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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: Professor John Potter

Name of your organisation: University of East Anglia

Are you (tick all that apply):

Yes 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? 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.

The technology in question here is rivaroxaban, which is a direct factor Xa inhibitor. Rivaroxaban is currently licensed in the prevention of venous thromboembolism in patients undergoing elective hip or knee surgery. This is the only indication in which rivaroxaban is currently licensed for in the UK. This submission is regarding the potential use of rivaroxaban for the prevention of stroke and non CNS systemic embolism in patients with Non Valvular Atrial Fibrllation (AF).

Background

Atrial Fibrillation is the most common cardiac arrhythmia of clinical significance (1) and is one of the most common cardiovascular conditions in the UK. The prevalence of AF is increasing due to a number of factors including an aging population and increasing survival from the conditions predisposing to AF (e.g. heart failure, coronary heart disease, hypertension (2). Patients with AF are at increased risk of stroke and non-CNS systemic embolism. The main prophylactic therapy option, currently in patients with AF when an anticoagulant is indicated, are vitamin K antagonists, typically warfarin (3). However, treatment with warfarin can be inconvenient for both clinicians and patients due to the requirement of frequent monitoring and dose adjustment throughout treatment. Anticoagulation itself is also not without complications, primarily associated with increased risk of intracranial and extracranial bleeding, with these side effects increasing with age (4). Poor INR control is considered a further risk factor, associated with increased rates of stroke, bleeding and death (5,6).

Currently, if a patient is not eligible or able to take warfarin, the only therapeutic option is aspirin. However, this is not as effective in the prevention of thromboembolic events in AF as Warfarin (7).

New therapies for stroke prevention in AF must therefore be comparable in terms of the efficacy and safety profile of warfarin and should provide additional benefits, especially in terms of improved convenience (e.g. easy to administer - oral, no monitoring requirements, predictable pharmacokinetics).

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Therefore, on the basis of the recently published trial results (22) and clinical profile, I would expect that rivaroxaban would be an appropriate drug to potentially replace warfarin in patients with non-valvular AF post-stroke, TIA or systemic embolism and in those with AF and an additional risk factor(s) for stroke and non CNS embolism. However, patient sub groups which could be considered for the initial introduction of rivaroxaban would be (1) patients poorly controlled on warfarin requiring more regular INR monitoring and dose adjustment, (2) warfarin unsuitable – e.g. discontinued due to reason other than bleeding or clinician feels patients would have difficulty managing regular INR monitoring and dose adjustment (3) warfarin naïve.

Risk factors for stroke in patients with AF
The risk of stroke in patients with AF varies ranging from an annual risk of 1% in patients aged over 65 years old with no risk factors, to over 12% per year in patients who have a history of prior stroke, transient ischaemic attack or thromboembolism (8). The level of risk influences the choice of thromboprophylaxis.
There are different ways of assessing risk, including:
1. NICE stroke risk stratification (8)
The NICE algorithm suggests that high risk patients should receive warfarin, if not contraindicated and low risk patients should receive aspirin. Patients at moderate risk can either receive warfarin or aspirin.
2. CHADS2 score
The CHADS2 [cardiac failure, hypertension, age, diabetes, stroke (doubled)] risk index is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age >75 years, a history of hypertension, diabetes, or recent cardiac failure (9).
The original validation of this scheme classified a CHADS2 score of 0 as low risk, 1-2 as moderate risk, and >2 as high risk (9).
3. CHA2DS2-VASc
The most recent risk scoring system extends CHADS2 by considering additional stroke risk factors where a score ≥2 (out of 9) in patients would indicate the need for anticoagulation (9).

