NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
British Cardiovascular Intervention Society	The British Cardiovascular Intervention Society (BCIS) will leave to others such as the BCS and HRUK to comment on this.	Comment noted
Anticoagulation Europe(ACE)	**Equality and access to anticoagulant treatment** Approximately 1.5 million people in the UK suffer with Atrial Fibrillation (AF) AF suffers are up to five times more likely to suffer with a stroke. It is estimated that approximately 12,500 strokes per year are attributable to AF.	Comment noted
Anticoagulation Europe (ACE)	NICE Guidelines 36 (under review)– Atrial Fibrillation – The management of atrial fibrillation, advises that patients with AF who are assessed at moderate to high risk of having a stroke be anticoagulated with warfarin and patients at lower risk, with aspirin. Anticoagulation therapy when used is highly effective and can lower the risk of stroke by about two –thirds in AF patients	Comment noted
Anticoagulation Europe(ACE)	Within the CG 36 Costing report, it estimates that about 46% of AF patients that should be on warfarin are not receiving therapy. The NHS Improvement –Heart – Anticoagulation for Atrial Fibrillation overview (2011) states that *'anticoagulation services vary in quality and effectiveness across the country and there are many people not being prescribed anticoagulation when indicated, and many receiving sub-optimal therapy.'* Warfarin is currently the most widely used anticoagulant but requires frequent monitoring and necessary dose adjustments in order to maintain a target INR. Patients are required to attend anticoagulation clinics in primary and secondary care settings and this can be disruptive, inconvenient and costly. Carers and family members may have to support and manage these visits on behalf of an elderly or immobile patient and with an aging population, some AF patients are in work and have to factor blood tests around their work responsibilities.	Comments noted. The Committee heard that the need for regular monitoring and dose adjustments with warfarin is disruptive and inconvenient and can have an adverse impact on people's work, social and family life. See FAD Section 4.2

Consultee	Comment	Response
Anticoagulation Europe (ACE)	Venous sampling causes pain, bruising and scarring to the veins. Anxiety can occur when patients are unable to stabilise within their recommended INR range – they worry that they may have a stroke and this can exacerbate their general health and well-being.	Comment noted. The Committee heard that the main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the therapeutic. See FAD section 4.2
Anticoagulation Europe (ACE)	As warfarin interacts with many foods, drinks and over the counter drugs, clinicians may have concerns relating to the effectiveness and safe management of this therapy for some of their patients. They may be reluctant to prescribe warfarin to patients who may have difficulty in achieving the recommended INR to keep them in therapeutic range or have demonstrated intolerance to the drug.	Comment noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
Anticoagulation Europe (ACE)	Adherence to the AF guidelines is inconsistent across the UK leaving many AF patients unprotected and at risk of a stroke. These patients are disadvantaged – being unable to take responsibility and be empowered in reducing their risk of stroke and staying healthy. Rivaroxaban being one of the new orals should be made available and accessible as an *alternative* treatment for all eligible AF patients who are not currently being offered any anticoagulant treatment or, for those who need to increase their protection against stroke. *Rivaroxaban, one dose a day, with no monitoring required will provide a choice of treatment for AF patients and therefore the decision by NICE not to recommend this drug is detrimental and prejudicial; creating inequities of access to care among patients with long –term health conditions.*	Comments noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

Consultee	Comment	Response
Arrhythmia Alliance	It is estimated that the UK diagnoses just 60 -70% of AF patients, of those, 97% are believed to be of moderate to high risk of stroke and based on the most recent international professional consensus guidelines, should be anti-coagulated. The NICE review of literature in 2006 showed that only 54% of these patients were actually prescribed warfarin. Looking at these figures, it suggests that the risk of stroke is only reduced in 18%-21% of patients with AF. 45% of all embolic strokes are caused by AF; the stroke is usually more severe resulting in more death and disability. In the first year following a stroke, the medical outlay is £9,500 - £14,000 with embolic strokes being the most costly. Clinical trials show that Warfarin can potentially reduce stroke risk by 50% - 70-%, however in routine clinical practice, this potential is not being achieved, risking the possibility of thousands of preventable strokes. There are many reasons for the under prescription of warfarin ranging from fear of associated bleeding risk to the complexity of dosing and patient management. At the moment, almost 50% of patients with AF for whom warfarin is suitable for, are not prescribed warfarin and so remain at risk of a stroke with devastating consequences.	Comment noted.
Arrhythmia Alliance	Patient and physician resistance to using warfarin is a major factor in the lack of stroke prevention. Warfarin is a time consuming and complex drug for primary care practitioners and the elderly, those at most risk of stroke, are the most likely not to be prescribed warfarin due perceived fear of complications	Comment noted.
Arrhythmia Alliance	Data collected from younger AF patients who, according to NICE guidelines should be prescribed anti-coagulants, including 'those with a history of stroke and those aged 65 years or over with one of the following; diabetes, coronary artery disease, or hypertension' reveals that 54% of those prescribed warfarin state that it has impacted on their job and employment enormously, suggesting the need for an alternative to warfarin. For those who are prescribed warfarin, there are large numbers of people that are difficult to keep within therapeutic range and can spend more that 60% out of	Comment noted. The Committee heard that the need for regular monitoring and dose adjustments with warfarin can be disruptive and inconvenient. See FAD Section 4.2 The Committee heard from the patient expert that people taking warfarin often have poorly controlled INR. See FAD Section 4.2

Consultee	Comment	Response
	therapeutic range and so causing warfarin to be of no benefit.	
Arrhythmia Alliance	NICE's 2006 review of literature concluded that of the patients indicated, just 54% of patients actually receive warfarin and of those, just 56% are within therapeutic range at any one time. These numbers would suggest that just 18% - 21% of AF patients on warfarin are effectively and safely protected from the risk of stroke.	Comment noted The Committee heard from the patient expert that people taking warfarin often have poorly controlled INR. See FAD Section 4.2
Arrhythmia Alliance	Cost effectiveness must of course be considered, but when comparing an alternative then effectiveness must also be taken into account including the wide gap between clinical trial data and real clinical practice.	Comment noted
Arrhythmia Alliance	Arrhythmia Alliance believes that the comparison of Rivaroxaban with well controlled warfarin ignores the cost of stroke in those patients for whom warfarin is ineffective or impossible to use. It would be reasonable then to compare Rivaroxaban to aspirin or to nothing. It would therefore suggest that denial of a new, safe and more effective treatment for these patients is not based on a fair comparison. A-A would advocate that use of Rivaroxaban for the following patients, based on their risk of stroke using the $CHADS_2$/$CHADS_2VASc_2$ system: • Those patients for whom INR monitoring will limit their opportunity to access work, maintain employment and access promotion • Those patients for whom warfarin is poorly controlled, that spend less than 70% in therapeutic range or in whom complications such as bleed, TIA or stroke result from poor control.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Arrhythmia Alliance	Conclusion The prime concern of the NHS is to reduce the number of strokes and so A-A does not consider that the current recommendations are reliable or that they represent an appropriate basis for guidance to the NHS. These recommendations act against the	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-

Consultee	Comment	Response
	priority of the NHS to lower the number of strokes, despite trial evidence and expert witness statements. Arrhythmia Alliance believes that this will result in – • A continued rise in the number of strokes due to Atrial Fibrillation • Discord between patients and clinicians • No local guidelines, leading to inequality of services, care and cost efficiencies • Promotion of unwarranted inequalities in stroke risk reduction A-A therefore asks the Committee to issue guidance on Rivaroxaban, taking into consideration the points raised in the response to the appraisal document.	valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Atrial Fibrillation Association	AFA is mindful that budgetary pressures within the NHS are ever-present and inevitable, and as a result, cost effectiveness has to be a reasonable expectation before new therapies can be recommended. However, when comparing treatments, it is important to not only consider cost but also effectiveness. These considerations should take into account the wide gap between clinical trial data and real clinical practice. While this difference has been recognised for some time it is probably best summarised by the QIPP, Right Care programme, 'Commissioning for Value': 'Value must also be measured by outputs, not inputs. Hence it is patient health results that matter,'	Comment noted.
Atrial Fibrillation Association	1. AF is the single most powerful risk factor for stroke, increasing an individual's risk of stroke by nearly 500%. Consequently, antithrombotic therapy should be considered routine in most people with atrial fibrillation. 2. Strokes as a result of AF are considerably more severe than non-AF strokes. AF-related strokes result in greater disability, social dependency and death; , they are more expensive and they are more likely to recur in the absence of effective treatment. 3. . Current guidelines recommend that 97% of AF patients should be prescribed an oral anticoagulant (OAC) to ensure adequate reduction of stroke risk. Yet, data from the National Institute of Health and Clinical Excellence (NICE) indicates that only 54% of AF patients in need of OAC treatment are receiving treatment. Even accounting for those unsuitable for OAC therapy, this represents vast under-utilisation of life-saving	Comment noted.

Consultee	Comment	Response
	anticoagulation treatment.	
Atrial Fibrillation Association	NICE comments that more than 166,000 known AF patients should be on OAC but are not. Given that AF is directly responsible for 12,500 stokes in the UK each year, a clear opportunity to save thousands from death and disability is being missed by a significant margin. • For the last 50 years, a group of drugs called the vitamin K antagonists (VKAs) have been the mainstay of OAC treatment. Of these drugs only one, warfarin, is used routinely in clinical practice. Multiple clinical trials have shown that well-controlled, dose-adjusted warfarin is a safe and effective therapy, having been shown to reduce the risk of stroke in AF patients by up to 68%. However, warfarin has a narrow therapeutic range and it interacts with many common foods and medicines. Consequently, warfarin requires close monitoring and frequent dose adjustments to ensure that patients receive a dose that consistently maintains a reduced risk of stroke without increasing the risk of bleeding. "You have to visit the hospital very regularly, sometimes every week or every fortnight if the drug does retain the normal therapeutic level, but more often than not, it fluctuates." Evelyn, 89	Comments noted. The Committee heard that the need for regular monitoring and dose adjustments with warfarin is disruptive and inconvenient. See FAD Section 4.2
Atrial Fibrillation Association	Despite the wealth of clinical trial evidence, warfarin is only prescribed for 54% of those in need of it and, among those on warfarin, only 56% are found to be within therapeutic range. As a result, a significant majority of AF patients, in need of OAC, remain at high risk of stroke. "I worry if I have a glass of wine on a Sunday with my daughter, or if I eat green vegetables. I love sprouts but they have been such a problem." Alice, 59	Comments noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
Atrial Fibrillation Association	The challenge is to effectively reduce the risk of stroke in key groups of patients with AF:	Comments noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and

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	i) Those among the 45% not receiving the OAC therapy that they need; ii) Those among the 44% not currently within the therapeutic range of warfarin; and iii) Those unable to tolerate warfarin therapy. In light of this, AFA does not believe that the current recommendations are sound or that they represent a suitable basis for guidance to the NHS. An NHS priority is to reduce the number of strokes. The current recommendations act against this priority, despite trial evidence (ROCKET-AF) and expert witness statements, given before and at the appraisal meeting. AFA believes that this will result in: - Continued rise in the event of strokes due to AF - Conflicts between patients and clinicians - No local guidelines, leading to inequality of services and care and cost inefficiencies - - Promotion of unwarranted inequalities in stroke risk reduction	systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Atrial Fibrillation Association	AFA calls upon the NICE committee to issue guidance on rivaroxaban with consideration to the considerable challenges of current therapy options, and mindful of the vulnerable AF patient groups at high risk of stroke. These patients could be summarised as those with a $CHADS_2Vasc$ score of 1 or more and poorly controlled on warfarin (<60% of time in therapeutic range) or allergic/intolerant of warfarin. These might include both true allergies and side effects or: • Individuals with multiple risk factors and, hence, on polypharmacy causing considerable issues to successful and safe management of warfarin therapy • Those intolerant of warfarin • Individuals who are unable to manage multiple doses who also require regular review and likely changes to their dosage • Those living within care settings where drug management relies upon non-medical staff reluctant to support management of difficult medication which can be potentially life threatening	Comment noted.

Consultee	Comment	Response
	• Those who are liable to dose error due to mental health issues • Those who are needle phobic • Those with limited ability to attend monitoring appointments such as the immobile, those in care homes and those living in rural areas • The most vulnerable patients such as the elderly, who are often at greater risk both of stroke and by multiple risk factors, polypharmacy, dementia, non-adherence to therapy and by inconsistencies in approaches to anticoagulation management throughout the health service. • Those who struggle and are simply unable to manage warfarin successfully due to work and lifestyle issues The importance of these lifestyle changes was recently endorsed in a statement from the British Medical Association, "...It is all well and good to say that everyone with atrial fibrillation should be on warfarin, but the reality is that patients do not always want it ... Warfarin is not always right for patients – warfarin can be very dangerous for patients, and we have to make the right choice for the patient." BMA 2011	
Atrial Fibrillation Association	In conclusion, Little can be done to prevent Atrial Fibrillation or to reduce personal risk of stroke due to AF. Therefore managing this risk is paramount. Aspirin in high risk AF patients is inadequate. Warfarin is currently the only option, and this is neither successful nor suitable for all those at risk, an alternative is desperately needed. We would also suggest that it is likely that dabigatran will be approved in some form for prevention of stroke in AF. Competition is important to the NHS to drive down prices and therefore having competitive OAC approved by NICE is going to improve value for the NHS. AFA asks the Committee to act to protect these vulnerable patient groups and issue guidance for Rivaroxaban in the prevention of stroke and systemic embolism in Atrial	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

Consultee	Comment	Response
	Fibrillation.	
AF-CGC	Please find below, comments from a previous GDG member on behalf of the AF GDG The ROCKET-AF was a trial where high risk AF patients were targeted for inclusion … this after 10% of $CHADS_2$ were recruited, patients needed to be $CHADS_2$ 3 or above, or with prior stroke. Thus the concern about generalisability to the general AF population remains. This is in contrast to other trials, which included patients with 1 or more stroke risk factors. 55% of the study population was secondary prevention – and the mean $CHADS_2$ score was 3.5, again reflecting the high risk nature. Rivaroxaban was given as 20mg OD, when its half-life is even shorter than dabigatran which is administered as a BID regime. There was no Phase 2 AF trial to guide dose selection	Comments noted. The Committee was made aware by the manufacturer that a systematic review of the literature had suggested that there does not appear to be an interaction between treatment effect and baseline $CHADS_2$ risk. The Committee heard from the manufacturer that rivaroxaban would be indicated for atrial fibrillation in people with one or more risk factors for stroke, which equates to a $CHADS_2$ score of 1 or more The Committee noted that the European Medicines Agency had stated in the 'European public assessment report' for rivaroxaban that efficacy results were essentially consistent in important subgroups, such as different $CHADS_2$ scores ($CHADS_2$ scores 2 to 6). The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of ROCKET-AF would not translate to people with a lower $CHADS_2$ score. See FAD section 4.5

