NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome [ID532]

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:

Name of your organisation

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? 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?

Patients with acute coronary syndromes receive aspirin, clopidogrel as antiplatelet treatment and iv unfractionated heparin, sc low molecular weight heparin or fondaparinux at presentation. The most recent change in practice has been the introduction of new antiplatelet agents with a more potent and predictable effect than clopidogrel (less dependent from the genetic variations modifying hepatic activation of clopidogrel). In particular ticagrelor, because of the protocol followed in PLATO, can be used at the time of presentation with a loading dose of 180 mg while the early use of prasugrel, started only after angiography if indications to angioplasty was present in TRITON TIMI 38, is discouraged based on the results of ACCOAST. The lack of clinical benefit (except stent thrombosis) with in ambulance use of Ticagrelor with a trend to increased mortality and bleeding was observed in ATLANTIC. The ATLAS trial studied the NOAC rivaroxibam at a dose of 2.5 or 5.0 mg bd, much lower than the current dose recommended in patients with atrial fibrillation (20 mg od or 15 mg od in GFR between 15 and 50 ml/min). The drug administered within 7 days from presentation reduced mortality with a better safety profile (and unusually also efficacy) at the lower dose.
Currently there is a trend, supported by the European Guidelines in NSTEMI, STEMI and Coronary Revascularisation and by NICE, to switch from clopidogrel to ticagrelor and prasugrel but the rate of change in the UK is uneven, with very low penetration in the last data presented by BCIS for 2012. This element is relevant because rivaroxibam HAS NOT been studied in association with these new antiplatelet agents and their use contraindicates the association of rivaroxibam.
Currently antithrombotic drugs are stopped after the patient completes revascularisation, indicated in the majority of patients, with the exception of patients still bed bound (prevention DVT) or with other indications to anticoagulation (atrial fibrillation, treatment of DVT, left ventricular thrombosis, mechanical valves). Please note that for the last indication NOACs are contraindicated at present based on repeated episodes of valve thrombosis after dabigatran.

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?

Especially patients with NSTEMI/ACS are stratified according to various risk scores (GRACE, TIMI, etc) for their risk of mortality and recurrence. There are also risk scores applicable for bleeding in order to identify the optimal balance in individual patients. Based on the ATLAS data, however, it is difficult to identify subgroups with particular benefit from the administration of Rivaroxibam.

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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)?
The drugs should only be started in hospitals by cardiology specialists after the diagnosis of ACS is established and the absence of contraindications ascertained.

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?
Rivaroxiban is currently used at very different doses and in a single administration per day as an alternative to warfarin for prevention of embolisation in patients with atrial fibrillation and >1 CHADS-VASC2 score treatment of DVT. Currently the NHS requests proofs of inability to maintain a correct INR level with warfarin before NOACs are considered. The criteria to switch from warfarin are liberally interpreted with conflicting opinions in the medical profession.

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.

Not applicable. There are no NICE guidelines on the issue under discussion.

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

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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?

Rivaroxibam for this indication is not an alternative but an addition to current treatment of aspirin, thienopyridine, statin, beta-blocker, ACE-inhibitor for survivors of a "heart attack". We just heard at the 2014 ESC in Barcelona from Dr Fuster that more than 40% of patients with ACS/STEMI stops some or all drugs within 6 months (hopefully results are different in the UK where drugs are free) and the addition of another tablet bd will not help compliance. Patients in ATLAS-ACS in the active arm stopped treatment in >25% of cases mainly but not exclusively because of side effects. It is hard to expect patients to maintain motivation for 2 years. Whatever the decision of NICE I do not expect a large scale adoption of this further escalation in an already complex pharmacological strategy. On the other side, the advantage in terms of hard end-point reduction of 2% (approx 50 patients needed to treat to spare a death) is quite compelling and a combined inhibition of platelet reactivity and coagulation cascade is rational in a syndrome where events are caused by atherothrombotic phenomena..

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.
Applying treatment to sicker patients than in the trial (older, etc) will require surveillance.

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?
The trial addressed cardiovascular mortality, stroke, myocardial infarction and recurrent ischaemic episodes requiring revascularisation and positive changes were present for mortality alone. These are major and not surrogate endpoints. The differences in the characteristics of the ACS population in the UK, including addition of new drugs not tested in combination, are highlighted in the premeeting breefing and I tend to agree with its caveats. Still, overall the differences are not such that the seriously challenge the applicability of the ATLAS results to the UK real life population and very similar criticisms can be raised for almost all the other trials that still prompted changes in NICE recommendations in the past.

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?
Routine clinical practice for Rivaroxibam is based on different indications. The fact that Rivaroxibam obtained the greatest penetration among the available NOACs likely reflect good tolerability (as well as its use once daily for AF). Of course we are

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speaking of patients threatened by a high stroke risk per year and they might be more resilient to minor side-effects than ACS patients. Most of these patients were also exposed to the bleeding risk and complexity of treatment monitoring of warfarin and consider themselves privileged for being able to use a new expensive treatment.

Equality and Diversity

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

None of the statements above is relevant to this discussion

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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.

Difficult to go beyond the very comprehensive evidence presented in the pre-screening document

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)?

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The addition of this new drug does not require specific monitoring different from the routine GP and specialist visits ACS patients anyway need in the first months after hospital discharge