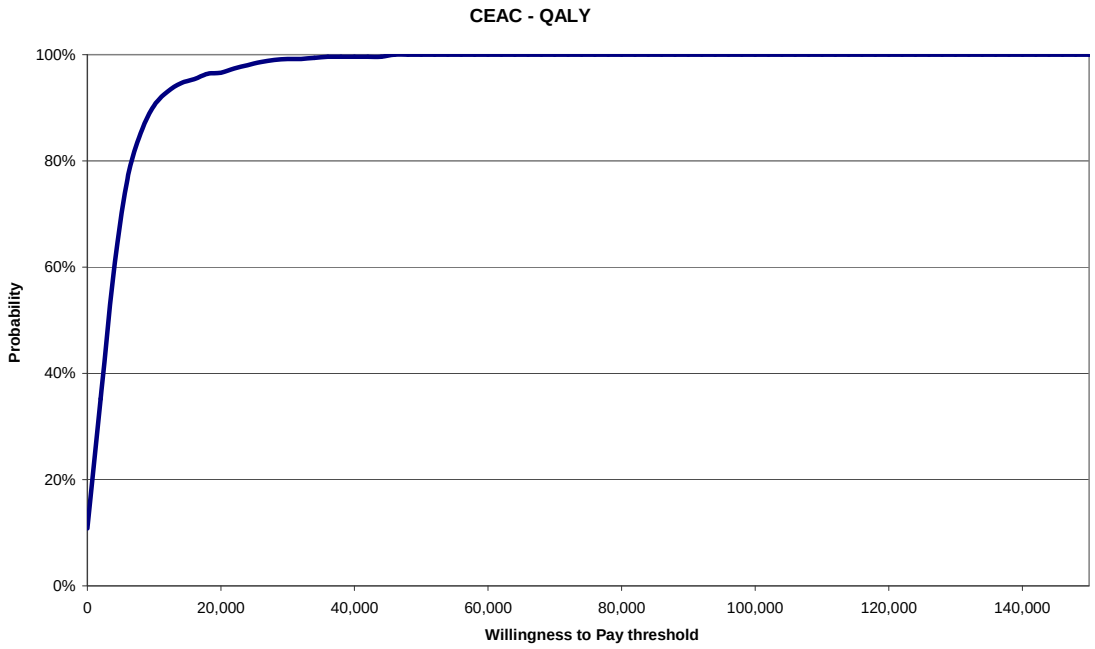
The probability of being cost effective in this population at a threshold of £20k is 100%



Warfarin "unsuitable"

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aspirin based on the IDC	£4,371	9.0662	6.8784				
Rivaroxaban based on the IDC	£7,092	9.3540	7.1751	£2,722	0.2878	0.2968	£9,170

The probability of being cost effective in this population at a threshold of £20k is 97%.



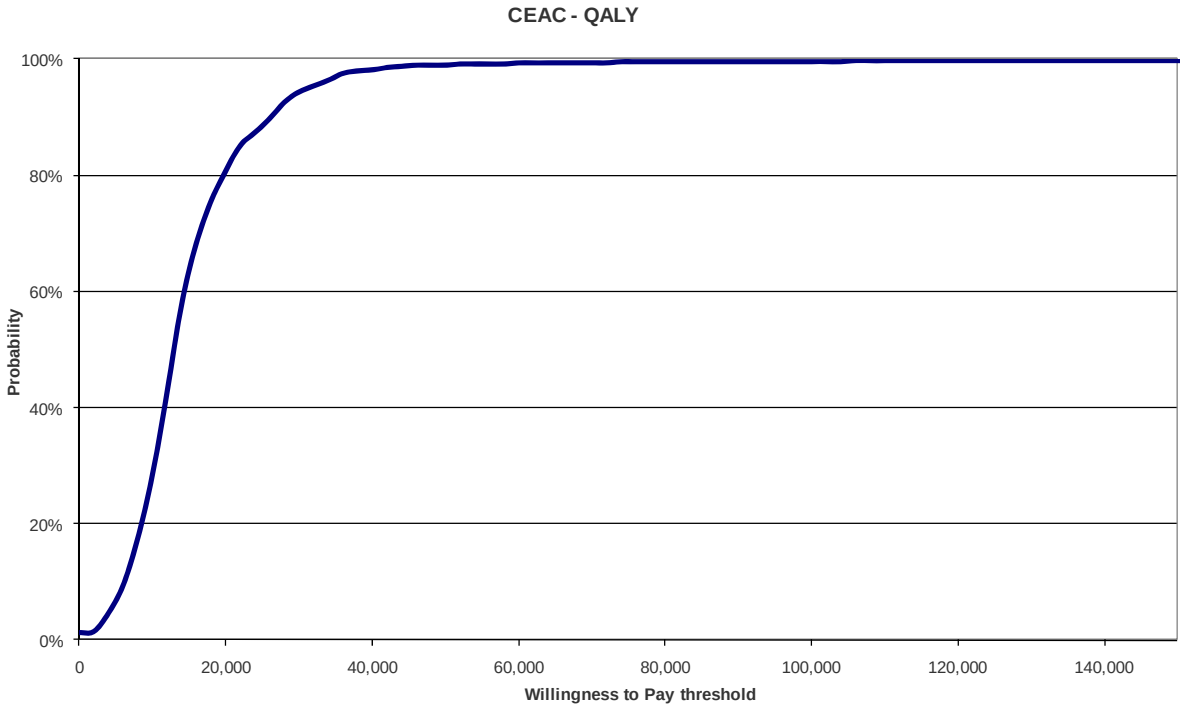
Results of analyses applying Appraisal Committee recommendations (A-D)

Even applying the final recommendation **(D)** of incorporating a fixed annual warfarin INR monitoring cost of £242 per person, the ICERs fall below the £20k threshold.

Licensed population

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£4,695	9.3529	6.9953				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£2,220	0.0821	0.2459	£9,031