Consultee	Comment	Response
AF-CGC	The average TTR in ROCKET AF was 55%, which is not good, compared to other trials The excess of adverse events in patients transitioning from rivaroxaban back to warfarin when the trial concluded is noted, and may be a concern. The higher GI bleeds with rivaroxaban vs warfarin is noted (also seen with dabigatran 150mg BID) Hence the committee's comments in section 4 are entirely reasonable	The Committee was concerned that the effectiveness of warfarin could be underestimated if the proportion of time in therapeutic range was low, and that the UK context might be better reflected by results from centres where the time in therapeutic range in the warfarin arm more closely matched the usual levels in the UK. The Committee concluded that the trial results were broadly applicable to a UK setting, but for those already taking warfarin the current level of INR control should be taken into account in any decision to switch to rivaroxaban. See FAD section 4.4
AF-CGC	For the Markov model essentially it is dependant upon the various model assumptions and what has been assigned as the cost of warfarin monitoring, which does seem to vary in different settings.	Comment noted.
AF-CGC	Another example: a 74 year old man with AF and peripheral artery disease … most sensible (!) cardiologists would anticoagulate such a patient but this patient has a $CHADS_2$ score=0! However, he has a CHA2DS2-VASc score of 2, and by the current state of the art ESC guidelines, he would at least get anticoagulation. The 2006 NICE guidelines on AF are outdated (but are in the process of being updated) and the current state of the art ones are the 2010 ESC guidelines.	The Committee concluded that the results of the ROCKET-AF trial were generalisible to UK clinical practice. However the Committee was mindful of the very small number of patients recruited to the ROCKET-AF trial with a baseline $CHADS_2$ score of less than 2. .See FAD section 4.5
Boehringer Ingelheim	As a commentator on the above STA, Boehringer Ingelheim Ltd (BI) submits the following comments on eight matters arising from the ACD for consideration by the Appraisal Committee.	Comment noted. The Committee concluded that the results of the ROCKET-AF trial were generalisible

Consultee	Comment	Response
	Text highlighted in blue is commercial in confidence. Text highlighted in yellow is academic in confidence. 1. The inclusion/exclusion criteria for ROCKET-AF match neither the UK AF population, nor the licensed indication for rivaroxaban. The Appraisal Committee recommends that the characteristics of the cohort included in the economic model should represent people with atrial fibrillation in the UK. However, the inclusion/exclusion criteria for ROCKET-AF mean that a clinical evidence base for rivaroxaban in this indication is available for only 22% of the UK AF population. A recent study (unpublished manuscript, Appendix 1, abstract submitted as academic in confidence) based on [redacted] patients with AF identified from the UK General Practice Research Database (GPRD), found that of those at intermediate/high risk of stroke and eligible for anticoagulant treatment (CHA2DS2-VASc≥1; [redacted] the proportion who would have been eligible for inclusion into ROCKET-AF was [redacted]). Across all AF patients, only [redacted] met the inclusion criteria for ROCKET-AF. The main differentiator between the UK AF population and the patients in ROCKET-AF is that only three patients with CHADS2 < 2 were included in ROCKET-AF. (Patel et al. 2001). As the extremely limited clinical evidence for the use of rivaroxaban in these patients, clinical effectiveness (and therefore cost-effectiveness) cannot be robustly assessed. In Summary: • Only [redacted] of the UK AF population are estimated to meet the inclusion criteria of ROCKET AF. • Any recommendation for the use of rivaroxaban in patients with $CHADS_2$ <2	to UK clinical practice. However the Committee was mindful of the very small number of patients recruited to the ROCKET-AF trial with a baseline $CHADS_2$ score of less than 2.

Consultee	Comment	Response
	would be unsupported by clinical evidence.	
Boehringer Ingelheim	2. One of the clinical experts at the 1st Appraisal Committee Meeting was nominated by the manufacturer, in contravention to the principles set out in the NICE 'Guide to the methods of technology appraisals'. (NICE 2008) This led to a potential bias at the meeting in favour of the manufacturer, and therefore this expert's comments should be removed from the account of the appraisal meeting. The ACD states: "Professor John Potter, Professor of Ageing Stroke Medicine, nominated by Bayer HealthCare – clinical specialist" (Appendix B, page 36, of the ACD) However, the "Guide to the methods of technology appraisals" (NICE 2008) states: "4.5.1 Two groups of experts – clinical specialists and patient experts – are selected by the Committee Chair from nominations provided by (non-manufacturer) consultees and commentators. Clinical specialists and patient experts provide written evidence and attend the Committee meeting to help in the discussion of the technology being appraised." The inappropriate use of a clinical expert nominated by the manufacturer is a clear breach of this principal and calls into question the impartiality of the evidence given by the clinical expert at the Committee Meeting. As a consequence, we believe the opinions and evidence submitted by this clinical expert should be removed from consideration in the formulation of the Final Appraisal Determination (FAD), and replaced with those of an independent clinical expert nominated by a professional body.	Comment noted. The Guide to the Single Technology Appraisal (STA) process 2010 pg 20 states that "*Consultees and commentators nominate clinical specialists and patient experts. Manufacturers or sponsors of the technology or comparator technology can only nominate clinical specialists".*

Consultee	Comment	Response
	In Summary: • Use of clinical expert evidence provided by an expert nominated by Bayer Healthcare leads to potential bias towards the manufacturer.	
Boehringer Ingelheim	3. A technical error in the economic model leads to a bias in favour of the manufacturer. This would invalidate the current results, so additional corrected results would be required for any recommendation. Annual event rates are provided for the warfarin patients in Table 18 of the manufacturer's submission (Page 112 of the Evaluation Report), per 100 patient-years. These event rates are incorrectly converted by the manufacturer into quarterly probabilities (in line with the 3-month Markov cycle in the economic model) using the following formula and the example of the rate for ischaemic stroke: Quarterly rate = 1- (1-annual rate)^(1/4) (page 187 of the Evaluation Report) = 1 – (1 – 0.0142)^(1/4) = 0.357% The reference quoted for this calculation is Briggs et al. (2006). However, this reference has been incorrectly used. The correct conversion of a rate into a probability is: P = 1 – exp (-rt) = 1- exp (-0.0142 x 0.25) = 0.354%. This re-calculated value represents the probability of one event, per patient, per timestep, and is the correct value that should be used. This error introduces a bias in favour of rivaroxaban since cost-effectiveness is driven by the absolute risk reduction between the new technology (i.e. rivaroxaban) and the comparator (i.e. warfarin). Using the incorrect calculation submitted by the	Comment noted. The ERG carried out an assessment of the impact of correct ing the formulae for converting rates into probabilities and found it had a minimal impact on the ICER, increasing the revised base case ICER by £39. See the evaluation report.

Consultee	Comment	Response
	manufacturer leads to a larger absolute baseline risk, leading to an increased absolute risk reduction when the relative risks (for rivaroxaban) are applied. Although this error, when considered in isolation in a single event and a single timestep, is relatively small, the error is proliferated across additional clinical outcomes, the whole modelled cohort and the entire duration of the model timeframe (i.e. patient's lifetime). Further to this, as the model is nonlinear, and risk of stroke is dependant on stroke history, the impact of this error is further amplified. We were unable to assess the impact of this error on the modelled results as the version of the economic model provided to us could not be re-run. However, the bias would be expected to be in favour of rivaroxaban. In Summary: • Baseline risks for patients on warfarin are over-estimated, leading to a bias in favour of rivaroxaban. • This bias exists over multiple outcomes and is applicable across the whole modelled cohort and entire patient life-time. • The impact of the error is amplified as the model is non-linear. • The economic model should be corrected before any recommendation using results based on it can be made.	
Boehringer Ingelheim	4. Base-case ICERs derived from the PSA should be used in line with Section 5.9.3 of the "Guide to the methods of technology appraisals". This omission favours rivaroxaban. The NICE "Guide to the methods of technology appraisals" (NICE 2008) states: "5.9.3. When models consist of non-linear combinations of parameters, probabilistic sensitivity analysis should be used to generate mean costs and QALYs. In such models, setting parameters to their mean values will not provide the correct estimates	Comment noted

Consultee	Comment	Response
	of mean costs and QALYs." The manufacturer's model for this appraisal is non-linear (i.e. the risk of additional acute clinical events is dependant on occurrence of previous acute clinical events, e.g. stroke rate is dependant on risk of stroke, which changes if a patient has had a previous stroke). Therefore, costs and outcomes should be calculated from the PSA results in accordance with the above guidance. Evidence of a bias in favour of rivaroxaban by omission of the PSA results can be illustrated by comparing the ICERs calculated from the point estimates and the median ICER estimated from the PSA graphs (results section of the manufacturer's submission). Insufficient detail is provided by the manufacturer to estimate the size of this effect. However, from the information provided, this difference appears substantial (~£10,000 per QALY, see deterministic ICER and PSA median on Page 295 and 297 of the Evaluation Report). In Summary: • The NICE methods guide states that ICERs should be calculated from PSA results for non-linear models to avoid bias. • This does not appear to have been done by the manufacturer and there appears to be bias in favour of rivaroxaban as a result of this omission. • Results from the PSA should be given due consideration.	
Boehringer Ingelheim	5. Dabigatran etexilate is a relevant comparator and should not be disregarded from any further analyses related to this appraisal. This comparison was performed by both the manufacturer and the ERG, therefore it should be considered in order that NICE is able to provide clear guidance to prescribers on the use of rivaroxaban with respect to dabigatran. In the final scope for rivaroxaban, dabigatran is listed as a relevant comparator within the PICO table. Dabigatran has since been recommended by the Appraisal Committee	The Committee discussed the indirect clinical-effectiveness evidence for rivaroxaban compared with dabigatran etexilate and aspirin. It agreed that the clinical-effectiveness estimates for rivaroxaban compared with dabigatran etexilate and aspirin obtained from the network meta-analyses and indirect

Consultee	Comment	Response
	(FAD currently subject to appeal) reinforcing the validity of this comparison. In addition, we note the comment from the ERG, that "The ERG considers that a fully incremental analysis of rivaroxaban, dabigatran, warfarin, aspirin and no treatment (placebo) is both possible and desirable" (ERG report p127) and that "the incremental analyses revealed that the relevant comparison was between dabigatran and rivaroxaban" (ERG report p16). We therefore consider it surprising that the Committee has reached the following conclusion: "The Committee concluded that it would not consider further the clinical effectiveness of rivaroxaban compared with aspirin or dabigatran etexilate" (ACD section 4.7). Whilst it appears that the committee regards the indirect evidence as insufficiently robust to provide a recommendation on the use of rivaroxaban with respect to dabigatran, we agree with the ERG that such an analysis is both possible and desirable. There are data available to support a comparison of rivaroxaban with dabigatran, as detailed in the manufacturer's submission, and in the ERG report. For example, the ERG states that: 'There is a general trend in favour of dabigatran etexilate for ischaemic stroke, major extracranial bleed, and intracranial bleed, and a statistically significant difference (at the 5% level) in favour of dabigatran etexilate for minor extracranial bleed. There is a trend in favour of rivaroxaban for systemic embolism and a significant difference (at the 5% level) favouring rivaroxaban in MI and discontinuation. However, the ERG also considers it important to note that in the trial informing the rivaroxaban MI data set, (ROCKET AF), significantly more people had a history of prior MI at baseline in the warfarin group compared with the rivaroxaban group ($p < 0.05$). The ERG thus considers that as previous MI is one of the risk factors for future MI, the benefit observed with rivaroxaban in reducing the risk of MI compared to dabigatran etexilate may be confounded and should be interpreted with caution' (ERG report p74).	comparison were unreliable because of the wide confidence intervals, resulting in efficacy point estimates which were subject to considerable uncertainty. The Committee concluded that it would not consider further the clinical effectiveness of rivaroxaban compared with aspirin or dabigatran etexilate. See FAD sections 4.7.

Consultee	Comment	Response
	Note that 'the ERG has conducted exploratory analysis into the effect of assuming equivalence between rivaroxaban and dabigatran in MI prevention' (ERG report p 127). The ERG's analyses showed that dabigatran is cost effective compared with rivaroxaban, in that it yields a higher number of QALYs than rivaroxaban, at an additional cost that yields an ICER which is well below the acceptable cost effectiveness threshold. The ERG report states that: 'The results of the comparison between rivaroxaban and dabigatran on point estimates from the ERG's NMA [Network Meta-Analysis] indicate that dabigatran is the more effective treatment, with an ICER of £34,680 per QALY gained [for dabigatran compared with rivaroxaban]. Following incorporation of the ERG's recommended adjustments, the ICER decreases to £12,701, with the exploratory analysis assuming equivalence of MI prevention between treatments yielding an ICER of £3,578. However, the ERG notes that the model is highly sensitive to changes in the discontinuation rates used and advises that the ICER of £12,701 per QALY gained, be considered in the context of the associated uncertainty' (ERG report, page 130, see also table 61). Given that the ERG advises that an ICER of £12,701 per QALY gained [for dabigatran compared with rivaroxaban], should be considered in the context of the associated uncertainty, it seems unsubstantiated that the Committee has concluded that the results from the network meta-analysis are unreliable and that no comparison can be made between dabigatran and rivaroxaban. This is despite the ERG stating that a fully incremental analysis of rivaroxaban, dabigatran, warfarin, aspirin and no treatment (placebo) is both possible and desirable. The rationale for the Committee's opinion that 'the manufacturer's and ERG's network meta-analyses contained wide confidence intervals and therefore the resulting efficacy	

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	point estimates were subject to considerable uncertainty', seems unsubstantiated, given the ERG's revised network meta-analysis. The ERG states: 'Overall, use of a network of randomised controlled trials restricted to those that directly inform the decision problem that is the focus of this STA results in a more consistent analysis that provides greater precision around the effect estimates than that provided in the MS.' The confidence intervals calculated by the ERG are not unusually large. Further, running a model probabilistically using distributions to reflect the uncertainty around model parameters is a standard procedure within economic modelling and one which specifically aims to reduce parameter uncertainty. Therefore we would be interested to see the results of a PSA comparing dabigatran with rivaroxaban using the ERG's NMA. Importantly we also note that in section 3.21 of the ACD, the ICER is reported as being £3,578 for rivaroxaban compared with dabigatran etexilate. This is incorrectly reported. It should read £3,578 for dabigatran etexilate compared with rivaroxaban (see above). In Summary: • Dabigatran etexilate is a relevant comparator • This view is supported by the Scope and the ERG • • The ERG has already provided estimates for the cost-effectiveness of dabigatran vs. rivaroxaban that should not be disregarded.	
Boehringer Ingelheim	6. Using an ITT population in the appraisal of rivaroxaban is more appropriate than the safety on treatment population, since that would ensure higher applicability to the treatment decision in real-life, consistency across appraisals and comparability across results. For the primary efficacy endpoint of stroke or systemic embolism, in the safety on treatment (SOT) population from the ROCKET-AF trial, the hazard ratio (HR) for rivaroxaban compared with warfarin was 0.79 (95% = CI 0.65 to 0.95). (Patel et al. 2011) For the same endpoint for dabigatran in RE-LY using the SOT population, the	The Committee noted that the intention-to-treat population included people who had either had no treatment or switched treatment during the trial, and agreed that the estimates derived from the safety-on-treatment population of the ROCKET-AF trial provided an adequate basis for evaluating clinical effectiveness.