Clinical guidelines
Anticoagulants or antiplatelet agents are recommended for thromboprophylaxis to reduce the risk of stroke in patients with AF (8,9). Treatment choice is based on risk of stroke, other patient factors such as risk of bleeding and patient preference. Meta-analysis has shown that adjusted dose warfarin was associated with a 64% relative risk reduction in stroke compared to placebo or no treatment, corresponding to an absolute annual risk reduction of 2.7% for primary prevention and 8.4% for secondary prevention (10). Antiplatelet therapy has been associated with a 22% relative risk reduction in stroke compared to placebo or no treatment, corresponding to an absolute annual risk reduction of 0.8% for primary prevention and 3.8% for secondary prevention.(10)
NICE guidelines (8) recommend oral anticoagulation with warfarin for patients in AF at high risk of stroke and as an option for those at moderate risk of stroke according to their stroke risk stratification algorithm. Aspirin is recommended as an alternative for those at moderate risk and in all those at low risk of stroke. NICE guidelines are currently being considered for review and update.

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The Scottish Intercollegiate Guidelines Network (SIGN) issued a clinical guideline on antithrombotic therapy in 1999 (19) although the recommendations are being updated.
Recently published European guidelines (9) advocate use of CHADS2 and CHA2DS2-VASc.
Challenges with current oral anticoagulant therapy
Warfarin is an oral anticoagulant which is effective at the prevention of stroke in patients with AF. However, it has a number of limitations, including:

- A narrow therapeutic index with a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage
- The requirement for dose adjustment using frequent, inconvenient and costly INR monitoring. The frequency of monitoring varies depending on individual patient characteristics. Typically difficult to manage patients include elderly patients with co-morbid conditions and concomitant medications. Patients who are particularly difficult to maintain on warfarin within the target INR range and require more frequent INR tests and dose adjustment, potentially consume a greater amount of NHS and resource.
- Response that is significantly influenced by concomitant medications, diet, herbal supplements and intercurrent illness
- The need for individualised patient dosing and adjustment, often requires warfarin to be supplied in a number of different strengths and tablets. This may increase the risk of accidental overdose and requires additional patient education, especially in older people, who typically take additional concomitant medications.

The NPSA issued a patient safety alert to healthcare organisations in England and Wales in 2007 (11) regarding best practice actions to make anticoagulation therapy safer.
Despite the higher risk associated with stroke in the elderly, as well as the greatest benefit of anticoagulation, the elderly are the group of patients where there is suboptimal use of thromboprophylaxis for AF. This is thought to be because of the perceived increased risk associated with co morbidity, interactions with concomitant drug therapies and risk of bleeding in these patients (8). Audit data suggests that current anticoagulant management of AF is not optimal, NICE estimated that 46% of patients that should be on warfarin were not receiving it (12), such patients either receiving aspirin or no treatment (13,14,15,16,17). An interrogation of primary care databases from over 310 practices in 48 primary care trusts in the UK involving more than 47,000 patients with atrial fibrillation, showed that only 51.4% of patients with CHADS2 >1 were receiving warfarin (18), and an audit across 151,000 patients in primary care in Leeds showed that amongst patients with a CHADS2 score of 2 or greater, some 44% of patients were not receiving warfarin (19). When a cohort of 228,000 patients in York primary care trust were assessed for contraindications to warfarin, only 27% of the untreated high risk population had absolute contraindications to warfarin. The commonest reason for not giving warfarin to them was the reluctance of physicians to prescribe it (18).
Warfarin is usually managed within an anticoagulant service. There are several different models of anticoagulant service across the UK ranging from secondary care outpatient clinics to primary care led clinics and many variants in between.
Resources associated with warfarin management are not insignificant; for a consultant led anticoagulation service, a first appointment has a national average unit cost of £47.30 and £29.35 for each subsequent visit (20) NHS reference costs 2009-2010)

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Although diagnosis of AF and stroke risk are determined in secondary care, the management of AF and the use of the new oral anticoagulants for this indication will be done predominantly in primary care.