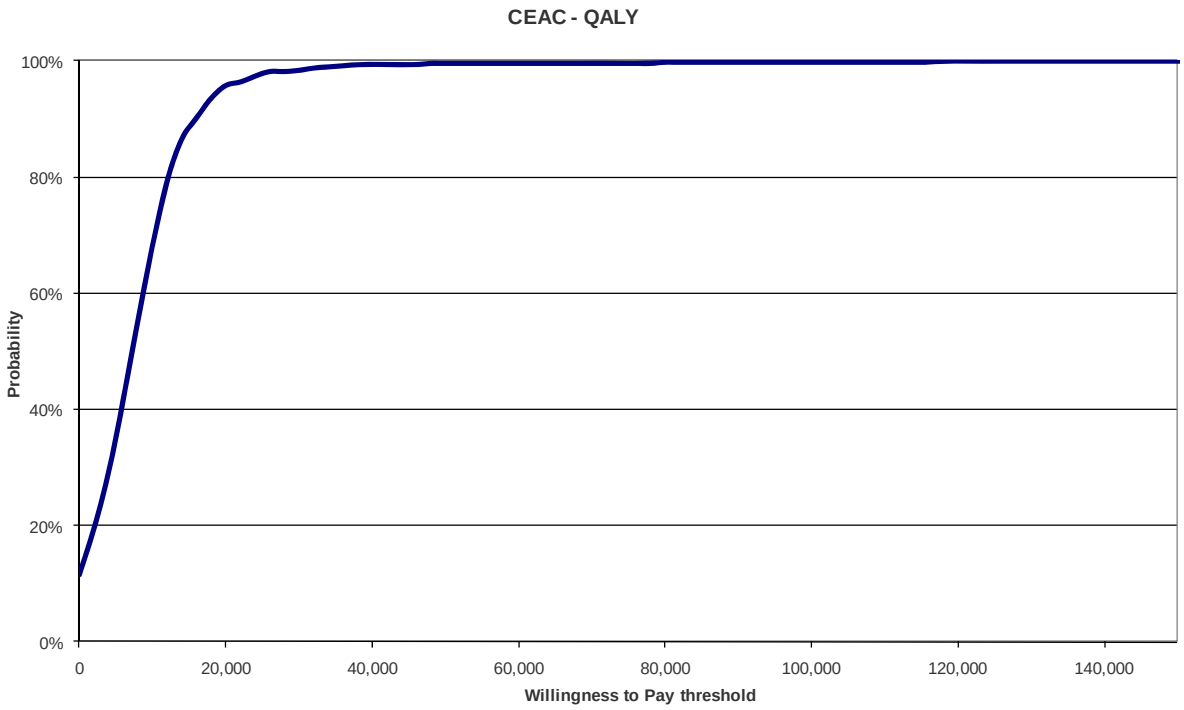
The probability of being cost effective in this population at a threshold of £20k is 81%



Patients poorly controlled on warfarin

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£5,808	9.3472	6.9865				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£1,108	0.0877	0.2547	£4,350

The probability of being cost effective in this population at a threshold of £20k is 96%



As highlighted in section 4.2 of the ACD, the Committee recognised that rivaroxaban offers potential benefits as an alternative to warfarin for people with atrial fibrillation. The limitations of warfarin, many of which do not apply to rivaroxaban, make it an appropriate choice for all those within the licenced indication but it's benefits are further enhanced in those who have difficulty in using warfarin. Such patients can be poorly controlled on warfarin or may be prescribed aspirin as an alternative.

Current standard of care

Warfarin is the current standard of care for prevention of stroke and systemic embolism in atrial fibrillation. It is however associated with a number of limitations.

Limitations of warfarin

Warfarin has a number of well documented limitations, which can lead to poor control or reluctance to prescribe including:

- A narrow therapeutic index with a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage
- The requirement for dose adjustment using frequent, inconvenient and costly INR monitoring. The frequency of monitoring varies depending on individual patient characteristics.
- Response that is influenced by diet, concomitant medications, herbal supplements and intercurrent illness

The need for individualised patient dosing and adjustment, often requires warfarin to be supplied in a number of different tablet strengths (0.5mg, 1mg, 3mg, 5mg). This may increase the risk of accidental under or overdose, so requires significant patient education as well as good communication between health professionals and patients. Each time the patient is out of therapeutic range, the healthcare professional needs to counsel them about the change in tablet or combination of tablets that they need to take. Sometimes they will also need to change from daily dosing to alternate day dosing. So, for example, they may be familiar with taking one blue tablet and one brown tablet on a daily basis and then have to take one pink tablet every other day. Alternate day dosing may increase risk of error.

It is therefore perhaps not surprising that warfarin is listed as one of the drugs commonly associated with preventable harm in general practice[3]. In a UK study[4], warfarin is ranked number

three on a list of drugs most commonly associated with hospital admissions due to adverse drug reactions. A recent paper from the US[5] reported that nearly all hospitalisation involving warfarin resulted from unintentional overdosages.

The NPSA was informed of 480 reported cases of patient harm from the use of anticoagulants in the UK up to the end of 2002. In addition, there were 120 deaths reported, of which 77% (92 reports) were related to warfarin use. The main causes for these fatal incidents were[6]:

- Inadequate laboratory monitoring
- Clinically significant drug interactions usually involving non-steroidal anti-inflammatories.

Concern about these issues may lead to under treatment in those eligible for anticoagulation. For those prescribed warfarin, associated limitations may put certain groups in society at particular risk of adverse outcomes (See Appendix IV).

Patients at particular risk of adverse outcomes include patients who:

- Are elderly (*factors such as: forgetfulness, vision, speech, hearing impairment*)
- Have difficulties with mobility (*regarding attendance for INR monitoring*)
- Have several co-morbidities and polypharmacy *(multiple interactions with warfarin)*
- Suffer with dementia
- English is not the first language or where there is poor understanding of English
- Have low literacy and numeracy skills
- Have an erratic lifestyle and/or mental illness

Populations who may gain particular benefit from rivaroxaban

As rivaroxaban is not associated with such limitations, it has additional advantages and is an effective alternative in those people currently poorly controlled on warfarin or in those for who clinicians are reluctant to prescribe warfarin. Therefore in addition to the licensed population, Bayer has conducted analysis in:

- **Those patients who are currently poorly controlled on warfarin**
- **Those patients considered to be unsuitable for warfarin:**
  - Those patients who have discontinued warfarin for reasons other than bleeding complications and currently receive aspirin. Reasons for discontinuation include:
    - Intolerance or hypersensitivity
    - Not being able to achieve suitable INR control
    - Diet or alcohol limitations
    - Multiple changes in prescribed medication
  - Those patients who have never been initiated on warfarin due to concerns about suitability:
    - The patient would be unable to maintain compliance or cope with variable dose adjustments in warfarin tablet taking due to confusion or failing memory

- There is an inability to manage regular INR monitoring due to factors such as poor mobility, the patient being housebound or having dementia / cognitive impairment
- The patient has all of his / her medication supplied in a monitored dosage system and the system may be unable to cope with variable dose adjustments to warfarin determined by INR monitoring
- Warfarin is unsuitable for other reasons including lifestyle factors

Patients poorly controlled on warfarin

The Committee heard that a substantial proportion of people taking warfarin have poorly controlled INR and are often not within the target therapeutic range at any one time. As warfarin has a narrow therapeutic index there is a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage. A recent systematic review and meta-analysis reported that the risk of thromboemboli increased significantly at ratios less than 2, and the risk of haemorrhage increased significantly at high international normalised ratios[7].

A UK paper[8] referenced in the costing report to NICE CG36[9], highlighted that patients in the studied population had INR tests 23 times a year on average, with 13.3% having weekly visits (52 per year) and 12.7% having bi-weekly (26 visits per year). This group of patients may be considered "poorly controlled on warfarin" or high resource users.

The Committee also heard that older people with atrial fibrillation are more likely to have poorly controlled INR due to medication taken for co-morbidities and the resulting drug interactions with warfarin.

