**Appendix G -Professional organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**Single Technology Appraisal (STA)**

# Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

[redacted]

**Name of your organisation: The Royal College of Pathologists**

**Are you (tick all that apply):**

- √ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS?
Patients with atrial fibrillation (Af) are usually assessed by their GP or by the doctor making the diagnosis who may refer them for cardiological assessment. Those at high risk (By CHADS2 or CHADS-VASC scores) and no contraindications to warfarin would normally be started on warfarin.
Those at low risk are may be given no antithrombotic or aspirin, although recent RCPE guidelines suggest that the role for aspirin in this situation is diminishing.
Patients at moderate risk may be offered warfarin.

Is there significant geographical variation in current practice?
No
Are there differences of opinion between professionals as to what current practice should be?
There is a consensus on treatment for patients with atrial fibrillation (Af) at high and low risk, with options for patients at moderate risk as summarised in NICE guideline 36.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Warfarin, Rivaroxaban and Dabigatran are the alternatives for patients who clearly require antithrombotic treatment. The Aristotle and Averroes trials demonstrate improved outcomes for apixaban compared with warfarin.
The new drugs have shorter half lives (Apixaban 10-15 hours, Dabigatran 12-14 hours and Rivoroxaban 6-10 hours compared to warfarin 36-50 hours). This can be advantageous in that minor bleeding can resolve more quickly by omitting the drug but is a disadvantage as it means that missed doses are more likely to lead to a thrombotic event.
Apixaban has the advantage of more predictable pharmokinetics, fewer drug interactions and is less influenced by diet and alcohol. It does not require monitoring.
Dabigatran is more dependent on renal function and, although it causes less bleeding overall, it is associated with a higher incidence of GI bleeding. There is a higher risk of myocardial infarction with Dabigatran as compared to warfarin.
The main advantage of warfarin is from greater familiarity with this drug and known procedures for handling the complications e.g. bleeding. There are differences between warfarin and others such as a lack of monitoring, fewer drug and lifestyle interactions. Between the new agents there is a variable dependence on renal function and different patterns of S/E dyspepsia, GI Bleeding. There is an increased incidence of dyspepsia with Dabigatran.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Yes – patients with CHADS2 or CHADSVASC scores are at higher risk of thrombosis.

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Patients with a history of bleeding, (and with other abnormalities as described in HAS-BLED, a scoring system for assessing bleeding risk) are at an increased risk of bleeding.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
Patients at highest risk of thrombosis (high CHADS2 & CHADSVASC scores) will gain the most and patients at greatest risk of bleeding will be most put at risk.
Patients currently taking interacting drugs, who drink alcohol (particularly if inconsistently) and who have an inconsistent diet will benefit.
Patients who are not well controlled on warfarin will gain most from apixaban; it is not yet clear at what level of time in therapeutic range (TTR) this effect will occur.
Patients unable to take warfarin because of potential drug interactions.

Yes – as above and patients with poor renal function may be at risk from apixaban.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
All patients on treatment with anticoagulants should be managed according to the NPSA guidance with reviews of the efficacy and safety of treatment. This can be done in primary or secondary care.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
There should not be any need for additional input above the level currently provided for anticoagulant management .However some PCTs and CCGs have approved other new anticoagulants on the basis that they receive clinical reviews – which may be more frequent than those for patients on warfarin.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Current experience is with the licensed indication for thromboprophylaxis in surgery. There is geographical variation in its licensed use and little use off license at this point in time

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The situation for Af is described well in **NICE guidelines 36 (atrial fibrillation)** and **249** (Dabigatran and atrial fibrillation) addresses similar issues. There is a consensus on treatment for patients with atrial fibrillation (Af) at high and low risk, with options for patients at moderate risk as summarised in guideline 36. The Scottish HIS document on management of AF includes recommendations for use of warfarin, rivaroxaban and dabigatran

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There are detailed guidelines on managing patients on warfarin, which do not include newer drugs but are a useful reference source, e.g. **BCSH Guidelines on oral anticoagulation with warfarin – 4th edition 2011**
Describes how anticoagulation with warfarin should be managed; this is a compilation of evidence from trial data and decades of clinical experience. The major sources of the recommendations are from meta-analyses of trials by Hart (2007), Andersen(2008), the recommendations by the American College of Chest Physicians (2008) and the Stroke Prevention in Atrial Fibrillation (SPAF) trials

**Advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

It will be easier to use in general because of reduced drug interactions, lack of effect of diet, the absence of a need for routine monitoring of drug levels by laboratory testing and fixed drug dosing. However complications will be more difficult to manage as there is no reliable measure of the anticoagulant effect to determine whether an individual is achieving an effective level of anticoagulation nor if the level is excessive and likely to cause bleeding. In addition interpretation of routine coagulation tests which might be performed on emergency admissions is a potential area for concern. These can be addressed by work being performed by the national external quality assurance scheme for coagulation and by improved education.