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	HR for dabigatran 150mg compared with warfarin was [redacted] (Boehringer Ingelheim Ltd, 2009). By comparison, for the primary efficacy endpoint of stroke or systemic embolism for the ITT population in ROCKET-AF, rivaroxaban was shown to be not significantly different from warfarin, where the HR was 0.88 (95%CI = 0.75 to 1.03). (Patel et al. 2011) For the same primary efficacy outcome in RE-LY for the ITT population, there was a significant difference between dabigatran 150mg compared with warfarin, with a HR of 0.65 (95% CI = 0.52 to 0.81). (Connolly et al. 2009, Connolly et al. 2010) Clearly the results are significantly affected by the analysis set selected for use. The figures above show that using the safety on treatment analysis leads to more favourable results, compared with when the intention to treat population is used. It is important to be clear that the results from the ITT population from RE-LY were used in the appraisal of dabigatran, not the safety on treatment analysis set, as was incorrectly stated at the Appraisal Committee meeting. It was also suggested that, in line with the NICE methods guide, similar assumptions should be applied consistantly across technology appraisals for similar indications, to ensure a fair and transparent approach. For avoidance of doubt, the economic analyses considered in the appraisal of dabigatran etexilate were solely based on the ITT analysis set from RE-LY. The ERG also states “that the ITT population would better reflect the treatment effectiveness results that would be seen in clinical practice” (page 4 of the Evaluation Report). ITT is more appropriate for the treatment decision of a physician as he/she does not know what will happen during the treatment afterwards, e.g. discontinuations due to side effects. The SOT population is by definition a post-randomisation analysis, and since the results of this analysis are subject to bias, it cannot be concluded that patients who will be treated in real life will approximate to the SOT analysis, unlike an ITT population. Clearly any cohort of patients selected for treatment in routine practice would be a de facto ITT population. Therefore the outcomes experienced by these	See FAD section 4.3

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	patients are best approximated by the ITT population, not the SOT population. This is of particular importance given the relatively high reported discontinuation rate for rivaroxaban patients in ROCKET-AF (35.44%, page 608 of the Evaluation Report). It is also worth mentioning that in the STA for dabigatran etexilate, the economic model submitted by Boehringer Ingelheim not only used the clinical findings from the ITT population, thus giving a conservative estimate of the efficacy of the drug, but in addition included the discontinuation rates as observed in RE-LY (and modelled beyond the trial duration for up to 6 years). Both these actions yielded conservative estimates for the ICERs for dabigatran etexilate vs. warfarin. One potential concern, that an ITT analysis may be overly optimistic in assessing non-inferiority in clinical studies, does not actually hold in the circumstance of this STA, as the safety on treatment population is used to claim superiority in the primary endpoint, and not to assess the non-inferiority. "In superiority trials the full analysis set is used in the primary analysis (apart from exceptional circumstances) because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis, since the non-compliers included in the full analysis set will generally diminish the estimated treatment effect. However, in an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully." (ICH Expert Working Group, 1998) Further to this, Fleming and Emerson (2011) state: "Even in noninferiority trials, per-randomization analyses should be conducted. These analyses avoid the bias that occurs with per protocol on-treatment analyses when patients discontinue their randomized treatment for reasons related to the treatment itself and the patients who do so have a different risk profile from those who don't. The importance of per-randomization analyses is very apparent in ROCKET-AF. The on treatment analysis was based on observations that were truncated at 2 days after	

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	discontinuation of randomized treatment — a time frame likely to miss events related to inadequate coagulation during the transition to alternative treatment.“ In addition the idea that an ITT analysis may be overly optimistic (and not conservative) in assessing non-inferiority in clinical studies is based on situations where the PP estimate lays between unity and the non-inferiority margin, whereas the ITT estimate is within the same range, but more close to unity due to discontinuations, treatment cross-overs, etc. In this situation PP is regarded as the more conservative analysis for non-inferiority. But if, even in a non-inferiority trial, the estimate shows some (e.g. numerical) superiority in PP (i.e. estimate is not in the range between the non-inferiority-margin and unity), the ITT estimate which is usually closer to unity is the more conservative estimate. Therefore the statement that PP is more relevant and conservative in non-inferiority studies cannot be applied to all data situations. In Summary: • The ERG stated in their evaluation report that the trial population from RE-LY was similar to the ROCKET-AF SOT population (page 578 of the evaluation report), which may have led the Appraisal Committee to state at the appraisal meeting that the SOT population was used for the dabigatran STA. This is incorrect since the ITT population was used in that appraisal. • For consistency, the ITT population should also be used in this current STA, and the ERG states that this is the preferred analysis. • The SOT population does not best reflect routine clinical practice. • The most valid analysis consistent with other STAs, and the general principles of economic evaluation, would be based on the ITT population. • • In any indirect comparison of rivaroxaban extreme care must be taken to compare results from corresponding analysis populations. A previously published network meta-analysis comparing dabigatran etexilate to other treatment options used ITT populations. (Roskell et al. 2010)	

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Boehringer Ingelheim	7. The control group in ROCKET-AF does not reflect the UK population since their average time-in-therapeutic range is below that which would be expected in routine UK practice. The validity and applicability of the comparative efficacy of rivaroxaban versus warfarin was correctly called into question by the Appraisal Committee (Page 19, Section 4.4 of the ACD) due to the low mean (55%) and median (57%) percentage time in therapeutic range (TTR) recorded for warfarin patients within the ROCKET-AF trial. (Patel et al. 2011) This was also noted by the FDA, who stated that in ROCKET-AF, warfarin was not used "skillfully" (Fleming & Emerson 2011) and hence the standard by which the experimental observations were evaluated was lower than those recorded in clinical practice. The average TTR values from ROCKET-AF are considerably lower than analogous values observed in other contemporary clinical trials (see Table below). These values concur with a study by Dolan et al. (2008) who performed a systematic review and meta-analysis of previous clinical trials within the same indication with a target INR of 2.0-3.0, and found that the mean TTR was 61.3%. (Table – not reported here) In addition, the mean TTR in UK clinical practice appears to be better than the values observed in ROCKET-AF. A study by Gallagher et al. (2011), based on the GPRD which included 27,458 patients treated with warfarin with at least three INR measurements, found that the mean TTR was 63%. Lower TTRs are associated with poorer clinical outcomes such as increased risk of stroke or bleeding events (Hylek et al. 2006, Fuster et al. 2006, Morgan et al. 2009). This view is further supported by a study by Jones et al. (2005) which found that: "...a 10% increase in time out of (therapeutic) range was associated with an increased risk of mortality (odds ratio (OR) 1.29, p<0.001) and of an ischaemic stroke (OR 1.10, p=0.006) and other thromboembolic events (OR 1.12, p<0.001)".	The Committee was concerned that the effectiveness of warfarin could be underestimated if the proportion of time in therapeutic range was low, and that the UK context might be better reflected by results from centres where the time in therapeutic range in the warfarin arm more closely matched the usual levels in the UK. The Committee concluded that the trial results were broadly applicable to a UK setting, but for those already taking warfarin the current level of INR control should be taken into account in any decision to switch to rivaroxaban. See FAD section 4.4

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	The Committee has requested that sub-group analyses of patients with improved centre TTR should be conducted in an attempt to model the UK population. However, it should be noted that: 1. This analysis should be done in the ITT population (see 6 above) based on the published standard Connolly method (used in ACTIVE-W and RE-LY), since, as the FDA has pointed out, differences in quartile %TTR ranges between the unpublished Bayer method and Connolly method exist: • Bayer-Quartiles: I: <=50.6%; II: 50.7-58.5%; III: 58.6-65.7%; IV: >65.7% • FDA-Connolly method Quartiles: I: <46.8%; II: 46.8-55.9%; III: 55.9-63.9%; IV: >63.9% 2. In RELY the post-hoc cTTR quartile analysis (ITT) was based on the following quartile ranges: I: <57.1%; II: 57.1-65.5%; III: 65.5-72.6%; IV: >72.6% (Wallentin et al. 2010) 3. In RE-LY there was a preplanned cTTR analysis (ITT) for centers above 60% and 65%. Because ROCKET-AF has limited data from centres where warfarin therapy was skillfully applied (e.g. with a cTTR above 72%, i.e. the lower border of the upper quartile in RE-LY), the confidence in any conclusion drawn from such an analysis would be low. In Summary: • The mean TTR from ROCKET-AF is unusually low and not reflective of UK clinical practice • • In RE-LY, the upper quartile for cTTR was 72.6%; ROCKET-AF has too few data from centres where warfarin was skilfully applied to make any meaningful comparison with rivaroxaban.	

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Boehringer Ingelheim	There are two further errors in the model of significance: • increased utilities for patients with additional clinical events • three-month event-free period following an event (identified by the ERG) There appears to be the potential for an increase in utility in the model following a clinical event. This occurs when a patient has a stroke (and experiences the associated decrease in utility) and then subsequently has an AMI. The utility value for the AMI is higher than for the stroke, so the patient's overall utility improves. This is counter intuitive and not reflective of the likely patient experience. It is unclear whether this bias would be in favour of rivaroxaban. The ERG identifies an event-free period following a clinical event, which is considered a low priority as the bias is toward the less effective treatment. However, for comparisons with dabigatran, the bias would likely be in favour of rivaroxaban. References not reported here	Comment noted
British Association of Stroke Physicians	1. ITT vs. safety-on-treatment (see paragraph 4.3) We agree that for a non-inferiority study, the most conservative analyses are the 'per protocol' or the 'safety-on-treatment' patients (the former the most conservative), in order to test that the OR/HR/RR =1. However, the most conservative analysis for the superiority analysis is the intention to treat population. As the superiority estimates are used to populate the model, it would seem more reasonable to use the ITT population (as one would do for any other drug), rather than safety-on-treatment to make estimates about the efficacy in a population.	Comment noted. The Committee noted that the intention-to-treat population included people who had either had no treatment or switched treatment during the trial, and agreed that the estimates derived from the safety-on-treatment population of the ROCKET-AF trial provided an adequate basis for evaluating clinical effectiveness. See FAD section 4.3
British Association of Stroke Physicians	2. Underuse of effective anticoagulation Not all those with high risk of stroke and AF are treated with warfarin, to a large degree because of patient or doctor concerns. The proportion of these patients who would take rivaroxiban instead is not made explicit. The likely preference of warfarin refusers for the convenience of rivaroxaban could be made explicit in sensitivity	Comment noted

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	analyses. It is in these patients that the real advantage of a drug that needs no monitoring might be seen (though they are unlikely to have taken part in ROCKET-AF).	
British Association of Stroke Physicians	3. Weighting of bleeds A major clinical concern to stroke physicians is the risk of ICH with treatment. There is a very small difference in these proportions between rivaroxaban and warfarin. However, stroke physicians will know of the different average severities of ICH and ischaemic strokes, though the weighting applied to ICH in the models is redacted.	Comment noted. The Committee acknowledged there was a significant reduction in the rate of fatal bleeds and intracranial haemorrhage with rivaroxaban compared with warfarin. See FAD section 4.6.
British Association of Stroke Physicians	4. Paragraph 3.7 The last sentence draws inappropriate attention to a difference in the p value of 2 post-hoc subgroup analyses; it seems unlikely that there is an interaction in treatment effect by prior use of vitamin K antagonists.	Comment noted.
British Association of Stroke Physicians	5. Age as a risk factor for all adverse outcomes Age is a plausible risk factor for all the adverse outcomes mentioned in paragraph 3.13.	Comment noted.
British Association of Stroke Physicians	6. Paragraph 3.18 We agree that the health care costs of TIA should enter model, though we think that the health weighting of these events is very small (and are not convinced this has been reliably estimated).	Comment noted
British Association of Stroke Physicians	7. Paragraph 4.5 Anticoagulants don't control AF, but rather mitigate its thrombolembolic complications.	Comment noted
BCIS	The British Cardiovascular Intervention Society (BCIS) will leave to others such as the BCS and HRUK to comment on this.	Comment noted
Bristol-Myers Squibb Pharmaceuticals	Bristol-Myers Squibb Pharmaceuticals Ltd. and Pfizer Ltd. welcome the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the ongoing appraisal of rivaroxaban for the prevention of stroke and systemic embolism	Comments noted.

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and Pfizer	in atrial fibrillation (AF). BMS/Pfizer believe that patients with atrial fibrillation should have access to all efficacious medicines in the UK. However, we have some concerns about the basis of the Appraisal Committee's (AC) conclusions relating to the appraisal of rivaroxaban. In summary:	
Bristol-Myers Squibb Pharmaceuticals and Pfizer	1. We note the higher rate of GI bleeding in ROCKET-AF and suggest rivaroxaban is not recommended in patients at higher risk of bleeding	The Committee were aware of the risk of bleeding associated with rivaroxaban. See FAD sections 2.2 and 3.7. The Committee discussed the safety data from the ROCKET-AF trial and concluded that concluded that the primary safety end point (all major and non-major clinically significant bleeding events) showed no statistically significant difference between rivaroxaban and warfarin.. See FAD section 4.6
Bristol-Myers Squibb Pharmaceuticals and Pfizer	2. We are concerned that the ROCKET-AF trial is not generalisable to the UK primary care population with AF, and suggest that rivaroxaban is restricted to a secondary care AF patient population	The Committee concluded that the results of the ROCKET-AF trial were generalisible to UK clinical practice. However the Committee was mindful of the very small number of patients recruited to the ROCKET-AF trial with a baseline $CHADS_2$ score of less than 2. See FAD sections 4.5
Bristol-Myers Squibb Pharmaceuticals	3. We are surprised that no conclusions were drawn from the clinical or cost-effectiveness comparison with dabigatran etexilate, and ask the Appraisal Committee to outline its reasoning	The Committee discussed the indirect clinical-effectiveness evidence for rivaroxaban compared with dabigatran

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and Pfizer	We therefore ask the Appraisal Committee to take these comments into account in its reconsideration of its preliminary recommendation	etexilate and aspirin. It agreed that the clinical-effectiveness estimates for rivaroxaban compared with dabigatran etexilate and aspirin obtained from the network meta-analyses and indirect comparison were unreliable because of the wide confidence intervals, resulting in efficacy point estimates which were subject to considerable uncertainty. The Committee concluded that it would not consider further the clinical effectiveness of rivaroxaban compared with aspirin or dabigatran etexilate. See FAD section 4.7. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Bristol-Myers Squibb Pharmaceuticals and Pfizer	Detailed Comments in ACD Our detailed comments on the ACD and Evaluation Report are structured under the four questions posed by NICE in the consultation: 1. Has all of the relevant evidence been taken into account? BMS/Pfizer consider that all relevant clinical evidence has been taken into account, and we are not aware of any additional clinical or cost-effectiveness evidence that should be considered.	Comment noted.