A UK paper by Yousef et al[10] supports this observation by reporting that the number of INR tests increased significantly with age in patients with AF. Correspondingly, the interval between tests shortened significantly with increasing age, such that those aged <65 years had an average of 17.4 tests per year and those >75 years had 45.7 visits per year.

The paper by Jones et al[8], reported that on average, the patients in the quartile with worst control were out of target range for 71.6% of the time.

The proportion of patients that fall in to the category of "not well controlled on warfarin" and the associated number of visits presented in the manufacturer's submission, were determined from a Real World Evaluation in a UK anticoagulation clinic[11].

Patients considered "warfarin unsuitable"

Those patients currently considered to be warfarin unsuitable are prescribed aspirin. Aspirin was listed as a comparator "in people for whom warfarin is unsuitable" in the decision problem for this appraisal. A comparison between rivaroxaban and aspirin was conducted as part of the NMA submitted as part of Bayer's original submission. The Appraisal Committee felt that the results of the NMA were too uncertain and therefore, in order to reduce the uncertainty, Bayer have conducted an additional indirect comparison (see **Appendix II**). This analysis considers only studies comparing rivaroxaban with warfarin (the ROCKET-AF study) and studies comparing

warfarin with aspirin (seven studies). The studies were identified during a systematic review of the literature to support the submitted NMA.

By excluding studies including other regimens, heterogeneity is substantially reduced. No significant heterogeneity was found in the meta-analysis of studies comparing warfarin with aspirin when considering the following endpoints:

- Total stroke
- Ischaemic stroke
- Haemorrhagic stroke
- MI
- Cardiovascular death
- All cause death
- Intracranial bleed
- Systemic embolism

Significant heterogeneity (P<0.05) was found only for two endpoints: major bleeding and extracranial bleeding. When significant heterogeneity is detected this can be accommodated using a random effects meta-analysis.

					Random effects							
	ROCKET				**ASA Trials**				**Indirect comparison**			
Safety	RR	95% confidence interval			RR	95% confidence interval			RR	95% confidence interval		
Total stroke	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Ischaemic stroke	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Haem' stroke	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
MI	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
CV death	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Death	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Major bleed	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Extracranial bleed	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Intracranial bleed	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Systemic embolism	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
ITT												
Total stroke	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Ischaemic stroke	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Haem' stroke	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
MI	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
CV death	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Death	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Systemic embolism	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	

The meta-analysis by Hart and colleagues[12], found that warfarin was associated with an approximate 40% relative risk reduction in strokes compared to aspirin. The results of the indirect comparison also demonstrate a similar benefit of rivaroxaban compared with aspirin.

This indirect comparison has been used in the economic modelling, the results of which can be found on page 18.

Additional analyses requested by the Appraisal Committee

The Appraisal Committee has requested that Bayer conduct further analyses which are detailed below for the licensed population and two sub groups; poorly controlled on warfarin and warfarin "unsuitable", presented in Bayer's original submission. Bayer has, in addition, responded to other points raised in the ACD, particularly in regard to the effect on health related quality of life for people taking warfarin.

Bayer can accept the first three recommendations of the Appraisal Committee and these have been reflected in an updated model:

- **A.** The characteristics of the cohort in the model should represent people with atrial fibrillation in the UK
- **B.** Clinical effectiveness data from the safety on treatment population of the ROCKET AF study should be used considering all point estimates
- **C.** The effect of low TTR on warfarin in the ROCKET AF study should be accounted for

However, Bayer believes that the final recommendation **(D)** of incorporating a fixed annual warfarin INR monitoring cost of £242 per person is not warranted.

Furthermore, as outlined in section 4.2 and page 26 of the ACD, The Appraisal Committee acknowledge a drop in health related quality of life for those on warfarin – for example "anxiety about the difficulty of keeping the INR within the satisfactory therapeutic range". This was not previously reflected in the modelling but has now been incorporated by applying the reported disutility figures for a GP led clinic and a hospital led clinic[1] and weighting these by the UK distribution of primary and secondary care anticoagulation management[2] – See **Appendix III** – Treatment related utility.

Appraisal Committee observations

A. The characteristics of the cohort in the model should represent people with atrial fibrillation in the UK.

In the revised cost-effectiveness analysis, Bayer has:

- Used data from GPRD to provide event rates according to baseline level of risk (according to the $CHADS_2$ classification system)[13]
- Used the distribution of patients with different $CHADS_2$ scores from the Gallagher 2008 paper[14]

In addition, to further represent people with AF in the UK, Bayer has used data for warfarin from GPRD to calculate a 'relative risk' for discontinuation of being in the 'real-world'. This is then also used to make an adjustment to the rivaroxaban arm. Sensitivity analysis without this adjustment can be found in Appendix I – sensitivity analysis (Tables 2,4,6,8,10).

The GPRD database and Gallagher 2008 paper are the sources recommended in the ACD.

B. The analysis should use clinical-effectiveness data from the safety-on-treatment population of the ROCKET-AF trial and use all point estimates from this trial regardless of statistical significance

In the revised cost-effectiveness analysis, Bayer have used all point estimates from the safety on treatment population regardless of statistical significance.

C. The effect of the low proportion of time in therapeutic range on warfarin in the ROCKET AF trial should be accounted for by considering subgroup analyses by country or centre.

In the revised cost-effectiveness analysis, the event rate in the warfarin arm has been revised to reflect the time in therapeutic range achieved in trial centres in Western Europe.

D. The analyses should incorporate a fixed annual warfarin INR monitoring cost of £242 per person.

Bayer has conducted this analysis. Bayer however asks the committee to consider the following points.

Rationale for using the figure of £242 per person

The rationale given for the annual monitoring cost of £242 was to ensure consistency with the appraisal of dabigatran for the prevention of stroke and systemic embolism in people with atrial fibrillation.

However, Bayer presented additional data in the appraisal of rivaroxaban that was not available to the committee at the time of the appraisal of dabigatran. Bayer considers that the Committee has failed to follow a fair process, in that additional evidence submitted was not appropriately considered.

Bayer believe that the reason given for not considering the new evidence - to ensure consistency with an unrelated decision - is not sufficient to justify the Committee's failure to appropriately consider new evidence. It is the purpose of the Appraisal Committee to consider evidence and to make recommendations. Failing to consider new evidence because it differs from a prior unrelated decision is not reasonable.

Bayer presented information and arguments regarding the costing of INR monitoring in the company's submission, and in the response to the ERG. Bayer provides additional information below.

Change to the evidence base

The primary care cost component of the £242 figure is based on the costing report to support NICE CG36. This in turn based figures for primary care on the cost elements outlined in "*a web article on setting up an anticoagulation clinic in primary care*", referenced to "INR Star", a clinical decision support software. However the basis for the amount of resource used is not identified in the NICE costing report and while the absence of this information has precluded full investigation of the issue, Bayer believe the figure is too low. Therefore there is a lack of transparency regarding the evidence base used to support this costing exercise which is unacceptable in view of the central importance of monitoring costs to the value of the ICERs in this appraisal.