Unlike warfarin, but like dabigatran and rivaroxaban, there is no known effective antidote to apixaban for use in case of haemorrhage or emergency surgery.

The current evidence suggests that it is more efficacious than warfarin without any monitoring however a validated monitoring test could possibly help to improve efficacy and safety.

Changing treatment from warfarin to apixaban and bridging treatment (e.g. with LMW Heparin) to cover surgery or interventional procedures will require development of evidence based protocols.

The management of bleeding complications will require development of evidence based protocols.
Interactions with CYP3A4 inhibitors have been reported.

Successful treatment will depend on compliance, which usually declines as the frequency of dosing increases – i.e. from once daily for warfarin and aspirin to twice daily for apixaban.
Compliance will be more difficult to assess.

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If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

It should only be used by clinicians familiar with anticoagulant management and patients should be reviewed in accordance with the NPSA guidance on anticoagulation.
Review of anticoagulant records will identify patients who are poorly controlled on warfarin, who may benefit from Apixaban

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Co morbidities are common in the elderly and trials in this age group are necessarily selective to avoid confounding variables. The patient groups were younger than in my practice with a lower level of NSAID and antibiotic use – both common in clinical practice. The nature of the clinical studies indicate that we need to be cautious about the generalisabilty of these studies in patients who fall out with the trial entry criteria. I do not think that they could be reliably extrapolated and that observational studies in the UK with the general AF population will be required.

Assessing compliance will be more of a problem without the detailed follow up of the trial situation and without any monitoring tests.

The Time in Therapeutic Range (TTR) for the warfarin group with a median of 66% and mean of 62% is significantly lower than the figures achieved by most UK anticoagulant services .The most recent figures from Dawn Benchmarking, based on 235,944 patients with a target range of 2-3 show a median of 71% and mean of 69% TTR.
This suggests there will be less benefit in using Apixaban in the UK.

The important outcomes, stroke, bleeding and all-cause mortality were included in the Aristotle trial.
The important outcomes, stroke and bleeding were included in the Averroes trial.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

life? Are there any adverse effects that not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The most important side effect is bleeding, as discussed above – other effects may become apparent with increased use.

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The benefit of apixaban over warfarin will vary according to the TTR of the warfarin patients, which correlates with the clinical outcomes. It would be useful to find out if there are unpublished data from the trial to demonstrate if the outcomes were better for patients with a better TTR. .

There are unpublished data in the databases of anticoagulant computer records. One software company (4S-Dawn) operates an opt-in benchmarking service for its users –as quoted above.(4S Clinical information Systems, 4 the Square, Milnthorpe, Cumbria LA7 7Q3 have supplied medical software since 1984 and their Dawn anticoagulant software is extensively used. They have run a six monthly Benchmarking exercise for the last 14 years. This data is from general clinical use and is, I believe probably the most representative of actual performance in anticoagulant control in the UK. The company has ISO9001 and 2701. There are other software programs in use.

Self testing and self management may also reduce costs and improve compliance - depending on how they are managed.

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The guidance will be most useful if it can identify those patients or categories of patients that will benefit from it as opposed to standard care with warfarin.
This might be achieved by starting patients who do not have a contraindication on to warfarin and assessing their response after a reasonable period
There will also be some patients for whom there is a relative contraindication e.g. those who are housebound where testing is problematic.
In view of the increased costs, decisions on funding will be made by CCGs.

Except for the management of bleeding, education should not be a major issue for clinicians involved in haemostasis and thrombosis who will be aware of apixaban and its limitations but other clinicians who may wish to use it must agree protocols with their local haematologists in respect of patient selection and management of complications.
The management of bleeding complications – in the absence of a specific antidote is an area where more research and education will be needed. It is an area of particular concern to our anaesthetic & surgical colleagues and haematologists will be required to advise on perioperative management.

There is a very real need for a sound protocol for the management of bleeding and urgent interventional procedures. Until we have evidence of safe management of these complications we must advise clinical colleagues and patients of these problem areas.

In terms of the cost of anticoagulant monitoring this will also vary according to how well a patient is controlled as well as how the local clinic operates. However, even with adoption of Apixaban savings on anticoagulant services will likely be small through the necessity of these services to continue to run for patients continuing on warfarin.

A new costing report will be required , the previous one being 2006 as there have been reconfigurations of laboratories to improve efficiency and the use of telemedicine e.g. automated telephoning, emailing and texting of results have improved efficiency.

Although the newer anticoagulants are licensed for use without laboratory monitoring, many PCTs and CCGs are approving their use subject to clinical review and

therefore the additional cost of monitoring warfarin should address the laboratory costs separately from the cost of clinical supervision.
If the patients receiving the newer drugs are to have clinical reviews then the only saving will be in laboratory costs.

The NICE Management of Atrial fibrillation costing report gave an average cost of warfarin monitoring of £565 however this could easily be reduced through judicious use of computerisation and dosing by Biomedical Scientists and Clinical Nurse Specialists.

**Equality**
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I do not consider that there are any relevant issues affecting equality legislation.