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	2. .Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Clinical evidence: Higher rate of GI bleeding in rivaroxaban patients Although results from the as-treated population in the ROCKET-AF study indicate that rivaroxaban is superior to warfarin in preventing stroke and systemic embolism, the gastrointestinal bleeding rate was significantly higher for the rivaroxaban cohort than for warfarin (3.15% vs 2.16%; p<0.001), as reported in the Supplementary Appendix of the main trial paper [Patel et al, 2009]. In light of this important safety concern, we would suggest that consideration is given to not recommending the use of rivaroxaban in patients at high risk of bleeding.	The Committee were aware of the risk of bleeding associated with rivaroxaban. See FAD sections 2.2 and 3.7. The Committee discussed the safety data from the ROCKET-AF trial and concluded that concluded that the primary safety end point (all major and non-major clinically significant bleeding events) showed no statistically significant difference between rivaroxaban and warfarin.. See FAD section 4.6
Bristol-Myers Squibb Pharmaceuticals and Pfizer	ROCKET-AF population not generalisable to primary care The average risk of stroke, as measured by the $CHADS_2$ stroke risk tool in randomised patients in ROCKET-AF, was 3.5, and only 0.2% of the trial population had a $CHADS_2$ score of 0 or 1. Patients with AF presenting in UK primary care settings frequently have a $CHADS_2$ score between 0 to 2 [Gallagher et el, 2008; Mant et al, 2007], and therefore a lower risk of stroke. This implies that the results based on the ROCKET-AF trial population cannot be generalised with confidence to all AF patients managed in UK general practice, and suggests that rivaroxaban should be recommended only for patients at higher risk of stroke, consistent with the trial population.	The Committee was also made aware by the manufacturer that a systematic review of the literature had suggested that there does not appear to be an interaction between treatment effect and baseline $CHADS_2$ risk. The Committee heard from the manufacturer that rivaroxaban would be indicated for atrial fibrillation in people with one or more risk factors for stroke, which equates to a $CHADS_2$ score of 1 or more The Committee noted that the European Medicines Agency had stated in the 'European public assessment report' for rivaroxaban that efficacy results were essentially consistent in

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		important subgroups, such as different $CHADS_2$ scores ($CHADS_2$ scores 2 to 6). The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of ROCKET-AF would not translate to people with a lower $CHADS_2$ score. See FAD section 4.5
Bristol-Myers Squibb Pharmaceuticals and Pfizer	Mean TTR of ROCKET-AF population was low at only 55% The mean time in therapeutic range (TTR) for the warfarin arm of the ROCKET-AF study was 55%, which the clinical experts consulted by the Appraisal Committee agreed was at the low end of the range expected in UK clinical practice. We agree with the Appraisal Committee that this could under-estimate the effectiveness of warfarin in real-life UK clinical practice. This raises further questions over the generalisability of the ROCKET-AF results to patients with AF in the UK.	The Committee was concerned that the effectiveness of warfarin could be underestimated if the proportion of time in therapeutic range was low, and that the UK context might be better reflected by results from centres where the time in therapeutic range in the warfarin arm more closely matched the usual levels in the UK. The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of ROCKET-AF would not translate to people with a lower CHADS2 score. However the Committee was mindful of the very small number of patients recruited to the ROCKET-AF trial with a baseline CHADS2 score of less than 2, but concluded that the results of the

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		ROCKET-AF trial were generalisable to UK clinical practice. See FAD section 4.5
Bristol-Myers Squibb Pharmaceuticals and Pfizer	Baseline imbalance of myocardial infarction in ROCKET-AF Despite randomisation, the number of patients with a history of prior myocardial infarction (MI) at baseline was significantly higher for the warfarin arm of ROCKET-AF (18.0% vs 16.6%; p<0.05). The trial publication reports 0.9% rate of MI in the rivaroxaban group and 1.1% in the warfarin group (HR 0.81, 95% CI 0.63, 1.06; p=0.121). However, the higher baseline MI rate in the warfarin group calls into question the validity of this apparent numerical advantage for rivaroxaban on the MI secondary endpoint.	Comment noted
Bristol-Myers Squibb Pharmaceuticals and Pfizer	*Exploratory network meta-analysis* The ERG undertook a new, exploratory network meta-analysis (NMA) to reduce the degree of heterogeneity in the network. Three studies of warfarin versus aspirin were included, stating that 'comparable dosing strategies were included.' However, the aspirin studies selected all used 300mg/day doses, while the licensed UK dosing for aspirin is 75-300mg/day (NICE CG36, p.65). Furthermore, an additional selection criterion was studies utilising a 'target INR range between 2 and 3' (the recommended UK range for VKA anti-thrombotic therapy in AF (NICE CG36, p.65). However, one of the studies included in the new NMA, SPAF2, had a target INR range of 2-4.5. It is therefore unclear whether the new NMA is entirely relevant to UK clinical practice	Comment noted.
Bristol-Myers Squibb Pharmaceuticals and Pfizer	Safety on treatment population used for secondary endpoint analysis The secondary efficacy outcomes in ROCKET-AF were presented for the as-treated safety population, not the ITT population as is usual for clinical efficacy. The ACD states (pp.18-19) that the clinical specialists considered the trial ITT population to be the gold standard for estimating clinical effectiveness in a superiority trial but, since ROCKET-AF was a non-inferiority trial, the primary analysis was different. The Appraisal Committee considered that the ITT population included people who had	The Committee noted that the intention-to-treat population included people who had either had no treatment or switched treatment during the trial, and agreed that the estimates derived from the safety-on-treatment population of the ROCKET-AF trial provided an adequate basis

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	either had no treatment or switched treatment during the trial, and concluded that the estimates derived from the safety-on-treatment population of the ROCKET-AF trial provided an adequate basis for evaluating clinical effectiveness. However, non-inferiority trials are required to consider both ITT and per-protocol populations as equally important in determining whether non-inferiority has been met [Lesaffre, 2008: p.154], a view endorsed by the EU regulatory agency [EMEA, 2000: p.6; Schumi & Wittes, 2011: p.4]. Furthermore, when considering superiority in a non-inferiority trial, this is acceptable from a statistical perspective provided the ITT population is given the most weight (EMEA 2000, p.6; Lesaffre 2008, p.154). The ROCKET-AF trial tested for non-inferiority and superiority on the ITT (all randomised patients) in addition to the on-treatment populations (Patel et al, 2011, p.885). Therefore, it is unclear why the Appraisal Committee have concluded that the on-treatment population (all ITT patients who received at least one dose of study drug and were followed-up for events, NICE rivaroxaban ACD, p.18) is the more appropriate analysis for consideration of primary and secondary efficacy outcomes in this instance. This conclusion appears to be incorrect, and BMS/Pfizer request that the Appraisal Committee reconsider this and use the ITT data for the clinical efficacy outcomes as the base case in the rivaroxaban submission	for evaluating clinical effectiveness. See FAD section 4.3
Bristol-Myers Squibb Pharmaceuticals and Pfizer	Comparison with dabigatran etexilate. While BMS/Pfizer concede that the Appraisal Committee's conclusion that clinical effectiveness estimates from the network meta-analyses for rivaroxaban compared with dabigatran etexilate and aspirin may be unreliable, we are surprised that the Committee further concludes that it will not consider this comparison further. Could the Appraisal Committee provide an explanation of the reasoning behind this decision, and how it intends to consider the relative cost-effectiveness of rivaroxaban compared to dabigatran etexilate and aspirin?	The Committee discussed the indirect clinical-effectiveness evidence for rivaroxaban compared with dabigatran etexilate and aspirin. It agreed that the clinical-effectiveness estimates for rivaroxaban compared with dabigatran etexilate and aspirin obtained from the network meta-analyses and indirect comparison were unreliable because of the wide confidence intervals, resulting in efficacy point estimates which were subject to considerable

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		uncertainty. The Committee concluded that it would not consider further the clinical effectiveness of rivaroxaban compared with aspirin or dabigatran etexilate. See FAD sections 4.7.
Bristol-Myers Squibb Pharmaceuticals and Pfizer	3. The provisional recommendations are a sound and suitable basis for guidance to the NHS BMS/Pfizer consider the provisional recommendations set out in the ACD are not a sound basis for guidance to the NHS. BMS/Pfizer advocate that patients with AF should have access to all efficacious medicines and note that the ROCKET-AF trial suggests that rivaroxaban is superior to warfarin in the prevention of stroke and systemic embolism. However, BMS/Pfizer note the higher rates of gastro-intestinal bleeding with rivaroxaban and would therefore suggest that patients at high risk of bleeding are specifically excluded from any recommendation by NICE. In addition, given the considerable questions over the generalisability of ROCKET-AF to a primary care population with AF, we suggest that the most appropriate recommendation for rivaroxaban may be for patients with atrial fibrillation who are being managed in a hospital clinic.	Comments noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Bristol-Myers Squibb Pharmaceuticals and Pfizer	4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? BMS/Pfizer do not consider there are any aspects of the recommendations that need particular consideration regarding unlawful discrimination against any group.	Comments noted

Consultee	Comment	Response
CSAS	On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. We are in agreement with the recommendations in the ACD not to recommend rivaroxaban for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
CSAS	• Adjusted dose warfarin with good control is the most cost effective treatment in patients with atrial fibrillation. The manufacturer's base-case analysis of rivaroxaban versus warfarin resulted in an incremental cost-effectiveness ratio (ICER) of £18,883 per quality-adjusted life year (QALY) gained. The evidence review group (ERG) identified several limitations with the manufacturer's model, including comparison with populations whose warfarin control (time in therapeutic ratio) was less satisfactory than generally expected in the UK. The ERG presented an alternative base-case ICER of £33,758 per QALY gained.	Comment noted
CSAS	• The manufacturer of rivaroxaban has included higher INR monitoring costs associated with warfarin than estimated in the ongoing appraisal of dabigatran etexilate, and these are likely to be higher than the usual costs for NHS patients. The manufacture had estimated INR monitoring costs at £535 per person. The ERG considered that the manufacturer's cost-effectiveness model was particularly sensitive to assumptions about the cost of monitoring warfarin. This means that if the manufacturer overestimates the cost of warfarin monitoring, this will make rivaroxaban appear more cost-effective. Modelling alternative anticoagulation costs resulted in an ICER for rivaroxaban of £62,568 per QALY. The Appraisal Committee has asked the manufacturer to provide revised cost-effectiveness analyses which incorporates a fixed annual warfarin INR monitoring cost of £242 per person.	Comment noted

Consultee	Comment	Response
CSAS	• Time in therapeutic range (TTR) for warfarin should be accounted for in the cost-effectiveness analysis. In the ROCKET-AF trial, which formed the basis of the manufacturer's submission, the mean TTR for warfarin was 55% (58% median). The ERG considered that this was lower than the TTR generally reported in the UK and in other clinical trials. This would make rivaroxaban appear more effective compared to warfarin as used in the UK, and consequently these results may not be applicable to UK practice. The Appraisal Committee has asked the manufacture to provide revised cost-effectiveness analyses which accounts for the low TTR on warfarin seen in the ROCKET-AF trial.	Comment noted
CSAS	• There were other limitations to the generalisability of the research. The population in the ROCKET-AF trial had more severe disease than the population of UK patients expected to be eligible to receive rivaroxaban. It is unclear whether apparent benefits from rivaroxaban seen in the ROCKET-AF trial would actually be achieved in people with more moderate disease. The Appraisal Committee has asked the manufacture to provide a revised model with a baseline risk of strokes and other events more representative of people with AF in the UK. This should be derived from the General Practice Research Database or a UK GP practice-based survey.	Comment noted
CSAS	• There were also limitations to the quality of the research. The results of a single large RCT have been submitted by the manufacturer. The ROCKET-AF trial compared rivaroxaban with dose-adjusted warfarin. The manufacturer submitted a network meta-analysis in people for whom anticoagulation therapy is considered suitable to compare rivaroxaban indirectly with aspirin and dabigatran etexilate. The estimates for rivaroxaban compared with dabigatran etexilate obtained from the network meta-analyses were unreliable and therefore the committee has been unable to say whether rivaroxaban is more effective or cost effective than these alternatives.	Comment noted
CSAS	• The provisional cost of rivaroxaban is quoted as £2.10 per day and £766.50	Comment noted

Consultee	Comment	Response
	annually (per patient). This is lower than the BNF cost for 10mg rivaroxaban, which is currently approved for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee surgery. There must therefore be uncertainties about the actual cost of rivaroxaban for the prevention of stroke or systemic embolus to the NHS, and consequently uncertainties about the relative cost-effectiveness of rivaroxaban compared to warfarin in the NHS.	
CSAS	• Under the proposed indication, all patients with non-valvular AF with $CHADS_2$ score ≥1 would be eligible for rivaroxaban. This would mean that approximately 1,146 patients per 100,000 would be eligible for rivaroxaban. This is more than the 2006 figures for the number receiving warfarin quoted in NICE's costing report on the management of atrial fibrillation, which suggested that 30% of currently-detected AF cases receive oral anticoagulants, while 36% receive aspirin, equating to approximately 384 patients per 100,000 receiving anticoagulation for atrial fibrillation.	Comment noted
NHS Berkshire cluster	I am writing on behalf of NHS Berkshire East (now NHS Berkshire Cluster), as a named consultee, in response to the NICE ACD for Rivoroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. I would agree with the initial findings from the ACD to not recommend the treatment and agree with the points made in the letter submitted to you from CSAS. I would echo the views that the cost of warfarin has been estimated as too high by the manufacturer as we currently spend approximately £310,000 on warfarin and associated testing for the Berkshire East population of approximately 376,500 (based on figures from 2010/11), unfortunately it is not easy to break down the warfarin figures for those being treated for AF but it is considerably less than the estimated £2.8 million that the cost of rivaroxaban for AF patients eligible for treatment (based on rivaroxaban costs of £766.50/year).	Comment noted. The Committee concluded that that there was uncertainty about the cost of warfarin INR monitoring in clinical practice. See FAD section 4.10