Bayer however, commissioned a Real World Study which comprised of a series of local service evaluations to determine the true cost of anticoagulation services. This work, using robust methodology, found the costs in primary care to be somewhat higher than those determined on the grounds of the costing exercise cited above. The cost identified in this study for a primary care clinic was [redacted][15] .This was made up of the weighted cost of clinic visits in the GP surgery and home visits, using the conservative approach of using only staff and biochemistry costs (**See Appendix V**). This compares to the proposed variable cost for primary care of £165.67[16].

Method of determining the figure of £242 per person

In the appraisal of dabigatran, the figure of £242 was justified as it represents the variable annual cost of warfarin monitoring only, and excludes fixed costs and overheads.

It is not standard practice in costing to ignore some cost components and solely use variable costs. Refer for example to Drummond et al *"When … generalisation of cost consequence to a national level is necessary, the use of average or integral costs [as opposed to marginal costs] is recommended"*[17].

Bayer note that the methods guidance issued to ERG groups refers to Drummond, and that including only variable cost is contrary to the costing instruction NICE gives to ERG groups.

Bayer also note that the 2008 Guide to the method of technology appraisals suggests that *"A first point of reference in identifying such [NHS] costs and prices should be any current official listing published by the Department of Health and/or the Welsh Assembly Government"*. The NHS costing manual 2010-11[18] sets out the principles and practice of costing to be applied in the NHS. This manual supports the production of the National Schedule of Reference Costs and through this, the national tariff. It states that *"costing must be undertaken on a full absorption basis"* and that "*costs….. should reflect the full cost of the service delivered*".

> *Absorption costing is a method of costing a product in which **all fixed and variable costs** are apportioned to cost centres where they are accounted for using absorption rates" (www.businessdirectory.com).*

Bayer notes that including only variable cost is therefore contrary to NHS methods of costing, as recommended by NICE in the methods of technology appraisal.

Bayer note that numerous previous appraisals have used NHS reference costs without challenge. Bayer considers that the treatment of costs in this appraisal has been unfair when compared with the treatment of cost in other appraisals.

INR monitoring clinic infrastructure

The method described for costing an INR clinic assumes fixed costs will remain the same irrespective of the number of patients who attend for INR monitoring. No evidence is provided to support this view and Bayer believes that it is likely to be inaccurate. In particular, if the number of patients requiring INR monitoring decreases:

- The number of clinics and/or clinic sessions would reduce
- Efficiency within the NHS would dictate that facilities previously used solely for INR monitoring are shared and used for other NHS purposes during times when INR clinics are no longer required
- In some areas it may be possible for clinics to be merged or otherwise rationalised

In these circumstances Bayer believe it is incorrect to disregard fixed costs associated with INR monitoring when comparing resource associated with rivaroxaban and warfarin use.

Plausibility of the cost of £242 per person – all patients

The mean annual number of INR monitoring visits per patient is ≥20, based on information reported in the Anticoagulation therapy service commissioning and benchmarking tool[19] and supported by the literature[8]. The Committee is therefore asking Bayer to estimate the cost per visit to be £12.10 (£242 per year / 20 visits per year).

According to a survey of anticoagulation management by pH associates for the UK NHS in 2011[2] 34% of warfarin patients are managed in Secondary Care, and 66% in Primary Care.

The cost of an anticoagulation visit in secondary care in 2009/10 was £24.69[20].

Bayer note that the 2008 Guide to the method of technology appraisals suggests that "*A first point of reference in identifying such [NHS] costs and prices should be any current official listing published by the Department of Health and/or the Welsh Assembly Government",* and specifically mentions HRG costs. We suggest that this costing is consistent with NICE methods.

For these figures to be consistent with an average cost of £12.10 across all visits requires the cost of a visit in primary care to be £5.61 (see table below). Bayer notes that the cost of reagents to conduct an INR test is £3[19]. Hence for the annual cost of £242 to be consistent with all the evidence quoted, the average cost of a visit must be £9.10 and the cost of a primary care visit would be £2.61 (£5.61 total cost - £3 cost of reagents).

Table Average cost per anticoagulation visit: Appraisal Committee assumptions

Setting	Proportion of visits	Total cost per visit (£)	Cost of reagents per visit (£)	All non-reagent costs per visit (£)
Secondary care	34%	24.69	3.00	21.69
Primary care	66%	5.61	3.00	2.61
Weighted average		12.10		9.10

The PSSRU[21] – the standard reference source for primary care costs in UK economics evaluations – estimates the fully allocated cost of a GP surgery consultation to be £36, of a GP telephone consultation to be £22, of a nurse consultation to be £12 and of a nurse procedure to be £10.

An INR test in primary care requires that staff make an appointment, draw blood, send off the test, obtain results, calculate any dose adjustment, communicate back to the patient and prescribe any new tablets required. Bayer suggests that a cost of £2.61 for this process is implausibly low.

Bayer infers that a fully allocated cost of £12.10 per visit cannot reasonably be justified from the information presented to the Committee.

Plausibility of the cost of £242 per person – those poorly controlled on warfarin

The costing report for NICE CG 36[8;9] and the literature suggest that the average number of visits per year is ≥20. For those "poorly controlled on warfarin", the number of visits will be higher than average so the cost per visit based on £242 per patient per year becomes even less plausible.

Results of analyses applying Appraisal Committee recommendations (A-C)

Licensed population

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
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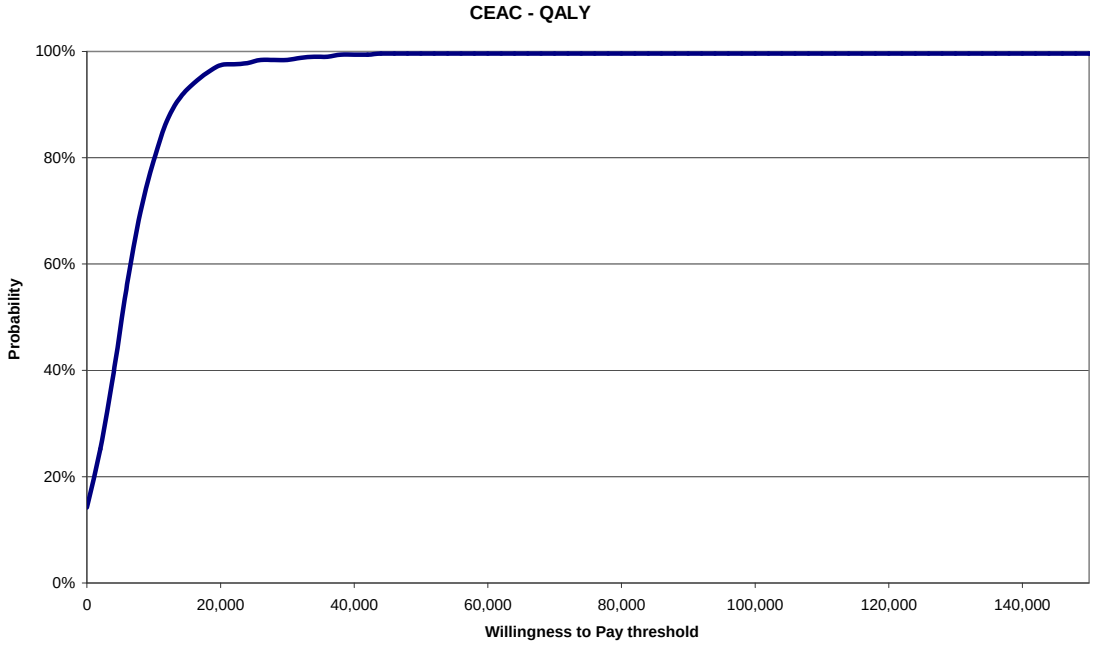
The probability of being cost effective in this population at a threshold of £20k is 97%