Proposed advantages over existing therapy

Rivaroxaban is a once-daily oral anticoagulant, currently licensed for the prevention of VTE in adult patients undergoing elective hip or knee replacement (21)

Rivaroxaban is a direct and highly selective inhibitor of Factor Xa, an enzyme at a pivotal point in the coagulation pathway. Inhibition of Factor Xa prevents the conversion of prothrombin to thrombin, thereby preventing the formation of blood clots.

Rivaroxaban is administered at a fixed dose once daily and there is no requirement for routine monitoring of coagulation parameters during treatment (21). In addition, once daily dosing and lack of routine coagulation monitoring requirements with rivaroxaban would make this potential alternative to warfarin straightforward for both patients and clinicians in both primary and secondary care.

Anticoagulation clinics will still be required for patients who continue to use warfarin for the management of their condition e.g. stabilised patients or for those conditions for which rivaroxaban does not have a licence. However, optimal use of rivaroxaban has the potential for generating cost savings in areas of the healthcare budget:

Directly:

- Through reductions in healthcare professional consultations and INR tests
- through a reduction in strokes and non CNS embolism associated with active treatment compared to warfarin with associated decreases in critical bleeds, fatal bleeds (including intracranial haemorrhage) and the concomitant reduction in associated interventions and services,.

In addition, cost savings may also be generated indirectly in terms of demand management for anticoagulation services with all of the associated infrastructure. Reducing the need for frequent and inconvenient routine monitoring may also potentially improve compliance, especially with long term treatment thereby improving patient outcomes.

2. **The 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?

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?

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As stated above, Rivaroxaban is administered at a fixed dose once daily and there is no requirement for routine monitoring of coagulation parameters during treatment (21). The once daily dosing and lack of routine coagulation monitoring requirements with rivaroxaban would make this potential alternative to warfarin straightforward for both patients and healthcare practitioners in both primary and secondary care. The potential advantages of rivaroxaban over the current standard of care (warfarin) are described above, but include fewer drug-drug and food interactions and a simplified dosing regimen. As there is no requirement for routine coagulation monitoring, patients do not require (and should not have) an INR measurement, as anticoagulation effect is predictable. Reducing the need for frequent and inconvenient monitoring may also improve compliance (particularly with a once a day dosing regimen), especially with long term treatment thereby potentially improving patient outcomes.

The pivotal trial for rivaroxaban in this indication was the ROCKET AF (Rivaroxaban once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation [22]). This was a large international randomised, double-blind, double-dummy, event-driven phase III study designed to establish the non-inferiority of rivaroxaban compared with dose-adjusted warfarin for the prevention of thromboembolic events in patients with non-valvular AF. This study design is generally considered the 'gold standard', and the primary and secondary efficacy and safety endpoints in line with other clinical trials in this area. All cause mortality was also measured as a secondary efficacy endpoint. ROCKET AF was a large international trial rigorous study design that included patients from the UK. Therefore, the trial would appropriately reflect current UK practice, and the results can be extrapolated to a UK setting.

It is important to note that all included patients were at moderate to high risk of future stroke, having a history of stroke, transient ischaemic attack (TIA) or systemic embolism or at least 2 additional independent risk factors.(22). Therefore, the patients recruited were those eligible for oral anticoagulation and with significant co-morbidity. This is a strength of the study as the positive results were achieved in a group of patients with significant co-morbidity and elevated risk of stroke and can thus be considered a rigorous test of the efficacy and safety of rivaroxaban

Employing a double blind, double dummy design and using sham INR testing in the rivaroxaban arm, did not allow any of the practical advantages over warfarin to be tested e.g. removing the need for regular clinic appointments for INR testing and dose adjustment. The trial may therefore underestimate such benefits that may be seen in clinical practice.

As was recently published in the New England Journal of Medicine (22), the ROCKET AF study met the primary efficacy endpoint of non-inferiority to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. Rivaroxaban was subsequently found to be superior to warfarin for the primary efficacy endpoint using the safety population during the on-treatment period, according to the pre-specified hierarchy of statistical testing.