Consultee	Comment	Response
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted
Professor John Potter	Thank you for your invitation to the second appraisal meeting on the 15th February. Unfortunately I am unable to attend, but would like the following points to be taken into account:	Comment noted
Professor John Potter	1. I understand from the literature that the average visits per year are approximately 20 per year (NICE costing report). Therefore £242 per year would seem low (£242/12 months equals approx £12.10 per visit). It is not clear whether this takes into account other costs during such visits, for example blood taking by clinic nurses, travel costs, time absent from work etc. Furthermore, there are a significant number of patients who have difficulties managing their INR with a wide variation in the numbers between centres in the UK. Such patients could visit up to once per week, making 30 plus visits per year not unusual.	Comment noted. The Committee agreed that £242 per person was likely to be a conservative estimate of annual anticoagulant monitoring for warfarin if fixed costs were fully included, and that there was uncertainty about the cost of warfarin INR monitoring in clinical practice. See FAD section 4.10
Professor John Potter	2. Patient groups report that patients are worried or anxious about staying within the INR range because of the consequences of being out of range. In my experience they are concerned about the effects of other changes in medication that may affect INR, diet, alcohol intake etc, and this should be taken into account in the appraisal.	Comments noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
Professor John Potter	3. There is no reason to believe that the results of the ROCKET trial should not be applicable to all patients eligible for an OAC, but not currently taking warfarin (i.e. patients with mental impairment and difficulties with dose adjustments). At this time, aspirin is the only other option to manage these patients. It has been shown in the literature in analyses undertaken in other trials, such as RELY and ARISTOTLE, which the treatment effect of the new OACS is independent of baseline CHADS risk.	The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of ROCKET-AF would not translate to people with a lower $CHADS_2$ score. See FAD section 4.5
Fiona Sayers	I have reviewed the enclosed papers. I agree with the questions raised and the	Comment noted The Committee discussed the costs associated with

Consultee	Comment	Response
	wording of these questions. I also agree with the discussion outlined within the clinical experts text related to my attendance. However, I am unclear how the revised figure of annual INR testing was made up and would like this to be broken down so it is more transparent to the user of such a guideline. The ROCKET –AF trial assumed the annual cost of INR testing to be £535. The revised cost assumed by the committee is stated to be £242. As this could influence the outcome significantly, a breakdown should be made available please. Description of problem: Breakdown of INR monitoring costings; Description of proposed amendment; Tabalised outline of expected annual cost of INR monitoring Result of amended model or expected impact on the result (if applicable); Cost breakdown of annual INR monitoring	warfarin INR monitoring See FAD section 4.10
RCN	Has the relevant evidence has been taken into account? The evidence considered seems comprehensive.	Comment noted
RCN	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We agree with the discussion outlined within the clinical experts text related to my attendance. However, we are unclear on how the revised figure of annual INR testing was made up and would like this to be broken down so it is more transparent to the user of the guidance. The ROCKET –AF trial assumed the annual cost of INR testing to be £535.	Comment noted The Committee discussed the costs associated with warfarin INR monitoring See FAD section 4.10

Consultee	Comment	Response
	The revised cost assumed by the committee is stated to be £242. As this could influence the outcome significantly, it would be helpful if a breakdown were to be made available. We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with atrial fibrillation. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	
RCN	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
RCN	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None that we are aware of.	Comment noted
RCN	Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document? We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted

Consultee	Comment	Response
The Royal College of Pathologists	• Has all of the relevant evidence been taken into account The committee has taken into account the available literature comparing rivaroxaban to warfarin for the prevention of stroke in atrial fibrillation (ROCKET-AF study). One other study (JROCKET-AF) was discounted as the population was dissimilar to that of the UK population and anticoagulation therapy with warfarin was not performed as it would be in other countries. To my knowledge no other literature regarding the use of rivaroxaban for the prevention of stroke and systemic embolization in AF is available. There is published evidence within the literature reporting predictors of stable anticoagulation therapy; it is notable that the presence of diabetes mellitus and heart failure predict the likelihood of unstable anticoagulant therapy (Witt DM et al, JTH 2010; 8:744-9). Given that there were significant numbers of patients with such comorbidities in the ROCKET-AF study, that might, in part, explain the relatively low time in therapeutic range. The revised cost-effectiveness analysis data requested from the manufacturer by the NICE committee, including that regarding subgroup analyses by country or centre, may help interpret this further.	Comment noted
The Royal College of Pathologists	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence The summaries of clinical effectiveness appear reasonable interpretations of the evidence. The decision to utilise the 'safety on treatment' analysis is reasonable, and best reflects the study data. The issue regarding the cost of monitoring warfarin is difficult; the costs vary considerably across the UK and between patients. The costs of monitoring unstable patients will inevitably be higher, both to the health economy and to the patient, and those patients have potentially the most to gain from an anticoagulant therapy that does not need regular monitoring.	Comments noted. The Committee agreed that a precise estimate could not be given because costs varied considerably between people (for example, they are higher in those with poor INR control) and between centres. The Committee agreed that there was uncertainty about the cost of warfarin INR monitoring in clinical practice. See FAD section 4.10
The Royal College of Pathologists	• Are the provisional recommendations sound and a suitable basis for guidance to the NHS The provisional recommendations (not to recommend rivaroxaban for the prevention	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-

Consultee	Comment	Response
	of stroke or systemic embolization in atrial fibrillation) do not appear to take into account the potential benefit of rivaroxaban to patients who are unable to be anticoagulated with warfarin anticoagulation (rivaroxaban ACD 3.19). There is a group of patients who would potentially significantly benefit from a novel anticoagulant (those with allergies/ unable to tolerate warfarin, those with unstable anticoagulation, those that cannot manage the difficulties in taking warfarin medication with its variable dose).	valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
The Royal College of Pathologists	• Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? No	Comment noted
The Royal College of Pathologists	• Are there any equality- related issues that need special consideration and are not covered in the appraisal consultation document? No.	Comment noted.
Stroke Association	Response to consultation on Rivaroxaban (atrial fibrillation/stroke prevention) The Stroke Association is the main UK-wide charity solely concerned with combating stroke. Our mission is to prevent strokes, and reduce their effect through providing services, campaigning, education and research. Our services directly help almost 21,000 stroke survivors and in the last year we have invested £2.6 million in stroke research. We also provide information for members of the public concerned by stroke as well as people affected by it and we campaign to prevent stroke and to ensure that stroke survivors are not denied access to the treatment and services they need. As a disclaimer, it should be noted that we are currently running a stroke prevention and AF risk awareness campaign – Ask First - partly funded by Bayer Healthcare and other pharmaceutical companies. You can learn more about our campaign by going to www.stroke.org.uk/askfirst	Comment noted

Consultee	Comment	Response
Stroke Association	Atrial fibrillation is a major risk factor for stroke with around one in every six strokes caused by AF. We therefore have a very strong interest in promoting the optimal management for anyone who has AF. One of the current issues we are aware of is patients with AF often being undiagnosed. However, more worryingly is that those that are diagnosed can often go untreated Therefore The Stroke Association campaigns for better diagnosis, treatment and management of people with AF, thereby preventing a number of strokes from happening. Where patients have been diagnosed and been found to have a medium or high risk of a stroke in the future, we understand that most are treated with warfarin. Despite evidence of improved outcomes for these patients from prescribing warfarin we believe there is a reluctance to prescribe it because of the associated risks such as falls and bleeding.	Comment noted
Stroke Association	The Stroke Association commissioned some research into this aspect and surveyed 1000 GPs throughout the UK asking why they felt there were currently problems with the diagnosis, treatment and management of AF. The main reason given (with 55% of GPs responding) was 'Associated risks of treatment i.e. anti-coagulants). We may conclude from this that GPs are reluctant to give their patients warfarin which in turn has the consequence that stroke survivors are not being treated and put at risk of having a stroke.	Comment noted
Stroke Association	We are also aware of other issues with warfarin, through anecdotal evidence. These include patients needing to be closely monitored, needing to take frequent time out to attend clinics and to modify their diet due to certain types of food that react with the treatment. Already a challenge for otherwise healthy people, it is harder for stroke survivors who also have to cope with co-morbidities and the effect of their stroke (mobility, memory and communication impairments). Taken together these restrictions, in addition to the cost of attending clinics, further impact on the patients' and carers' quality of life.	Comment noted The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke, and people taking warfarin often worry

Consultee	Comment	Response
	The Stroke Association therefore would welcome any new treatments for AF that ensure better take up and limits the risks associated with existing treatments.	about their level of INR control and they might find regular GP and hospital visits disruptive and inconvenient. They also heard that the need for regular monitoring and dose adjustments, occasionally involving complicated regimens such as different doses on alternate days, can cause difficulties with adherence to treatment.See FAD section 4.2

Comments received from members of the public

Patient 1	Section 1 (Appraisal Committee's preliminary recommendations	As an accountant I do not like the use of averages. I would like to see the proposal set out the incremental costs of the proposal (by cost category) so that anyone can comment on all assumptions. You should include the effect of volume changes. It would be good to have a simple Excel model. Secondly, what costs would be saved by implementing the proposal. For example I visit the warfarin clinic every few weeks for my INR check. What would be the reduction in staff costs etc of the proposal. This should be put in a way that can be compared to actual cost changes. Again a Excel model would be helpful. Thirdly, what are the expected costs of addressing the problems of side effects (on Excel). Fourthly, how many strokes and other problems does the proposal expect to stop (again on Excel) Fifthly, a summary that shows the full incremental cost/benefit of the proposal (on Excel) that can be presented for audit. Finally, and perhaps the most important aspect is transparency - the numbers should be published on the internet. Experience has taught me that all forecasts are (to a greater or lesser extent) wrong. We should all have the opportunity of learning.	Comments noted. The Committee discussed the costs associated with warfarin INR monitoring See FAD section 4.10. Implimentation tools such as a costing template and audit tools will be available for this appraisal on the NICE website

Patient 2	Notes	I would like to add that as a younger AF patient, of 30 years old, on anti-coagulation therapy, current drug requirements for constant monitoring make forward planning very difficult and this it a great time consumer. I am very lucky to have an understanding employer who allows a good level of flexibility, but I know that most people are not so fortunate. As such, I would plead that any drug that can lessen this impact be given the utmost consideration as ultimately for some people this very treatment could make the difference between them maintaining a full working life and being unable to work and balance all the requisite appointments as it the case at present.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11 Comment noted The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke, and people taking warfarin often worry about their level of INR control and they might find regular GP and hospital visits disruptive and inconvenient. They also heard that the need for regular monitoring and dose adjustments, occasionally involving complicated regimens such as different doses on alternate days, can cause difficulties with adherence to treatment. See FAD section 4.2
Patient 3	Section 1 (Appraisal Committee's preliminary recommendations)	It does appear to be expensive compared to Warfarin. However, without being able to analyse a warfarin clinic's expenditure with regard to assessing and maintaining correct and safe INR levels it is difficult to comment.	Comment noted. Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11 The Committee discussed the costs associated with warfarin INR monitoring See FAD section 4.10

	Section 2 (The technology)	As a patient taking Warfarin I do not experience any adverse reactions from the drug. The food and drink choices do not pose a problem. There is only a problem if you make one	Comment noted.
	Section 3 (The manufacturer's submission)	I do not feel qualified to comment on this	Comment noted
	Section 4 (Consideration of the evidence)	The manufacturer developed a Markov model that compares rivaroxaban (20 mg once a day) with warfarin (adjusted dose warfarin at 4.5 mg once a day, target INR 2.5, range 2.0 to 3.0), . I actually take a warfarin dose of 3mg daily to maintain an INR level of 2.5. However if on rivaroxaban I would have to take 20mg to achieve the same result.	Comment noted
	Section 5 (Implementation	I am sure that most PCTs would not include this new drug into their budgets as it does not appear to be proven as cost effective and there are no recognised benefits of taking Rivaroxaban over Warfarin	Comments noted The Committee discussed the costs associated with warfarin INR monitoring See FAD section 4.10 The Department of Health has issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. See FAD section 5.1

Patient 4	Section 1 (Appraisal Committee's preliminary recommendations	I have AF. I think there should be a choice of treatments to include warfarin and this new drug because, if clinicians have a choice they can better match medication to patients. The cost of warfarin is not just measured in the price of the drug, but in the provision of regular blood tests for patients meaning that patients have to attend a clinic. There is a cost to the health authority in providing clinics, staff, testing and sending out results. Patients like myself with mobility issues have extra difficulties. It can be painful and stressful to have to remember to attends clinics at the right time, and repeated tests often cause pain and soreness in the arm, especially if you dont have good veins.	Comment noted . Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke.. See FAD section 4.2
	Section 4 (Consideration of the evidence)	I sometimes have to be tested on a weekly basis. eg if Ive had to stop warfarin for a medical/dental proceedure it takes a long time to get my INR stable again. Im certain my tests cost a lot more than £242 pa.	Comment noted. The Committee agreed that £242 per person was likely to be a conservative estimate of annual anticoagulant monitoring for warfarin if fixed costs were fully included, and that there was uncertainty about the cost of warfarin INR monitoring in clinical practice. See FAD section 4.10 The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
Patient 5	Notes	I fully support any decisions taken by the AF Association.	Comment noted.
Patient 6	Section 6 (Proposed recommendations for further research)	I can now have Dabigatran thanks to the AFA for which I am most grateful.	Comment noted.