Patients poorly controlled on warfarin

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
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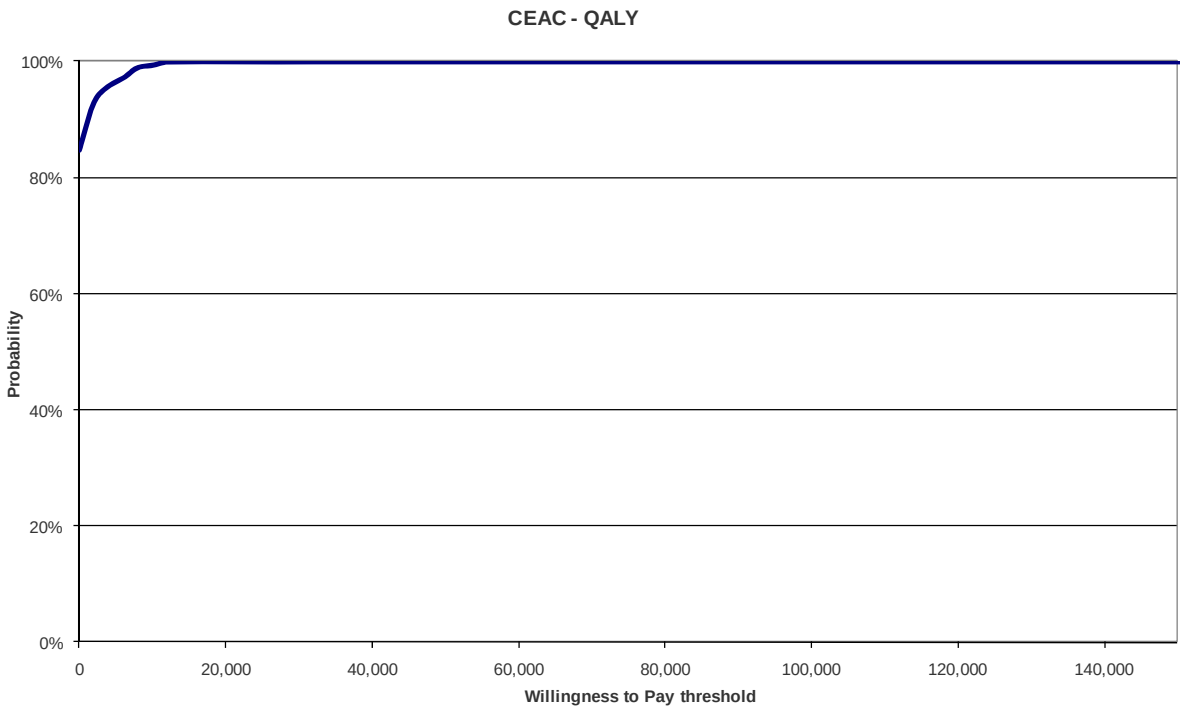
The probability of being cost effective in this population at a threshold of £20k is 100%



Warfarin unsuitable

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
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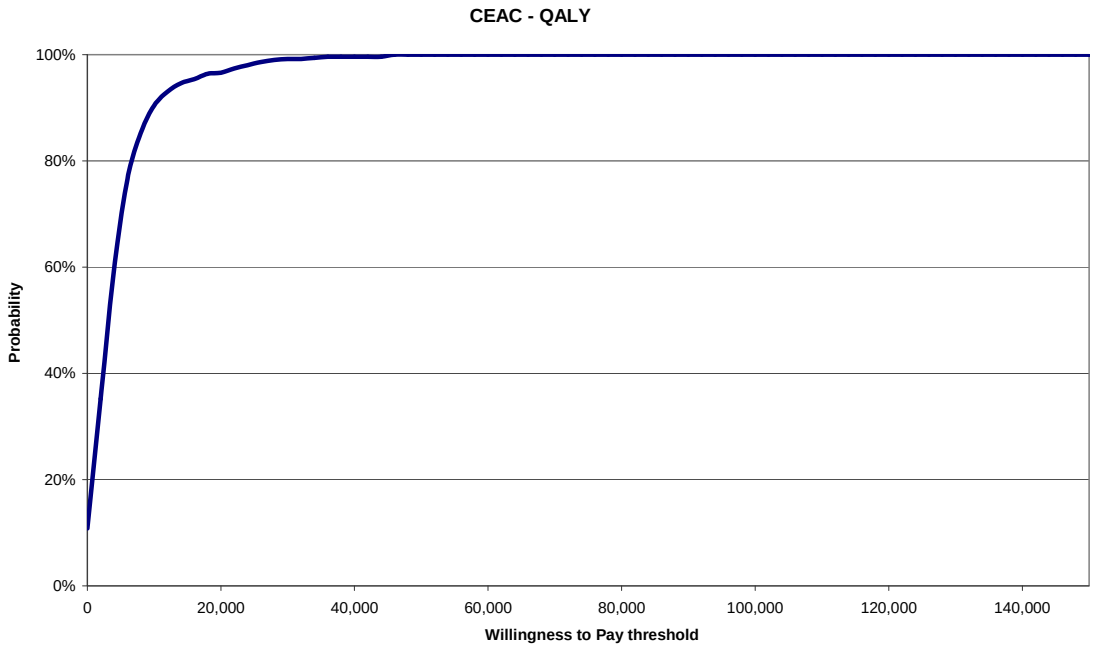
Rivaroxaban based on the IDC	£7,092	9.3540	7.1751	£2,722	0.2878	0.2968	£9,170

The probability of being cost effective in this population at a threshold of £20k is 97%.



