NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Your name: Dr Rhona Maclean

Name of your organisation Sheffield Teaching Hospitals NHS Trust

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)

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

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?

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.

Current therapy for stroke prevention for atrial fibrillation (SPAF) in the NHS comprises warfarin anticoagulation, aspirin, and now dabigatran, which earlier this year was licensed for that indication.
NICE clinical guideline CG36 (2006) allows for the use of aspirin in patients at low risk of thromboembolic complications, but recommends the use of anticoagulant therapy- warfarin- for those at high risk. Cardiologists also follow the recent European Society of Cardiology (ESC) guidelines (2010), which also recommend the use of oral anticoagulation in patients at high risk of thromboembolic complications.
There is general agreement and consensus regarding the indications for anticoagulation for stroke prevention in AF (SPAF), and until recently warfarin was the only option for such patients. Recently dabigatran has obtained its license, and has been the subject of an HTA, which is due to be formally published early in 2012.
Patients with atrial fibrillation have a very variable risk of developing a thromboembolic complication. They can be stratified as to their risk of developing a stroke using a scoring system such as the CHADS2 system, or an updated system- the CHADSVaSC system. The NICE CG36 offers a scoring algorithm similar to that of the CHADS2 system.

The main drawback of warfarin anticoagulation is the necessity of monitoring patients on a regular basis. It is not possible to predict the dose of warfarin patients will require until they start the drug and have its anticoagulation effect checked by undertaking blood monitoring tests. Warfarin requirements are influenced by lifestyle and other medication therapies, and for some patients very frequent monitoring is

required. Specialist staff and monitoring equipment is required to undertake this. Warfarin (and other vitamin K antagonists) are monitored both in secondary and primary care, and there are considerable geographical variations with respect to this in the UK.

Dabigatran has been used in the UK for prevention of venous thromboembolism after orthopaedic surgery and has recently been introduced for stroke prevention in atrial fibrillation. For the latter indication, there is little experience as yet in the UK, but emerging information from Canada, New Zealand and Japan where it has been in use for some months.

Rivaroxaban has been used in the UK for prevention of venous thromboembolism after orthopaedic surgery for approximately 18 months. It has recently been approved by the FDA in the US for stroke prevention in atrial fibrillation, but there is no substantial experience in its use for this indication as yet.

It is expected that Rivaroxaban would be used primarily in primary care for this indication, although may well be initiated by hospital staff (particularly until primary care develop experience in its use). Administration would be considerably easier than warfarin (fixed once daily dosing with no dose alterations required), and regular monitoring would not be required. It is not expected that specialist staff would be required.

The advantages and disadvantages of the technology

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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?

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.

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?

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 were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The evidence for the use of Rivaroxaban for SPAF is primarily based on the results from the Rocket AF trial. This was a double-blinded, double dummy event driven trial, aiming to demonstrate non-inferiority to warfarin in the prevention of stroke and systemic embolisation for patients with nonvalvular AF. This is in contrast to the RELY (dabigatran) study which was a PROBE design (open label warfarin, those patients on dabigatran were blinded as to whether were on dabigatran at the 110 or 150mg dose).

Those patients given rivaroxaban would qualify for anticoagulation as per current guidelines (NICE CG36 and ESC guideline).

The technology (Rivaroxaban) is considerably easier to manage than warfarin. There is no need for monitoring this drug, and there are few drug interactions. It is, however renally excreted (as is dabigatran) making it unsuitable for patients with renal failure.

This study has been criticised as the control patients on warfarin has INRs in the therapeutic range for only 55% of the study period, and that the benefit was in part a a result of the poor warfarin management. There has also been significant discussion as to the study design, with the switch of patients to alternative anticoagulation at the end of the study, and the data analysis (intention to treat vs. on treatment). Overall, it is likely there is no significant extrapolation required in applying these results to UK practice.

The entry criteria for the ROCKET-AF study meant that those patients included were at higher risk of stroke than those in the dabigatran study.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

The FDA approved rivaroxaban for this indication on 4th November 2011.

UK guidelines for warfarin use contain well developed and effective procedures for reversal of warfarin therapy in the event of emergency or haemorrhage but at present there are no similar data on how to reverse Rivaroxaban. A study has been performed that evaluated the use of prothrombin complex concentrates (PCC) on reversal of rivaroxaban in healthy volunteers. It appeared that PCC did normalise blood coagulation in these individuals, but there is little clinical experience at this point in time.

Rivaroxaban, at the study doses, appears to have a lower risk of intracranial bleeding compared to warfarin. This, and the lack of monitoring requirements, might warrant consideration of its' use in a larger group of patients that are currently considered for anticoagulation.

Rivaroxaban lacks many of the disadvantages of warfarin- it does not require monitoring, dose adjustments, and has few drug interactions. The fact it can be given once daily, and included in 'nomad' boxes and other medication aids, will be of considerable benefit to many patients.

Rivaroxaban does not appear to have the GI side effects that were found with dabigatran, however there did appear to be an increased risk of gastronintestinal bleeding with rivaroxaban compared with warfarin.

There have been no clinical studies comparing dabigatran and rivaroxaban.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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.

Implementation issues

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Single Technology Appraisal (STA)

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 implementation of this technology should be much more straightforward than that associated with warfarin anticoagulation. Considerably less staff training and resource would be needed for this technology when compared to warfarin, but it is difficult to identify how the current resource tied up in anticoagulant clinics could be released. A proportion of patients currently taking warfarin/ Vitamin K antagonist therapies (VKA) would be unsuitable for this new technology (renal failure, anticoagulation for other indications). There will also be the need to educate current NHS staff (both primary and secondary care) in this technology, which may make the transition difficult in the short term.
No additional facilities or equipment would be needed.
Laboratories would need to introduce new tests to evaluate the drug level should adverse outcomes occur (bleeding or thrombosis) despite there being no need for routine monitoring.
The above is very similar to that that will be needed to introduce dabigatran should that be approved.

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