Patient 7	Notes	I am sure there must be many like me who would welcome the new alternatives to Warfarin. It is such a trouble having to remember to go to the local hospital and wait for an hour or more to give a blood sample when one additional pill a day for we aged pill takers would be easy. Our local phlebotomists, blood couriers, lab technicians and doctors and surgery staff could then devote more of their precious time to others who need their services. The new medications do cost more but the savings accrued by those of us who would no longer need to be monitored would surely be worth it.	Comment noted.
	Section 1 (Appraisal Committee's preliminary recommendations	My response suggests that the new treatment would prove to be cost effective	Comment noted The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke.. In addition, they might find regular GP and hospital visits disruptive and inconvenient that the need for regular monitoring and dose adjustments, occasionally involving complicated regimens such as different doses on alternate days, can cause difficulties with adherence to treatment.. See FAD section 4.2 Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

	Section 2 (The technology)	In that case, is there a safer alternative product available?	Comment noted. The European Medicines Agency is responsible for evaluating the benefits and risks for patients of new technologies.
	Section 3 (The manufacturer's submission)	Has this medication been taken up by American hospitals in a country which treads very carefully in case patients sue for maltreatment?	Comment noted.
	Section 4 (Consideration of the evidence)	Warfarin has its risks. Which is greater?	Comment noted. The Committee discussed the safety profile of rivaroxaban. See FAD section 4.6
	Section 7 (Related NICE guidance)	Sooner, so far as patients are concerned surely.	Comment noted.
NHS professional 1	Section 1 (Appraisal Committee's preliminary recommendations)	With an ageing population and an accompanying likely increase in Atrial Fibrillation (AF) in the future, NHS Southampton City welcomes the investigation into possible treatmetns for AF. However, after considering the evidence, NICE concludes that adjusted dose warfarin is the most cost effective treatment for prevention of stroke and systematic embolism in patients with AF. NHS Southampton City supports this view.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

	Section 2 (The technology)	On balance rivaroxaban appears to be of comparable safety to warfarin. In the ROCKET-AF trial, the primary safety endpoint (major bleeding and clinically relevant non-major bleeding) showed no statistically significant difference between the two treatments. However, as it is new to the market, it has not been possible to explore the long-term safety outcomes of rivaroxaban, which would be relevant in patients with AF who are likely to be taking it for many years.	Comment noted. The European Medicines Agency is responsible for evaluating the benefits and risks for patients of new technologies. The Committee discussed the safety profile of rivaroxaban. See FAD section 4.6
	Section 3 (The manufacturer's submission)	Unit costs: the required dose for rivaroxaban was equivocal. The manufacturers quote incremental cost effective ratios (ICERs) per Quality Adjusted Life Year (QALY) for a dose of 10mg per day, but participants in the ROCKET-AF trial received 20mg per day. The manufacturers suggest that a dose of 10mg per day would cost £2.10 or £766.50 per year. The BNF 62 lists the price of 10mg rivaroxaban as £44.15 for a 10-tab pack. Eligible patients: the manufacturer asserts the prevalence of AF in 2010 to 1.4% in England. NICE uses the 2006 figure of 1.15%. All AF sufferers would be eligible for treatment.	Comment noted. The costs in BNF Number 62 are for Rivaroxaban for the treatment of venous thromboembolism.

	Section 4 (Consideration of the evidence)	In the ROCKET-AF trial Rivaroxaban (taken in a dose of 20mg daily) showed no statistically significantly different clinical outcomes (ischaemic and haemorrhagic stroke and non-CNS systematic embolism) when compared to warfarin in intention-to-treat analysis (Hazard ratio 0.88 95% CI 0.75 to 1.03). Subgroup analysis suggested rivaroxaban was favourable in patients who had not previously received vitamin K (HR 0.72 95% CI 0.53 to 0.97). NICE concluded that warfarin may be more beneficial in a real-life setting due to the ROCKET-AF sample containing unusually severe AF cases. There may be some patients with AF that are unable to take warfarin, and so it is important that safe, effective alternative drugs are developed.	Comment noted.

	Section 5 (Implementation)	Cost effectiveness: INR monitoring costs per annum have been estimated differently by the manufacturers and NICE at £242 and £535 respectively. The manufacturers? inflated cost estimates of anti-coagulant monitoring for patients on warfarin drives down the ICER per QALY of rivaroxoban (£18,883). NICE estimates the ICER to be much higher at £62,568. Impact on Southampton?s population: Estimated prevalence of AF in Southampton is between 2731 and 3325 (using NICE prevalence estimates, or manufacturer estimates respectively). At the current cost per QALY estimated by NICE, rivaroxaban would require substantial Primary Care Trust resource use, which might not be sustainable considering the large numbers of patients with AF and the simultaneous demand on resources to provide other services.	Comment noted. The Committee discussed the costs associated with warfarin INR monitoring See FAD section 4.10 The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. See Guide to the methods of technology appraisal 2008, section 6.2.14 Costing tools and support for audit are produced for all technology appraisals. See Guide to the methods of technology appraisal 2008, section 1.5.1
	Section 7 (Related NICE guidance)	At this time, more clarity is needed from the manufacturer about dose, prevalence of AF and monitoring costs on warfarin. We therefore support the NICE conclusion not to recommend rivaroxaban for the prevention of stroke and systemic embolism in people with AF, pending revised cost-effectiveness analysis.	Comment noted. The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. See Guide to the methods of technology appraisal 2008, section 6.2.14 Costing tools and support for audit are produced for all technology appraisals. See Guide to the methods of technology appraisal 2008, section 1.5.

Patient 8	Section 1 (Appraisal Committee's preliminary recommendations)	I am on warfarin and it works. If Rivaroxaban will do the job better than Warfarin and if it has been tested to British standards then if in the long term it both saves money and prevents stroke to a larger extent than warfarin then go for it. My Consultant says that he would be very reluctant to prescribe for elderly patients and the condition of each patient must be taken into account. A relation of mine in the the US has had to be taken off it due to bleeding and was informed that his Consultant should not have prescribed Rivaroxaban as he was not a suitable candidate. He is now back on Warfarin. So it looks to me that you pay your money and take your chances. If it aint broke why try and fix it. I suggest that it would be bette to leave all patients on warfarin and supply each patient with a teste,just look at the cost savings in the long term.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	If implemented then all costs will come down.	Comment noted.
	Section 3 (The manufacturer's submission)	manufactors will always produce stats to support their product	Comment noted.
	Section 4 (Consideration of the evidence)	Not convincing	Comment noted.
	Section 5 (Implementation)	With the proposed changes to the NHS this seems irrelevant	Comment noted.
	Section 6 (Proposed recommendations for further research)	CONFUSION is the only comment	Comment noted.

	Section 7 (Related NICE guidance)	OUt of date	Comment noted.
Patient 9	Section 4 (Consideration of the evidence)	As a sufferer of Paroxysmal AF for many years I was initially treated with aspirin and Sotalol. However I was soon advised to have a Catheter Ablation to hopefully ease my symptoms. I was anxious about this procedure and spent several years fending it off. However, after another visit to my very patient consultant I decided to go ahead with the procedure. This, of course entailed commencing Warfarin in March 2010. I could never get stable with Warfarin. My INR was either too high or too low despite being careful to be consistent with my diet. I had to have weekly testing which hugely interfered with my work and lifestyle. I travel widely in the UK and abroad. In September 2011 after a particular bout of my INR swinging widely I suffered an embolic infart. I failed Warfarin. I had therapeutic clexane for cover and then was lucky enough to have a very forward looking GP with the advice of my consultant haematologist to prescribe Dabigatran from November 2011. This has proved to be incredibly helpful in all manner of ways to help me lead a normal and full life. Rivaroxaban needs to be available for the thousands of people who find Warfarin damaging.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

Patient 10	Notes	Dear Sirs I am 65, white British, and am an UK resident. I had a stroke in Jan 2010 and discovered that I had Atrial Fibrillation. I have taken Warfarin subsequently aiming to keep my INR between 2.0 and 3.0. It is a nuisance to keep having INR checks frequently, whether in the UK or abroad, so I?d prefer a drug with a fixed dosage (even if it means taking twice-daily). I also have Chronic Lymphocytic Leukaemia (Stage A). There is no treatment at present, but there might soon. If such a cure conflicted with my Warfarin, it would be serious for me! I have had a Basal Cell Carcinoma excised from my forehead on Friday 27 Jan, and prescribed one week's penicillin to help avoid infection. I'm told that some people find that their INR is raised as a consequence so I need yet another INR check in a few days time. Please can you approved other anti-coagulants than Warfarin for Atrial Fibrillation patients.	Comment noted. The Committee heard that warfarin, although an effective treatment, it is associated with a number of problems. The main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the therapeutic range. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. See FAD section 4.2. The Committee heard from the clinical specialists 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. See FAD section 4.2 Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

NHS Professional 2	Section 1 (Appraisal Committee's preliminary recommendations)	I am concerned that this consultation document may not provide a fair appraisal of the potential role of Rivaroxaban for stroke prevention in people with atrial fibrillation. The standard drug, Warfarin, is highly effective in patients who are compliant with therapy and in whom INR remains in the therapeutic range. Although standards of anticoagulation control in the UK have improved dramatically in recent years, many Warfarin treated subjects have periods of variable length when INR falls outside the therapeutic range. In such patients, an alternative anti-thrombotic agent, such as Rivaroxaban, would provide a significant clinical advantage which cannot be determined by cost-effectiveness analysis in the whole population.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

	Section 2 (The technology)	Uniquely, participants in ROCKET AF had high risk of embolic events. These are the individuals in whom antithrombotic therapy is associated with the greatest absolute benefit. An alternative to Warfarin in such patients would represent an important therapeutic advance. Although lower risk patients were not included in ROCKET AF, the evidence from other studies (RE-LY and ARISTOTLE) suggest, as would be expected, proportional relative benefit across the range of risk.	The Committee was also made aware by the manufacturer that a systematic review of the literature had suggested that there does not appear to be an interaction between treatment effect and baseline $_{CHADS2}$ risk. The Committee heard from the manufacturer that rivaroxaban would be indicated for atrial fibrillation in people with one or more risk factors for stroke, which equates to a $CHADS_2$ score of 1 or more The Committee noted that the European Medicines Agency had stated in the 'European public assessment report' for rivaroxaban that efficacy results were essentially consistent in important subgroups, such as different $CHADS_2$ scores ($CHADS_2$ scores 2 to 6). The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of ROCKET-AF would not translate to people with a lower $CHADS_2$ score. See FAD sections 4.5

	Section 4 (Consideration of the evidence)	Finally, the Appraisal Committees preliminary recommendations ignore patient preference and quality of life issues. Warfarin is cheap and effective but has a clinical pharmacological profile which makes this anticoagulant highly unpopular with patients. In 40 years of clinical research, the only occasions on which study patients have requested to stay on the new drug have been in trials with novel antithrombotic agents. It would be a cause for regret if cost-containment meant that access of British patients to a therapeutic advanced was denied or delayed.	Comment noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
Patient 10	Notes	As a patient the monitoring appointments are sometimes disruptive and it can be difficult to travel to the appointment. Various other health issues may require an interruption in warfarin treatment which make it difficult to reach the relevant dose - requiring further/more frequent monitoring appointments. Doubt this is cost effective.	Comment noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
	Section 1 (Appraisal Committee's preliminary recommendations)	Is £242 per person for the cost of INR monitoring a realistic cost?	Comment noted. The Committee agreed that £242 per person was likely to be a conservative estimate of annual anticoagulant monitoring for warfarin if fixed costs were fully included, and that there was uncertainty about the cost of warfarin INR monitoring in clinical practice. See FAD section 4.10
	Section 2 (The technology)	I took rivaroxaban prophylactically following knee replacement surgery and had no side effects whatsoever	Comment noted. This appraisal is for rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation, this is a different indication.

Patient 11	Section 1 (Appraisal Committee's preliminary recommendations)	There isnt a cost suggested for finger tip testing and monitoring of INR which might be cheaper	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	I am amazed that a drug which may not have an antidote and which is caustic as the previous suggested ones are can cost so much. I dont think it is kind to inflict such medication on elderly people or high risk problems whilst the risk of bleeding is such a feature.	Comment noted.
	Section 3 (The manufacturer's submission)	There is a lot of detail about the dominance of the new medication in those who dont manage their warfarin which is well put but I have to take aspirin and warfarin and this is not a comparison I have seen addressed by the manufacturer.Thus far I have been ok - long term user-.	Comment noted.
	Section 4 (Consideration of the evidence)	Although there is a need to watch food and drink,and blood tests can be painful and frequent,warfarin is effective - well in my experience. If this drug is ever contemplated it must be a drug of last resort.	Comment noted.
	Section 5 (Implementation)	I remain of the view the introduction should only be for last resort and home INR monitoring should be examined more fully. I would welcome this as one who has to take aspirin and warfarin.	Comment noted.
	Section 6 (Proposed recommendations for further research)	There remains acceptance that warfarin alternatives are more caustic and dont have a specific antidote.	Comment noted.
	Section 7 (Related NICE guidance)	This seems good as more research may be available about other safer alternatives.	Comment noted.

Patient 12	Notes	Warfarin is not friendly for the patient, constant need to manage diet and fluid intake, wide variation and fluctuation in readings does not leve me feeling confident with this medication. Monthly blood checks is time consuming and for me living in a rural area a 25 mile round trip each time. Warfarin in my view is archaic and needs replacing with a modern drug	Comment noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
	Section 1 (Appraisal Committee's preliminary recommendations)	where a peron hs had a blod clot stroke and also has AF i belive they should be offered tivoraxaban as this is prevention were this evidence of a stroke	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	this in a par with Warfarin but with significant easier patient managment	Comment noted.
	Section 3 (The manufacturer's submission)	a better alternative to warfarin	Comment noted.
	Section 4 (Consideration of the evidence)	I have had one blood clot stroke so the fear and risk fo me is high and real. Warfarin is not my drug of choice because of low confidence caused by wide variation in INR readings anf the inconvenient long term management	Comment noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
Patient 13	Section 1 (Appraisal Committee's preliminary recommendations)	Can't comment, as the language used is far too technical for me,a lay person to understand!!	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	None	Comment noted

	Section 3 (The manufacturer's submission)	Sorry cant understand most of this..far,far too technical!!	Comment noted
	Section 4 (Consideration of the evidence)	I am new to Warfarin(4 weeks) but its impact on my quality of life is significant. Todays technology MUST be able to produce better alternatives!	Comment noted. The Committee heard that taking warfarin adversely affects quality of life. This is because people taking warfarin often have a poorly controlled INR, which increases the risk of stroke. See FAD section 4.2
	Section 5 (Implementation)	Patients,family,carers etc MUST have a say in these consultations. This is NOT the way to do it! What are you going to do about it?	Comment noted.
	Section 6 (Proposed recommendations for further research)	None	Comment noted.
	Section 7 (Related NICE guidance)	Why does it take so long?	Comment noted.
Patient 14	Section 1 (Appraisal Committee's preliminary recommendations)	feel it is unfair that af patients will be not allowed to benifit from this new med. inr checking costs far more at the moment esp if your dose cant be regulated.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	the technology far out wares warfarin it is more up to date and less risk	Comment noted. The Committee discussed the safety profile of rivaroxaban compared with warfarin. See FAD section 4.6