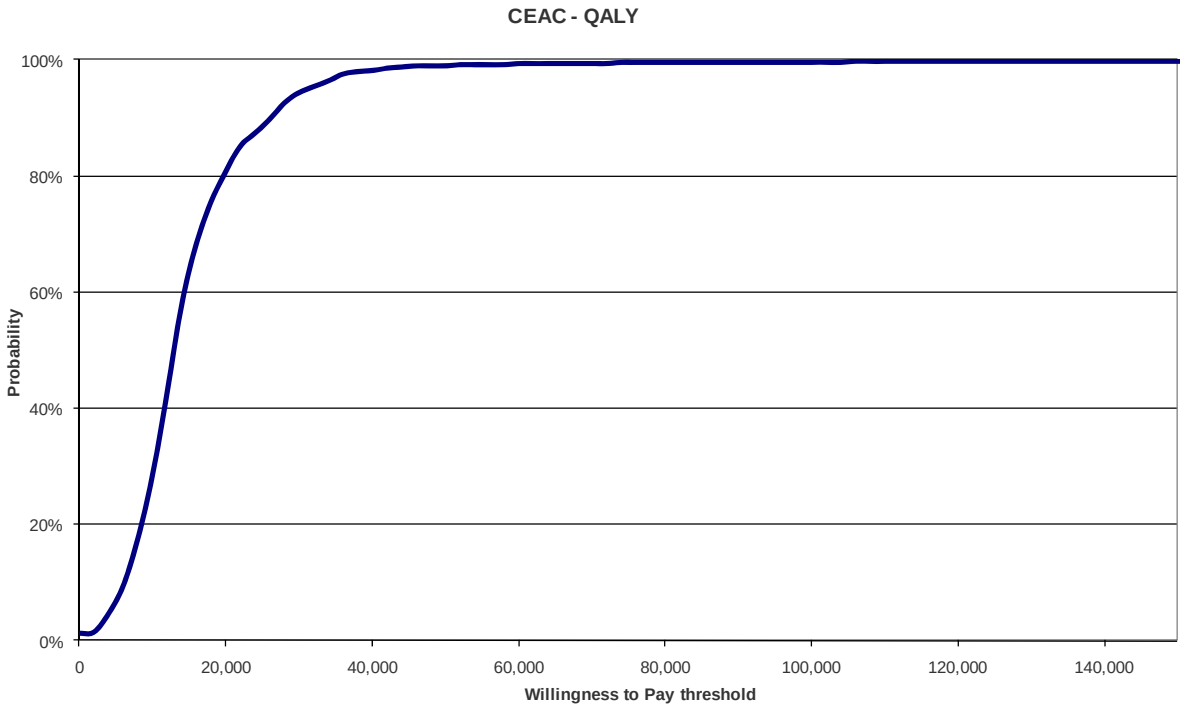
Results of analyses applying Appraisal Committee recommendations (A-D)

Even applying the final recommendation **(D)** of incorporating a fixed annual warfarin INR monitoring cost of £242 per person, the ICERs fall below the £20k threshold.

Licensed population

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£4,695	9.3529	6.9953				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£2,220	0.0821	0.2459	£9,031

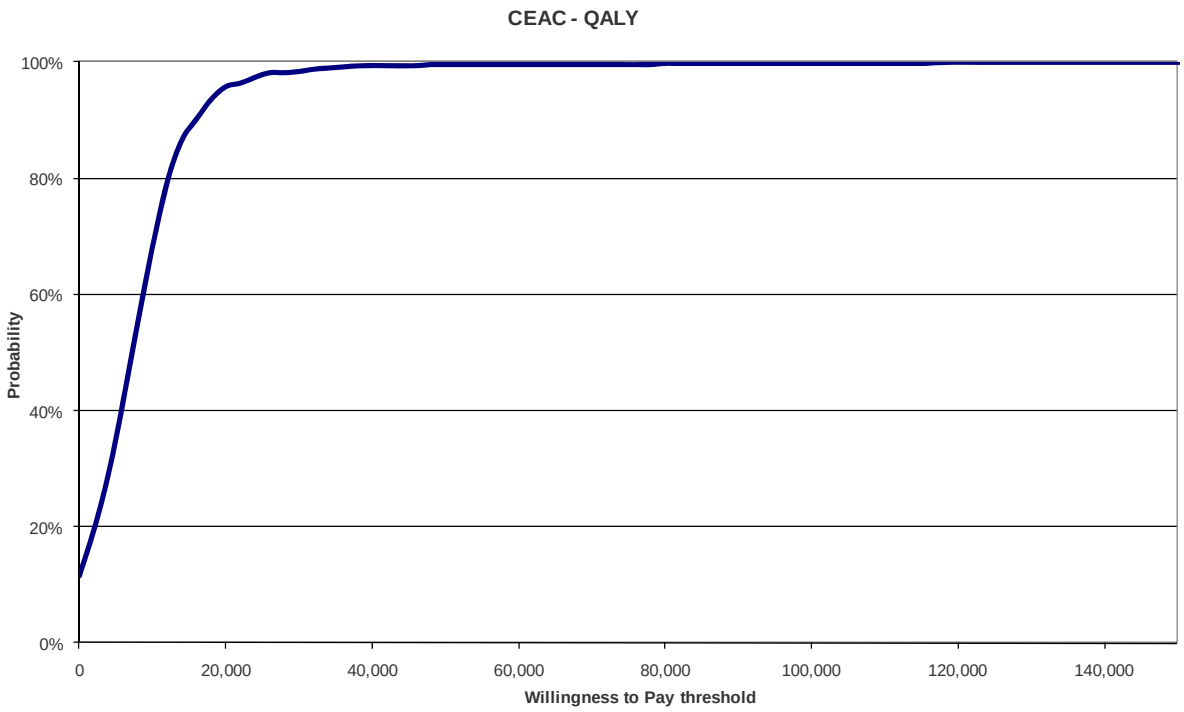
The probability of being cost effective in this population at a threshold of £20k is 81%



Patients poorly controlled on warfarin

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£5,808	9.3472	6.9865				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£1,108	0.0877	0.2547	£4,350

The probability of being cost effective in this population at a threshold of £20k is 96%



Sensitivity analyses are presented in Appendix I.

Other analyses and comments

Comparison with dabigatran

Dabigatran was identified as a comparator in the decision problem for this appraisal. The NMA conducted by the manufacturer was found to be too uncertain by the ERG and the Appraisal Committee. However, consistency with other appraisals[1] would say that a cost-minimisation analysis is most appropriate in these circumstances as there is no statistically significant difference between the interventions. If a cost-minimisation is conducted, there is extended dominance of rivaroxaban over dabigatran.

If a probabilistic approach to uncertainty is taken, this shows dabigatran to be dominant in 33.2%% of cases and rivaroxaban in 44.8% (5.6% needing evaluation and 16.4% with rivaroxaban having fewer costs and benefits). Furthermore this analysis only used the dabigatran 150mg b.d. dose.

To reflect the marketing authorisation of dabigatran, the lower dose must be used for patients older than 80. With a sequential intervention modelled for dabigatran where patients who over 80 years of age switch to the 110mg b.i.d. dose, dabigatran is dominant 26.6% of the time, and rivaroxaban is dominant 51.4% of the time (3.4% needing evaluation and 18.6% with rivaroxaban having fewer costs and benefits).