When conducting the ITT analysis to the point of site notification, rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint, but did not reach superiority due to dilution of treatment effect in the "off treatment" period, when patients were transitioned to open-label therapy. Treatment effects with regard to the primary efficacy endpoint were consistent across all pre-specified sub-groups.

For the primary safety endpoint (composite of all major and non-major clinically relevant bleeding events), results indicated comparable safety between rivaroxaban

and warfarin, with no statistically significant difference between the two treatments. The specific bleeding profile was different between the 2 arms, with patients on rivaroxaban experiencing fewer of the more devastating bleeds including critical organ bleeds (including intracranial haemorrhage) and fatal bleeds. Gastrointestinal bleeding was modestly increased with rivaroxaban as compared to warfarin. Other non bleeding adverse events were also similar between the 2 treatment arms. It is also important to note that the subsequent analyses undertaken in patients with previous stroke/TIA (secondary prevention) and moderate renal impairment (30-49ml/min treated with the 15mg dose) showed results in line with the primary study results. Rivaroxaban has not been used in routine clinical practice in the prevention of stroke and non CNS systemic embolism in patients with non valvular AF as it is not currently licensed in this indication.

3. **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 Garfield registry is an academic research initiative, led by the Thrombosis Research Institute (London, UK) and a multi-disciplinary Steering Committee which is funded by Bayer Healthcare. It is being conducted in collaboration with a global investigator network and a distinguished group of AF experts as National Coordinators. Site enrolment began in December 2009 and this registry is still on-going. The purpose of the GARFIELD Registry is to assess management and outcome of patients with newly diagnosed AF, eligible for oral anticoagulation therapy with a Vitamin-K-antagonist by 1). Describing the real-life treatment patterns in newly diagnosed patients with AF at risk of stroke. 2). Assessing stroke incidence in this patient group and systemic embolization and 3) Assessing the outcome of the patients with specific reference to the incidence of bleeding complications for patients on VKA therapy, INR fluctuations over time and therapy persistence

4. **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).

Rivaroxaban is expected to gain a licence for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, as seen with the recent CHMP positive opinion. However, it is recognised

that the rapid uptake and use of new oral anticoagulants in all of these AF patients could potentially have service delivery implications and that such changes are most appropriately made in a gradual fashion. Therefore, it is important to consider the different patient groups who would be appropriate for rivaroxaban.
These include:

- AF population with one risk factor for stroke– i.e. all patients eligible for oral anticoagulation according to the licence
- Patients who are unsuitable for warfarin – i.e. those who have discontinued warfarin (for reasons other than bleeding) and those who may have difficulty with regular INR monitoring and dose adjustments or allergy
- Patients currently taking warfarin but who are "difficult to manage", with difficulties maintaining an appropriate time in therapeutic range and needing intensive management with associated resource use

Once daily dosing and lack of coagulation monitoring requirements with rivaroxaban would make this potential alternative to warfarin straightforward for both patients and healthcare practitioners. Anticoagulation clinics will still be required for patients who continue to use warfarin for the management of their condition e.g. stabilised patients or for those conditions for which rivaroxaban does not have a licence. Therefore the current infrastructure would not require significant service re-design. However it is important to note that rivaroxaban could allow for potential savings in the healthcare budget either:

Directly:
Through reductions in healthcare professional consultations and INR tests
Through a reduction in strokes and non CNS embolism associated with active treatment compared to warfarin with associated decreases in critical bleeds, fatal bleeds (including intracranial haemorrhage) and the concomitant reduction in associated interventions and services.
In addition, cost savings may also be generated indirectly in terms of demand management for anticoagulation services with all of the associated infrastructure. Reducing the need for frequent and inconvenient coagulation monitoring may also improve compliance, especially with long term treatment thereby improving patient outcomes. Therefore, NICE Guidance on this technology would not require the Department of Health and the Welsh Assembly Government to vary this direction.

References

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