Comment [n1]: Could refer to UNG once guidance is published

	Section 3 (The manufacturer's submission)	full eplaantion covers all bases. promoting better lives for warfarin takers.. concern not many young peopl include in testing	Comment noted.
	Section 4 (Consideration of the evidence)	af causes upset in many lives the addition of warfarin and inr testing increase this pressure i havent worked for 18 months and i have to find an employer who will fit my inr apmt into my working day its very hard	The Committee heard that people taking warfarin might find regular GP and hospital visits disruptive and inconvenient.. See FAD section 4.2
	Section 5 (Implementation)	get it out now	Comment noted
	Section 6 (Proposed recommendations for further research)	af should have full access	Comment noted
	Section 7 (Related NICE guidance)	go for it	Comment noted

Patient 14	Notes	NICE appears to many of us who are tethered by warfarin to an anticoagulation clinic to be reaching conclusions more on the basis of individual biases than scientific data. When the US FDA and scientists in Scotland approve alternative drugs (like Dabigatran) and NICE doesn't, one has to suppose that the NICE panel is either arrogant ("we are smarter than the Americans and the Scots") or that it is letting its recommendations be influenced by something beyond the research findings. Year ago I read the autobiography of a doctor who was one of the worlds leading authorities on an obscure, rare, and deadly ailment. One day he himself developed the disease. He wrote something on the following lines: "Whenever I had to tell a patient that he or she had the disease, I would say I know how you feel. When I saw my test results and there was no escaping the fact that I now had the disease myself, I realized that I had had no idea at all of how my patients felt when I delivered the news. It was only when I myself was the one with the illness that I knew how they felt."I believe many members of the NICE panel on anticoagulants have (understandably) a similar inability to empathize with those of us who have the anxiety, inconvenience, and constraints on our lives imposed by the control and monitoring of INR levels and the uncertainty of how effective the warfarin is at any given time of reducing the risk of stroke without a high risk of bleeding.I see how clever panel members are at criticizing details of the research supporting the greater effectiveness and safety of other anticoagulants (and the much greater convenience for patients). What I dont see is much ability to weigh the methodological niceties, the clever criticisms, while at the same time having the empathy to take into account the human factors that make alternatives to warfarin so much more desirable to the patients themselves. If warfarin were so good, so safe, and so convenient I would not want to switch. But it is not, so I would take the quite small risk that further research will validate NICEs fastidious concerns.	Comment noted NICE has it's own process for appraising drugs. See Guide to the Single Technology Appraisal (STA) process 2010 and Guide to the Methods of Technology Appraisal 2008.

	Section 1 (Appraisal Committee's preliminary recommendations)	NICE appears to many of us who are tethered by warfarin to an anticoagulation clinic to be reaching conclusions more on the basis of individual biases than scientific data. When the US FDA and scientists in Scotland approve alternative drugs (like Dabigatran) and NICE doesnt, one has to suppose that the NICE panel is either arrogant ("we are smarter than the Americans and the Scots") or that it is letting its recommendations be influenced by something beyond the research findings. Year ago I read the autobiography of a doctor who was one of the worlds leading authorities on an obscure, rare, and deadly ailment. One day he himself developed the disease. He wrote something on the following lines: "Whenever I had to tell a patient that he or she had the disease, I would say I know how you feel. When I saw my test results and there was no escaping the fact that I now had the disease myself, I realized that I had had no idea at all of how my patients felt when I delivered the news. It was only when I myself was the one with the illness that I knew how they felt." contd... next box	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11. NICE has it's own process for appraising drugs. See Guide to the Single Technology Appraisal (STA) process 2010 and Guide to the Methods of Technology Appraisal 2008.

	Section 2 (The technology)	I believe many members of the NICE panel have (understandably) a similar inability to empathize with those of us who have the anxiety, inconvenience, and constraints on our lives imposed by the control and monitoring of INR levels and the uncertainty of how effective the warfarin is at any given time of reducing the risk of stroke without a high risk of bleeding. I see how clever panel members are at criticizing details of the research supporting the greater effectiveness and safety of other anticoagulants (and the much greater convenience for patients). What I dont see is much ability to weigh the methodological niceties, the clever criticisms, while at the same time having the empathy to take into account the human factors that make alternatives to warfarin so much more desirable to the patients themselves. If warfarin were so good, safe, & convenient I would not want to switch. But it is not, so I would take the quite small risk that further research will validate NICEs fastidious concerns. The evidence in favour of alternative anticoagulants is good enough for me and I'm the patient. Try, please, to put yourself in my position when making your decision.	Comment noted
Patient 15	Section 1 (Appraisal Committee's preliminary recommendations)	Clinical familiarity with alternatives to warfarin is vital, given the low level of warfarin patients, at 18%, who are in the thereapeutic INR range. We need more consistently effective treatments, and not just one alternative i.e. dabigatran.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	There may be good clinical reasons to not give warfarin such as patient intolerance to warfarin	Comment noted

	Section 3 (The manufacturer's submission)	Not qualified to comment	
	Section 4 (Consideration of the evidence)	Not agreed. The 55% compliance in rocket-AFd id not borne out by other studies which are much more pessimistic at 18%. Being on warfarin is difficult for patient and clinician, and restructs the patients QoL. I think we need a number of real alternatives to warfarin available to clinicians	Comment noted. The Committee heard that warfarin, although an effective treatment, it is associated with a number of problems. The main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the therapeutic range. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. See FAD section 4.2
	Section 5 (Implementation)	No comment	Comment noted
	Section 6 (Proposed recommendations for further research)	Yes but just one alternative, dabigatran, is insufficient. What if dabigatran has a serious problem needing withdrawal? If you dont allow anything else there will be no UK experience of alternatives.	Comment noted
	Section 7 (Related NICE guidance)	Too far out in a rapidly moving field, when you have effectively banned its use.	Comment noted
Patient 16	Section 1 (Appraisal Committee's preliminary recommendations)	there doesntappear to any consideration of people like myself who have multiple conditions one of which is AF.I have ahistoryn of strokes and TIAs.I take a huge quantity of drugs daily and my INR has been stable for 2 years. i would dearly like to cut down the numbers of drugs i take and reduce the risk of making amistake when counting out my warfarin dose	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

Patient 17	Section 1 (Appraisal Committee's preliminary recommendations)	More effort should be applied to improving TTR for warfarin therapy. Considerable increases in TTR can be achieved through home monitoring and Vit K supplementation. This would improve health overall and reduce cost a lot more than new drugs which have marginal benefits, if at all.	Comment noted
	Section 4 (Consideration of the evidence)	Warfarin with proper monitoring using a home monitor reduces the number of strokes and increases TTR.	Comment noted
Patient 18	Section 1 (Appraisal Committee's preliminary recommendations)	The wording contained here is very difficult for me to understand - despite being highly educated. All I know is that I have AF, am terrified of having a stroke but cannot tolerate warfarin. so i take aspirin but already after only a year have stomach erosions which the consultant nurse blames on the aspirin. I NEED THIS ALTERNATIVE DRUG - PLEASE	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	The wording contained here is very difficult for me to understand - despite being highly educated. All I know is that I have AF, am terrified of having a stroke but cannot tolerate warfarin. so i take aspirin but already after only a year have stomach erosions which the consultant nurse blames on the aspirin. I NEED THIS ALTERNATIVE DRUG - PLEASE	Comment noted
	Section 3 (The manufacturer's submission)	The wording contained here is very difficult for me to understand - despite being highly educated. All I know is that I have AF, am terrified of having a stroke but cannot tolerate warfarin. Â so i take aspirin but already after only a year have stomach erosions which the consultant nurse blames on the aspirin. I NEED THIS ALTERNATIVE DRUG - PLEASE	Comment noted

	Section 4 (Consideration of the evidence)	The wording contained here is very difficult for me to understand - despite being highly educated. All I know is that I have AF, am terrified of having a stroke but cannot tolerate warfarin. so i take aspirin but already after only a year have stomach erosions which the consultant nurse blames on the aspirin. I NEED THIS ALTERNATIVE DRUG - PLEASE	Comment noted
	Section 5 (Implementation)	The wording contained here is very difficult for me to understand - despite being highly educated. All I know is that I have AF, am terrified of having a stroke but cannot tolerate warfarin. so i take aspirin but already after only a year have stomach erosions which the consultant nurse blames on the aspirin. I NEED THIS ALTERNATIVE DRUG - PLEASE	Comment noted
	Section 6 (Proposed recommendations for further research)	The wording contained here is very difficult for me to understand - despite being highly educated. All I know is that I have AF, am terrified of having a stroke but cannot tolerate warfarin. so i take aspirin but already after only a year have stomach	Comment noted
	Section 7 (Related NICE guidance)	The wording contained here is very difficult for me to understand - despite being highly educated. All I know is that I have AF, am terrified of having a stroke but cannot tolerate warfarin. Â so i take aspirin but already after only a year have stomach erosions which the consultant nurse blames on the aspirin. I NEED THIS ALTERNATIVE DRUG - PLEASE	Comment noted

Patient 19	Section 1 (Appraisal Committee's preliminary recommendations)	Does the monitoring cost include staff pay & equipment? This total must be difficult to calculate as I know from my own experience my INR fluctuates quite widely and my monitoring visits are un-predictable because of this.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11. The Committee discussed the costs associated with warfarin INR monitoring. The clinical specialists agreed that the annual cost of anticoagulant monitoring for each person treated with warfarin was likely to be lower than the manufacturer's estimate in clinical practice, but a precise estimate could not be given because costs varied considerably between people (for example, they are higher in those with poor INR control) and between centres. See FAD section 4.10
	Section 2 (The technology)	See above comment. What are the extra costs for side-effects from warfarin as compared to rivaroxaban?	Comment noted. The costs associated with side effects with rivaroxaban and warfarin was included in the economic models.
	Section 3 (The manufacturer's submission)	Far too complicated for a patient to assess!	Comment noted

	Section 4 (Consideration of the evidence)	It appears that the committee are manipulating the statistics to support their argument. I know that my quality of life was better on an anti-coagulant that didnt require monitoring antwhere near as much as warfarin does. Its far easier to remember 1 tablet per day than a warfarin dose that varies from day to day & also from week to week, if my INR has fluctuated. I also get more side effects from warfarin, which, together with the frequent visits for monitoring do impinge on my quality of life. The supposed difference in cost between the two types of treatment appear negligible, looked on in the light of my experiences.	Comment noted The Committee also heard that warfarin, although an effective treatment, it is associated with a number of problems. The Committee was aware from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. This is because people taking warfarin often worry about their level of INR control and they might find regular GP and hospital visits disruptive and inconvenient.. See FAD section 4.2
Patient 20	Section 1 (Appraisal Committee's preliminary recommendations)	Are the committee focused on the expenditure comparisons only and not the patients as is the impression 1.2 above	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. The Committee recognised the potential benefits of alternatives such as rivaroxaban for people with atrial fibrillation, including the positive effect on quality of life of removing the restrictions and difficulties associated with taking warfarin. See FAD sections 4.2
	Section 2 (The technology)	From my point of view the advantages outweigh the disadvantages as a user.Again it seems the main focus is cost based.	Comment noted

	Section 3 (The manufacturer's submission)	I am happy to accept the manufacturers submission my only concern could be what are the long term effects upon patients.The quality of life would certainly improve in such aspects as diet and hospital visits.	Comment noted
	Section 4 (Consideration of the evidence)	Again I think in summary too much emphasis is being placed upon cost. My only other concern is the amount of studies csrried out. U.K.is thin on the ground but so long as the committee are satified then I feell there should be accceptance	Comment noted. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. The Committee recognised the potential benefits of alternatives such as rivaroxaban for people with atrial fibrillation, including the positive effect on quality of life of removing the restrictions and difficulties associated with taking warfarin. See FAD sections 4.2
	Section 5 (Implementation)	The comparison stastics are consistently refeered to especially regarding bleeding.However I dont think enough consideration has been given throughout the report to patients quality of life costs of travel and inconvenience of hospital attendance and diet. The report seems to broadly ignore these or certainly its detail.I repeat t again I think the new drugs should be accepted and that the committee should re consider its decision.	Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. The Committee recognised the potential benefits of alternatives such as rivaroxaban for people with atrial fibrillation, including the positive effect on quality of life of removing the restrictions and difficulties associated with taking warfarin. See FAD sections 4.2

	Section 6 (Proposed recommendations for further research)	I have not had time to read these to be able to comment constructively	Comment noted
	Section 7 (Related NICE guidance)	What is going to happen upto this date? Are trials going to continue in U.K.? Surely this is too long and if as I have said previously that too much emphasis has been placed on cost then pro rata in 2014 the cost will have raised and will this drug be a prioity bearing in mind the extensive restructure which is currently taking place in NHS.I would suggest you consider the increase in staff costs at hospitals if warfarin continues	Comment noted, Guidance may be reviewed before the review date when there is significant new evidence that is likely to change the recommendations. See guide to the methods of technology appraisal 2008 section 6.2
Patient 21	Section 1 (Appraisal Committee's preliminary recommendations)	The UK does not have available one of the newer anticoagulants, which are proved in world tests to be superior in many ways. To delay, as this recommendation will do, means that there will be more strokes, at a cost greater than the cost of the drug. Limited approval would be preferable. The trial of apixaban was stopped early because it was much better at prevention. Time delay means less chance to be stroke free.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	Looking at adverse reactions should not be a substitute for the overall benefits of a medication. Taken into account yes, but not used to prevent access if there are greater benefits for many patients. As a patient who needs this type of medication, and I have several factors to prefer it to warfarin, I think it should be available as soon as possible. At the moment I take asprin, and my chance of a stroke is greater. Â Should I have one the cost will be large and the effect on my life greater.	Comment noted The Committee concluded that the primary safety end point showed no statistically significant difference between rivaroxaban and warfarin. See Section 4.6

	Section 7 (Related NICE guidance)	Other countries have approved this medication long before the suggested review date. UK patients are getting a poor service by the delay.	Comment noted
Patient 22	Section 1 (Appraisal Committee's preliminary recommendations)	I agree not to recommend rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.9 and 4.16
	Section 2 (The technology)	The adverse reactions are a little worrying	Comment noted
	Section 3 (The manufacturer's submission)	Obviously, the manfacturers will be biased	Comment noted. The ERG critically evaluates the manufacturer's submission. See Guide to the Single Technology Appraisal (STA) Process 2010 Section 3.4.10
	Section 4 (Consideration of the evidence)	I agree	Comment noted
	Section 5 (Implementation)	I agree with the Secretary of State for Health and Social Services directions	Comment noted
	Section 6 (Proposed recommendations for further research)	I agree with NICE guidance	Comment noted
	Section 7 (Related NICE guidance)	The Guidance I feel sure that the Executive will make the right decision	Comment noted