Generalisability

The Appraisal Committee made the observation that the population included in the ROCKET-AF trial did not reflect all the people with AF in the UK eligible for treatment and therefore have questioned the generalisability of the results to UK clinical practice.

Whilst the ROCKET-AF study did not include patients with $CHADS_2$ scores <2, the results show that when the results of the primary efficacy endpoint is analysed by baseline $CHADS_2$ score the interaction p value is 0.739. There is therefore no reason to expect that the results found in the ROCKET-AF trial would not translate to patients with a lower $CHADS_2$ score. Indeed, the regulators concluded that the licence issued for rivaroxaban covers a broad spectrum of risk:

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

As such, Bayer consider that the results of the ROCKET AF trial are directly applicable to the population of AF patients in England and Wales who are eligible for oral anticoagulation.

Furthermore, a systematic review of the literature found that there does not appear to be an interaction between treatment effect and baseline risk of stroke. For example, in analyses undertaken in other recent trials, such as RE-LY and ARISTOTLE, the treatment effect of the new OACS is independent of baseline $CHADS_2$ risk.

[1] For example, Technology Appraisal Numbers 61 and 138

Case fatality

In the economic model submitted to support the manufacturer's original submission, 30 day case fatality data were used. The model has been updated with 90 day case fatality rates from ROCKET AF as this is more informative and aligns directly with the length of a Markov model cycle. The revised ICERs presented now therefore include 90 day case fatality data.

The impact of taking this adjustment out in addition to the adjustment based on real world persistence (highlighted on page 12) is presented as sensitivity analysis in Appendix I – sensitivity analysis - Tables 2,4,6,8,10.

Points of accuracy/ clarification

- Section 2.1 refers to the positive opinion from the CHMP. This should be updated with the following: "On the 19th December 2011, Bayer was granted a marketing authorisation for rivaroxaban in the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. "
- Section 3.1 states "The ROCKET-AF trial was designed as a non-inferiority trial in which a blinded dose of rivaroxaban (20mg or 15mg once a day) was compared with *open-label* warfarin….". This is incorrect, ROCKET AF was a double-blind, double-dummy study.
- Section 3.8 refers to the manufacturer using the ITT analysis in the NMA in the cost effectiveness analysis. For clarity, both ITT and SoT data can be selected in the NMA; the SoT data output was used for all submitted analyses. The ERG suggested that the SOT data from ROCKET were most comparable with ITT analyses from other trials.
- Section 3.8 refers to the RE-LY study as a trial comparing dabigatran etexilate with aspirin. This is a typo – this should say dabigatran etexilate compared with warfarin.
- Section 3.9 refers to the ERG network meta-analysis. It is stated that "only comparable dosing strategies were included (that is, rivaroxaban 20mg per day, dabigatran etexilate 150mg twice a day…….) Bayer would like to challenge the validity of the comparison made by the ERG. Dabigatran is licensed in two dosages – 150mg bd and 110mg bd and any comparison with rivaroxaban should include both doses, particularly given the MA granted to dabigatran, which necessitates the use of the 110mg dose in elderly patients. For clarity, in the ROCKET AF trial, patients randomised to rivaroxaban were given 20mg once daily. For those patients randomised to rivaroxaban who had moderate renal impairment (CrCL 30-49 ml/min), they received a reduced dose of 15mg rivaroxaban daily. The results of ROCKET AF reported in Bayer's submission and in the publication are the combined results of the 15mg and 20mg doses.
- Section 3.17, 3.18, 3.19 and 3.22 – The description of "suspension of risk of events" is inaccurate. The risk of certain clinical events in the post-event states are still accounted for within the model; that is, the consequences of the event (cost and disutility) are being attributed to each arm according to the clinical data in all subsequent cycles. The patients are simply accruing these pay-offs in the post-event state rather by creating new health states to account for these events.
- Section 4.6 – appears to imply that only those patients at high risk are managed in secondary care and low risk patients are managed in primary care. This would not always be the case; treatment pathways depend on local arrangements.

APPENDIX I – Sensitivity analysis

Revised model assumptions – persistence and case fatality

The Appraisal Committee requested a number of changes to Bayer's original economic model; in particular reflecting a cohort representative of the UK, use of SoT point estimates and the effect of low TTR. The Appraisal Committee also, in paragraph 4.10 of the ACD, referred to a loss of health related quality of life for people on warfarin. Bayer's revised base case includes these amendments but, in addition, includes changes to the persistence of warfarin and rivaroxaban (see page 12) and changes to case fatality (see page 22). Bayer therefore presents below, for transparency, the results of the modelling excluding the effects of persistence and case fatality.

Table 1 - Licensed population – revised base case

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£6,210	9.3529	6.9953				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£705	0.0821	0.2459	£2,869

The probability of being cost effective in this population at a threshold of £20k is 97%

Table 2 - Licensed population – revised base case excluding changes to persistence and case fatality

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£6,331	9.3641	6.9997				
Rivaroxaban based on the ROCKET AF trial SoT data	£7,043	9.4444	7.2479	£711	0.0803	0.2482	£2,866

The probability of being cost effective in this population at a threshold of £20k is 98%

Table 3 - Patients poorly controlled on warfarin – revised base case

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412				
Warfarin based on the ROCKET AF trial SoT data	£8,377	9.3472	6.9865	£1,461	-0.0877	-0.2547	Rivaroxaban dominates

The probability of being cost effective in this population at a threshold of £20k is 100%

Table 4 - Patients poorly controlled on warfarin – revised base case excluding changes on persistence and case fatality

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Rivaroxaban based on the ROCKET AF trial SoT data	£7,043	9.4444	7.2479				
Warfarin based on the ROCKET AF trial SoT data	£8,536	9.3581	6.9905	£1,493	-0.0863	-0.2574	Rivaroxaban dominates

The probability of being cost effective in this population at a threshold of £20k is 100%

Table 5 - Warfarin "unsuitable" – revised base case

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aspirin based on the IDC	£4,371	9.0662	6.8784				
Rivaroxaban based on the IDC	£7,092	9.3540	7.1751	£2,722	0.2878	0.2968	£9,170

The probability of being cost effective in this population at a threshold of £20k is 97%.

