NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery.

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.

Your name: Professor Roger M Atkins

Name of your organisation

British Orthopaedic Association

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**

About you

Your name:

Name of your organisation BRITISH ORTHOPAEDIC ASSOCIATION

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- 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?

The condition being treated is thrombotic load (venous thromboembolism, vte) after total hip and knee replacement. This manfests itself as asymptomatic calf vein deep venous thrombosis (dvt), and the clinical complications of clinical dvt and pulmonary embolism (pe). VTE prophylaxis aims to reduce clinical dvt and pe.

Currently vte prophylaxis is universally practised in joint replacement surgery. Methods include patient advice prior to surgery, use of spinal anaesthesia, modified surgical techniques, early mobilisation post surgery, use of passive leg compression garments, use of active foot and calf pumps and chemical anticoagulants, of which epixaban is one. Thus it must be emphasised and clearly understood that the use of chemical anticoagulants is the final step in the surgeon's anti vte strategy.

The currently available chemical anticoagulant strategies include aspirin, unfractionated heparin, low molecular weight heparin (lmwh), warfarin and the new anti factor Xa inhibitors, which are currently dabigatran, rivaroxaban and now apixaban.

Aspirin has few side effects but its efficacy is under question.
Heparins require injections which are painful and therefore compliance may be variable. In addition, there is the complication of heparin induced thrombocytopaenia (hit). This is rare with lmwh but the incidence of complications from hit with extended lmwh useage is roughly the same as the incidence of clinically significant vte events (see NICE guidance).
Warfarin is difficult to use and requires frequent blood tests.
The anti factor Xa drugs are efficacious, simple to use, oral, require no monitoring and are without side effects. So they are very attractive.

There is considerable geographical and personal variation in which chemical thromboprophylaxis strategy is used, based on the individual surgical practices. The major causes for this are the poverty of the evidence base, confusion concerning vte terminology and the complications and problems of the individual drugs.

The problem with the evidence base is that the total joint replacement patient is the guinea pig for the investigation of the efficacy of novel chemical anticoagulants. The end point of these level 1 studies is the incidence of asymptomatic calf vein dvt. These studies clearly demonstrate the efficacy of the agents in reducing asymptomatic dvt but there is scant data on the relationship between asymptomatic calf dvt and symptomatic vte in today's world in these patients. Such data as there is suggest that asymptomatic calf vein dvt is not a good predictor of clinical vte in modern total joint replacement patients.

There is a serious problem of terminological in-exactitude with commercial and academic interest groups deliberately blurring the line between asymptomatic calf

vein dvt and clinically important thrombotic events, in order to inflate the evidence of clinical efficacy of the chemical agents.

The level 1 studies suggest that the use of chemical thromboprophylaxis is not associated with bleeding. In fact all chemical anticoagulants inevitably cause bleeding direct proportion to their efficacy in anticoagulation. This very minor bleeding is deliberately not captured in the level 1 studies and may be hugely clinically important. The consensus statement of the orthopaedic community is that bleeding caused by LMWH is important and there is indeed evidence that the new factor Xa inhibitors may cause more surgically important bleeding than lmwh, to the point where some units have ceased to use them. This minor bleeding is associated with wound healing problems which contribute to deep surgical infection. Concern about wound healing causes surgeons to slow post-operative mobilisation which may itself contribute to the development of vte. Thus the very use of antithrombotic agents may perversely increase the thrombotic load.

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?

Total joint replacement has split into numerous sub-types. Unicompartmental knee replacement or patella-femoral arthroplasty are considerably lesser interventions than total knee replacement and logically will produce a lower thrombotic load. The risk of the technology is bleeding and wound problems. This is probably more important in knee replacement than hip replacement. The risk factors for vte are well documented. For total joint replacement the majority of patients are elderly and so this risk factor should not be applied.

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)?

Starting in secondary care once the risk of bleeding complications is past, moving into primary care for extended prophylaxis

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?

See above. There is a trend to factor Xa inhibitors being used in other surgeries where there is a clinical risk of vte and where heretofore lmwh would be employed

*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.*

American College of Chest Physicians, no largely discredited
American Academy of Orthopaedic Surgeons.
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SIGN

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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?

See above

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.

Commencing chemical thromboprophylaxis should be delayed after joint replacement surgery until the risk of bleeding is gone. The problem with this approach is that the evidence also suggests that the earlier the agent is started, the more efficacious it is.

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?

This is covered above. The level 1 studies use the surrogate marker of asymptomatic calf dvt. There is no data concerning whether this is predictive of clinical vte events. Theoretically it is unlikely that asymptomatic calf vein dvt will predict death from pe. The level 1 studies deliberately did not investigate the occurrence of minor but clinically significant bleeding.

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 significant side effect is minor bleeding which leads to poor wound healing and deep infection.

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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.

C. D. Jensen, A. Steval, P. F. Partington, M. R. Reed, and S. D. Muller
Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban: A RETROSPECTIVE COHORT STUDY
J Bone Joint Surg Br 2011; 93-B: 91-95

Rivaroxaban has been recommended for routine use as a thromboprophylactic agent in patients undergoing lower-limb arthroplasty. However, trials supporting its use have not fully evaluated the risks of wound complications. This study of 1048 total hip/knee replacements records the rates of return to theatre and infection before and after the change from a low molecular weight heparin (tinzaparin) to rivaroxaban as the agent of chemical thromboprophylaxis in patients undergoing lower-limb arthroplasty. During a period of 13 months, 489 consecutive patients undergoing lower-limb arthroplasty received tinzaparin and the next 559 consecutive patients received rivaroxaban as thromboprophylaxis.

Nine patients in the control (tinzaparin) group (1.8%, 95% confidence interval 0.9 to 3.5) returned to theatre with wound complications within 30 days, compared with 22 patients in the rivaroxaban group (3.94%, 95% confidence interval 2.6 to 5.9). This increase was statistically significant ($p = 0.046$). The proportion of patients who returned to theatre and became infected remained similar ($p = 0.10$).

Our study demonstrates the need for further randomised controlled clinical trials to be conducted to assess the safety and efficacy of rivaroxaban in clinical practice, focusing on the surgical complications as well as the potential prevention of venous thromboembolism.

M. A. McNALLY, E. A. COOKE, M. L. HARDING AND R. A. B. MOLLAN Attitudes to, and utilization of, low molecular weight heparins in joint replacement surgery.
J. R. Coll. Surg. Edinb., 42, December 1997, 407—409

A postal survey was carried out to determine the attitudes to the use of low molecular weight heparin (LMWH) in joint replacement among two representative groups of orthopaedic surgeons practising in the UK. 72% of hip surgeons and 51% of knee surgeons replying had used LMWHs for deep vein thrombosis prophylaxis in joint replacement patients. Of these, 48% had discontinued LMWH use due to bleeding complications. Among those continuing to use LMWHs, 88%

had witnessed excessive bruising around the wound and 53% had experienced increased wound bleeding or haematomas. Although LMWHs have been shown to reduce post-operative thromboembolism in these groups, clinical experience has revealed an increased incidence of bleeding complications associated with their use. This has prevented their routine use in joint replacement, as was the case with unfractionated heparin in the past.

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)?

No extra resources or education will be required.

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