Patient 23	Notes	My occupation prevents me from being a Warfarin patient so I presently take aspirin. If and when I have to go from Aspirin to Warfarin my professional life will be over so I am very dissapointed in your conclusions. Warfarin may be cheap but unless you are retired or unemployed it is not a practical drug. Rivaroxaban would have been ideal for my working life.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	Seems like good value,cheaper than being unemployed through Warfarin	Comment noted
	Section 3 (The manufacturer's submission)	Surely theres a case for giving it to some patients	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Patient 24	Section 4 (Consideration of the evidence)	Cost effectiveness- in the last year I have had to have a total of forty blood tests. Not only are these disruptive to everyday living but if the costs of the tests,threee anti-coagulant nurses employed in this area, administrative time,telephone calls, sealed stationary to inform patients and first class postage are taken into account then cost effectiveness must be closer. In addition bearing in mind that very many patients spend a great deal of time outside their therapeutic level it must be safer.	Comment noted The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. The Committee recognised the potential benefits of alternatives such as rivaroxaban for people with atrial fibrillation, including the positive effect on quality of life of removing the restrictions and difficulties associated with taking warfarin. See FAD sections 4.2 The Committee discussed the costs associated with warfarin INR monitoring. See FAD Section 4.10

Carer 1	Section 1 (Appraisal Committee's preliminary recommendations)	I have read through the whole of this document and can only understand/evaluate in a limited way. As a non medic but as a carer of a patient who has suffered long term cardio problems-may I make this appeal IF there are new /improved drugs out there that would benefit patient quality of life - Please,PLEASE enable them to be available for doctors to prescribe them to the benefit of their patients.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Patient 25	Section 1 (Appraisal Committee's preliminary recommendations)	Why is the monitoring cost, when methods of monitoring can very e.g. self-monitoring), included?	Comment noted See FAD section 4.10
	Section 2 (The technology)	It is important that the Committee considers the cost effectiveness . Warfarin is inexpensive, so any alternative that is expensive should be proportionately superior or otherwise discounted.	Comment noted. See FAD section 4.11
	Section 3 (The manufacturer's submission)	The inadequacy of testing parameters and precudres as shown above, would seem to justify the Committees report, bearing in mind the very substantial increased cost.	Comment noted

	Section 4 (Consideration of the evidence)	Supplying a substantially more expensive medication to people who are careless in using existing treatments should not be a cost borne by taxpayers. The high proportion of non-UK warfarin users in the manufacturers sample appears unsatisfactory. The incidence of problems associated with taking warfarin seems overstated. For all the reasons I have stated above, the Committeess decision not to approve the introduction of rivaroxaban appear fully justified.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Patient 26	Section 4 (Consideration of the evidence)	There needs to be an alternative for warfarin for people unable to maintain stable INR.Weekly blood tests are disruptive to life, expensive for NHS, mean travel is impossible and the INR fluctuations mean that the patient is not properly protected against stroke etc. Unsatisfactory experience of Warfarin can mean decreased compliance with the drug, which defeats the purpose.	Comment noted Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 489 and 4.11
NHS Professional 3	Section 1 (Appraisal Committee's preliminary recommendations)	Agree with preliminary recommendations and findings. Uncertainty around manufacturers submission around cost per QALY.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
	Section 2 (The technology)	The cost is lower than aquisition cost of dabigatran. The number possibly eligible under the licensed indication are more than actual number on warfarin. The financial impact therefore could be lot higher to NHS	Comment noted. The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. See Guide to the methods of technology appraisal 2008, section 6.2.14

	Section 3 (The manufacturer's submission)	The manufacturers submission regarding TTR is lower than actual values in the UK, therefore figures used should reflect UK figures as making benefit of rivoroxaban higher than actually is in practice. cost of INR monitoring does not reflect UK practice	Comments noted. The Committee noted that a key uncertainty highlighted by the ERG was the generalisability of the results of ROCKET-AF to people diagnosed with atrial fibrillation in the NHS. The Committee noted that the mean time in therapeutic range for the INR range of 2.0–3.0 for warfarin was 55% for the safety-on-treatment population in the ROCKET-AF trial. e. See FAD section 4.5
	Section 4 (Consideration of the evidence)	From the network metaanalysis conducted by the company, there are many uncertainties and unable to tell if superior to alternatives	Comment noted. The Committee noted that both the manufacturer's and ERG's network meta-analyses contained wide confidence intervals, and therefore the resulting efficacy point estimates were subject to considerable uncertainty. See FAD section 4.7
	Section 6 (Proposed recommendations for further research)	Could both dabigatran and rivoroxaban be looked at together. Could NICE be clearer on cohort of patients who may benefit rather than suggesting an option within licensed indication.	Comment noted. Consultees agreed at the scoping stage of the appraisal that it would be most appropriate to appraise rivaroxaban through the Single Technology Appraisal process in order to provide timely guidance. The length of time between guidance publication and the review date will vary depending on the available evidence for the technology, and knowledge of when ongoing research will be reported See Guide to the Single Technology Appraisal (STA) process 2010 section 6.1

Patient 27	Notes	I have AF & been prescribed Warfarin. It is difficult to control needing regular tests and has side effects that are affecting my quality of life. I am hoping for rivaroxaban to be approved by Nice. I understand it has the same function as Warfarin without all the problems.	Comment noted. The Committee heard that taking warfarin adversely affects quality of life. See FAD section 4.2 Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11
Patient 28	Section 1 (Appraisal Committee's preliminary recommendations)	There is no mention here of the benefits to patients. That is too important to leave out.	Comment noted. Comment noted. The Committee heard that warfarin, although an effective treatment, it is associated with a number of problems. The main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the therapeutic range. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. See FAD section 4.2. The Committee heard from the clinical specialists 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. See FAD section 4.2
	Section 2 (The technology)	There are hidden costs to Warfarin that aren'[t mentioned here.	Comment noted.

	Section 4 (Consideration of the evidence)	Check with patients please.	Comment noted. Comment noted. The Committee heard that warfarin, although an effective treatment, it is associated with a number of problems. The main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the therapeutic range. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. See FAD section 4.2. The Committee heard from the clinical specialists 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. See FAD section 4.2 Patient experts attend Appraisal Committee meetings as individuals and not as representatives of their nominating organisation. NICE aims to select a cross-section of individuals from the nominations received for clinical specialists and patient experts. For example, for patient experts, NICE would select a person with direct personal experience of the technology and a representative of a patient, carer or professional organisation. See Guide to the single technology appraisal process 2009

Patient 29	Notes	I have been taking warfarin now for over 4 years and the major issues I have with this medication are as follows: A) I am currently having fortnightly blood tests to measure my INR which obviously puts some pressure on the NHS in terms of cost of these tests - postage etc. B) Taking the medication means I have to be extremely careful when doing gardening, DIY and other activities as the slightest injury means I bleed profusely if, as nearly always happens, that the skin breaks and blood begins to flow. C) Visits to the dentist are always risky if I need treatment by the dentist or the hygeinist. The blood flow into my mouth is distasteful and my teeth and lips get covered in blood which to be honest does not look particularly good in my role as a salesman. D) My cardiologist has advised that I will almost certainly be on anti-coagulation for the rest of my life and the long term effects of warfarin give me some concerns.	Comments noted. Comment noted. The Committee heard that warfarin, although an effective treatment, it is associated with a number of problems. The main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the therapeutic range. The Committee heard from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. See FAD section 4.2. The Committee heard from the clinical specialists 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. See FAD section 4.2
NHS Professional 4	Section 1 (Appraisal Committee's preliminary recommendations)	Agree that rivaroxaban in AF does not appear to be cost effective compared to adjusted dose warfarin with good control.	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

	Section 2 (The technology)	The provisional cost of rivaroxaban is quoted as £2.10 per day and £766.50 annually (per patient). This is lower than the BNF cost for 10mg rivaroxaban, despite the dose for AF being higher than for VTE prophylaxis. There must therefore be uncertainties about the actual cost of rivaroxaban for the prevention of stroke or systemic embolus to the NHS, and consequently uncertainties about the relative cost-effectiveness of rivaroxaban compared to warfarin in the NHS. Under the proposed indication, all patients with non-valvular AF with $CHADS_2$ score would be eligible for rivaroxaban. This would mean that approximately 1,146 patients per 100,000 would be eligible for rivaroxaban. This is more than the 2006 figures for the number receiving warfarin quoted in NICE's costing report on the management of atrial fibrillation, which suggested that 30% of currently-detected AF cases receive oral anticoagulants, while 36% receive aspirin, equating to approximately 384 patients per 100,000 receiving anticoagulation for atrial fibrillation.	Comments noted. Comment noted. The costs in BNF Number 62 are for Rivaroxaban for the treatment of venous thromboembolism

	Section 3 (The manufacturer's submission)	There were limitations to the generalisability of the research. The population in the ROCKET-AF trial had more severe disease than the UK population expected to be eligible to receive rivaroxaban. It is unclear whether apparent benefits from rivaroxaban seen in the ROCKET-AF trial would actually be achieved in people with more moderate disease. The Committee has asked the manufacture to provide a revised model with a baseline risk of strokes and other events more representative of people with AF in the UK. This should be derived from the General Practice Research Database or a UK GP practice-based survey.	The Committee was also made aware by the manufacturer that a systematic review of the literature had suggested that there does not appear to be an interaction between treatment effect and baseline $CHADS_2$ risk. The Committee heard from the manufacturer that rivaroxaban would be indicated for atrial fibrillation in people with one or more risk factors for stroke, which equates to a $CHADS_2$ score of 1 or more. The Committee noted that the European Medicines Agency had stated in the 'European public assessment report' for rivaroxaban that efficacy results were essentially consistent in important subgroups, such as different CHADS2 scores (CHADS2 scores 2 to 6). The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of ROCKET-AF would not translate to people with a lower $CHADS_2$ score. See FAD sections 4.5

	Section 4 (Consideration of the evidence)	There were also limitations to the quality of the research. The results of a single large RCT have been submitted by the manufacturer. The ROCKET-AF trial compared rivaroxaban with dose-adjusted warfarin. The manufacturer submitted a network meta-analysis in people for whom anticoagulation therapy is considered suitable to compare rivaroxaban indirectly with aspirin and dabigatran etexilate. The estimates for rivaroxaban compared with dabigatran etexilate obtained from the network meta-analyses were unreliable and therefore the committee has been unable to say whether rivaroxaban is more effective or cost effective than these alternatives.	Comments noted. The Committee noted that both the manufacturer's and ERG's network meta-analyses contained wide confidence intervals, and therefore the resulting efficacy point estimates were subject to considerable uncertainty. See FAD section 4.7
NHS Professional 5	Section 1 (Appraisal Committee's preliminary recommendations)	Clinical Commissioning Consortia in Bradford and Airedale strongly endorse this recommendation. To recommend this treatment as an option for SPAF in the whole population would simply incur an opportunity cost that would be considerably greater than the benefit the technology brings. similar to the views we have already in the NICE appraisal of Dabigatran we do see that these new OAC agents have an important role in SPAF, but that their use (based on the balance of risk and benefit + affordability / opportunity cost) should be clearly limited to those who are unable to beenfit from the current standard of care - warfarin. It is important than NICE send out a VERY clear message to prescribers about absolute risk and benefit of RVX compared to Warfarin. This needs to be in paragraph 1 of the TA, as this is all that the majority of prescribers will EVER read	Comment noted. Rivaroxaban has now been recommended as an option for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. See FAD sections 1.1, 4.8 and 4.11

	Section 3 (The manufacturer's submission)	our interpretation of the ROCKET AF study is that the data on risk and benefit is not sufficient for this treatment to replace warfarin as the standard of care. We concur with the The evidence review group (ERG) when they identified several limitations with the manufacturer's model, including comparison with populations whose warfarin control (time in therapeutic ratio) was less satisfactory than generally expected in the UK. The ERG presented an alternative base-case ICER of £33,758 per QALY gained. The manufacturer of rivaroxaban has included higher INR monitoring costs associated with warfarin than estimated in the ongoing appraisal of dabigatran etexilate, and these are likely to be higher than the usual costs for NHS patients. The manufacture had estimated INR monitoring costs at Â£535 per person. The ERG considered that the manufacturer's cost-effectiveness model was particularly sensitive to assumptions about the cost of monitoring warfarin.	Comment noted.
	Section 4 (Consideration of the evidence)	ROCKET AF was NOT generalisable to UK AF population! Time in therapeutic range (TTR) for warfarin should be accounted for in the cost-effectiveness analysis. In the ROCKET-AF trial, which formed the basis of the manufacturer's submission, the mean TTR for warfarin was 55% (58% median). The ERG considered that this was lower than the TTR generally reported in the UK and in other clinical trials. This would make rivaroxaban appear more effective compared to warfarin as used in the UK, and consequently these results may not be applicable to UK practice.	The Committee was concerned that the effectiveness of warfarin could be underestimated if the proportion of time in therapeutic range was low, and that the UK context might be better reflected by results from centres where the time in therapeutic range in the warfarin arm more closely matched the usual levels in the UK. The Committee concluded that the trial results were broadly applicable to a UK setting, but for those already taking warfarin the current level of INR control should be taken into account in any decision to switch to rivaroxaban. . See FAD section 4.4

	Section 5 (Implementation)	We accept NICE is precluded from considering affordability. Should the TA committee reverse this ACD and recomend this medicine in all AF patients (as happened with dabigatran) the affordabilty is THE concern from commissioner perspective. It is important to remember that the levers commisisoners have to influence prescribing decisions (either in primary or secondary care) are weak - a headlong rush to switch patients from the standard of care to this medicine (which WILL happen on account of the "faf" factor associated with INR monitoring, the heavy promotion of the medicine to prescribers and to patients and the largely misinterpreted understanding of warfarin risks and benefits both in clinicians and patients) will not be in the best interests of patients, nor the taxpayer - this will not represent the most rational use of resources. As we have seen wit the Dabig TA, it would seem there is a dramatic under estimation of implementation cost (by a factor of 10 in the case of dabig). Commissioners will obviously be considering which services would need to be decommisisoned to make way for this drug should NICE reverse its decision. obviously these would be circulatory services	Comment noted.
	Section 6 (Proposed recommendations for further research)	All of the new oral anticoagulants DO need to be considered together against Warfarin as the standard of care, using data from UK clinical practice and the UK cohort. We don't anticipate this will happen for commercial reasons, but the scientifically and clinically valid question remains! Will anyone take it on	Comment noted.