Table 6 - Warfarin "unsuitable" – revised base case excluding changes on persistence and case fatality

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aspirin based on the IDC	£4,387	9.0802	6.8896				
Rivaroxaban based on the IDC	£7,215	9.3660	7.1841	£2,827	0.2858	0.2945	£9,601

The probability of being cost effective in this population at a threshold of £20k is 99%

Results of analyses applying Appraisal Committee recommendations (A-D)

Applying recommendations **A-D** (where for C, an adjustment is made using the results for Western Europe), and taking account of the disutility associated with warfarin, but not making any further adjustment for persistence or case fatality, gives the following ICERs:

Table 7 - Licensed population – revised base case

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£4,695	9.3529	6.9953				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£2,220	0.0821	0.2459	£9,031

The probability of being cost effective in this population at a threshold of £20k is 81%

Table 8 - Licensed population – revised base case excluding changes on persistence and case fatality

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£4,790	9.3641	6.9997				
Rivaroxaban based on the ROCKET AF trial SoT data	£7043	9.4444	7.2479	£2,252	0.0803	0.2482	£9,074

The probability of being cost effective in this population at a threshold of £20k is 81%

Table 9 - Patients poorly controlled on warfarin – revised base case

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£5,808	9.3472	6.9865				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£1,108	0.0877	0.2547	£4,350

The probability of being cost effective in this population at a threshold of £20k is 96%

Table 10 - Patients poorly controlled on warfarin – revised base case excluding changes on persistence and case fatality

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£5,922	9.3581	6.9905				
Rivaroxaban based on the ROCKET AF trial SoT data	£7,043	9.4444	7.2479	£1,121	0.0863	0.2574	£4,356

The probability of being cost effective in this population at a threshold of £20k is 98%

Sensitivity Analysis – Recommendation C - TTR

One of the analyses requested by the Appraisal Committee was to consider subgroup analyses by country or centre where the TTR was higher then in ROCKET AF. The revised base case therefore uses TTR from Western Europe (60.62%). However as the TTR for North America was higher (64.13%) than Western Europe Bayer has conducted a **sensitivity analysis** combining Western Europe and North American TTR.

Table 9 - Licensed population – revised base case but substituting WE/NA pooled TTR

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	£6,204	9.3534	6.9959				
Rivaroxaban based on the ROCKET AF trial SoT data	£6,916	9.4350	7.2412	£712	0.0815	0.2452	£2,902

The probability of being cost effective in this population at a threshold of £20k is 97%

APPENDIX II – Indirect comparison report

Attached to covering email.

APPENDIX III – Treatment related utility

The Appraisal Committee heard and considered the negative impact on health related quality of life for AF patients associated with the anxiety about the difficulty of keeping the INR within the satisfactory therapeutic range.

The disutility associated with warfarin therapy was identified as part of a systematic literature review conducted to support the manufacturer's submission. Six papers were identified that reported measurements of the disutility associated with warfarin[1;22-26].

Gage et al 1995[22] used the time trade-off method to elicit utilities in patients with AF. The mean values for aspirin and warfarin were 0.998 and 0.988, respectively.

Gage et al 1996[23] found that the utility for warfarin therapy was significantly (P<.001) lower than the utility for aspirin therapy in patients with AF, using the time trade off approach (mean value for warfarin therapy was 0.987 and that for aspirin therapy was 0.998).

Gage et al 1998[24] refers back to the study conducted by Gage et al 1996.

All three papers by Gage et al were conducted in the US.

A fourth paper, Protheroe et al[25], was based on a decision-analytic model and was not a utility value elicitation study in line with the NICE reference case.

Robinson et al (2001)[1] interviewed patients with AF in the UK using the standard gamble method and found that the mean utility value for patients on warfarin managed by a GP was 0.948 and for those managed in a hospital outpatient clinic was 0.941. This study was conducted in a UK population using standard gamble to elicit values, and was therefore deemed an appropriate source. A second paper, Thomson et al[26] was an earlier report from the same study.

The Appraisal Committee recognised the potential benefits of rivaroxaban for people with atrial fibrillation, including the positive effect on quality of life by removing the restrictions and difficulties associated with warfarin.

The original model submitted by Bayer did not consider any disutility associated with fear and anxiety related specifically to warfarin and the need for regular INR monitoring. Bayer therefore disagrees with the conclusion made in the summary table to the ACD:

"No health-related benefits were identified which were not used in the economic model".

As such, Bayer have considered disutility associated with warfarin management in the revised cost-effectiveness analysis.

APPENDIX IV – Patients at particular risk of adverse outcomes with warfarin

Concern about the limitations associated with warfarin may lead to under treatment in those eligible for anticoagulation. For those prescribed warfarin, associated limitations may put certain groups in society at particular risk of adverse outcomes. As rivaroxaban is not associated with such limitations, it has additional advantages and is an effective alternative in those people currently poorly controlled on warfarin or in those for who clinicians are reluctant to prescribe warfarin.

Characteristics associated with particular risk of adverse outcomes with warfarin

Dementia
Gallagher et al 2008[14] reported that a history of dementia reduced the likelihood of warfarin initiation.

In another paper[27], designed to assess patients knowledge of warfarin therapy, patients with dementia or cognitive impairment were excluded.

Age
Gallagher et al 2008[14] reported that elderly patients were less likely to initiate warfarin compared to younger patients.

Polypharmacy and drug interactions with warfarin
Another GPRD study[28] found that drug interactions are an independent risk factor for serious bleeding in patients on long-term warfarin therapy for stroke prophylaxis. They found that among 45 identified cases of incident idiopathic bleeds (resulting in hospitalisation within 30 days or death within 7 days) and 143 matched controls, more cases than controls took ≥1 potentially interacting drug within the preceding 30 days (62.2% vs. 35.7%) and used >4 drugs (polypharmacy) within the preceding 90 days (80.0% vs. 66.4%).

A study[29] investigated factors associated with complications (bleeding or thromboembolism) of anticoagulation in patients with atrial fibrillation. It found that patients who took ≤3 drugs had fewer complications than patients who took >3 drugs.

The SPAF investigators[30] investigated the risk factors for bleeding during anticoagulation. Increasing number of prescribed medications (P=.007) was an independent risk for bleeding at any site during anticoagulation.

Race/ English language
Lip et al (2002)[31] found that awareness of the beneficial effect of warfarin was significantly reduced in Indo-Asians and Afro-Caribbeans compared with white patients. Indo-Asians were particularly unaware of the adverse effects associated with warfarin therapy. Further, only a minority of Indo-Asians (30%) and Afro-Caribbeans (11%) with AF felt that their doctor had given them enough information about their warfarin therapy, and the majority from these ethnic

groups felt that they were careless about taking their warfarin. Another study from the same area in the UK[32] found that 45% of the Indo-Asians, compared with 18% of the white Europeans and 19% of the Afro-Caribbeans, felt they had difficulty understanding their anticoagulant management (P=0.04). Language barriers and doctor-patient interactions may therefore be an important consideration.

A study from Australia[33] found that "non-English-speaking background" patients with AF and acute stroke were less likely to be taking warfarin than "English-speaking background" patients (5.3% vs 46% respectively, p=0.001).

Literacy/ numeracy

When studying anticoagulant control, those with low literacy and numeracy were found to have poor anticoagulation control[34]. Given that warfarin therapy requires multiple dose changes with varying strengths or number of tablets per day, the association is not surprising. If poor anticoagulation control translates to worse clinical outcome, then low literacy and/ or numeracy may disadvantage this group in society.

APPENDIX IV – Real world costing exercise

Attached to covering email.

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