

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**GUIDANCE EXECUTIVE (GE)**

**Consideration of consultation responses on review proposal**

**Review of TA249; ‘Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation’, TA256; ‘Rivaroxaban for the prevention of stroke in atrial fibrillation and TA275; Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation with one or more risk factor for stroke or systemic embolism**

TA249 was published in March 2012 and TA256 was published in May 2012 and both pieces of guidance have a review date of October 2014. The guidance on apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation was published as TA275 in February 2013. The recommendation for reviewing TA275 is as follows: “The guidance on this technology will be considered for review alongside the related technology appraisals TA249 and TA256”.

**Background**

At the GE meeting of 22 January 2013 it was agreed we would consult on the review plans for this guidance. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

<p><b>Proposal put to consultees:</b></p>	<p>The recommendations of TA249 and TA256 and the recommendations on apixaban will be incorporated, verbatim, into the ongoing update of clinical guideline 36 'Atrial fibrillation'.</p> <p>The technology appraisals will be moved to the static list and will remain extant when the guideline is published. This has the consequence of preserving the funding direction.</p>
<p><b>Rationale for selecting this proposal</b></p>	<p>These technology appraisals overlap with the remit of an ongoing update of a clinical guideline. There is also a related quality standard.</p> <p>At the time the proposal was developed, no new or ongoing studies that would have been expected to change the recommendations and no direct comparisons of the drugs had been identified. Several indirect comparisons had been published but these relied on the same evidence base as was used for the development of TA249, TA256 and for the ongoing appraisal of apixaban for this indication. A related drug, apixaban had been discussed by the appraisal committee on 20th November 2012. This guidance has now been published as TA275.</p> <p>Given the lack of new evidence and evidence from trials that compare the drugs with each other directly, it is unlikely that a review conducted through the multiple technology appraisal process would be able to distinguish more clearly between the newer anticoagulants on the basis of clinical and cost effectiveness than was possible in the three separate single technology appraisals. It is likely that the guidance would not change and that all three novel anticoagulants would remain recommended as options. There may be other reasons for choosing one drug over another in particular situations, and these may flow from the contextualisation which the guideline update will provide.</p>

GE is asked to consider the original proposal in the light of the comments received from consultees and commentators, together with any responses from the appraisal team. It is asked to agree on the final course of action for the review.

<b>Recommendation post consultation:</b>	<p>The recommendations of TA249 and TA256 and TA275 will be incorporated, verbatim, into the ongoing update of clinical guideline 36 'Atrial fibrillation'.</p> <p>The technology appraisals will be moved to the static list and will remain extant when the guideline is published. This has the consequence of preserving the funding direction.</p>
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<b>Respondent</b>	<b>Response to proposal</b>	<b>Details</b>	<b>Comment from Technology Appraisals</b>
Medicines and Healthcare Products Regulatory Agency	No comment	We think this is an administrative matter, therefore, we shan't be sending any comments.	No action required.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Bayer	Agree	<p>We are not aware of any new evidence that is likely to have a material effect on the current recommendations in the TAs and therefore agree with the proposal that the technology appraisals TA249, TA256 and the final guidance for apixaban should be incorporated, verbatim, into the ongoing update of clinical guideline 36 'Atrial fibrillation'.</p> <p>Please find below some areas related to practicalities that may be useful for contextualisation within the guideline, along with relevant citations. These issues may be particularly relevant for patients with atrial fibrillation who are more likely to be older and may have other comorbidities.</p> <ul style="list-style-type: none"> <li>• Once-daily versus twice daily dosing regimens.</li> <li>• Special precautions for storage and use in dosette systems.</li> <li>• Recommendations regarding dose adjustments in adult patients required for age, body weight, renal impairment, concomitant medications, co-morbidities such as gastrointestinal conditions and assessment of renal and hepatic function.</li> <li>• Method of administration, including crushing or breaking of tablets/capsules.</li> </ul>	No action required

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Bayer (continued)		<p><b>Additional relevant registered and ongoing trials not discussed in the proposal paper include:</b></p> <p><i>NCT01606995 Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation (XANTUS)</i></p> <p><i>Currently recruiting</i></p> <p><i>Estimated Enrollment: 6000</i></p> <p><i>Study Start Date: June 2012</i></p> <p><i>Estimated Study Completion Date: December 2014</i></p> <p>Investigations regarding the reversal of the anticoagulant effect are also underway. A recent publication by Eerenberg et al 2011<sup>11</sup> showed that “prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects.” Bayer also recently announced a clinical collaboration agreement with Portola Pharmaceuticals, Inc., San Francisco / USA, to evaluate the safety of PRT4445, an investigational antidote for Factor Xa inhibitors, in healthy volunteers who have been administered rivaroxaban. This proof-of-concept study, comprising multiple cohorts with different anticoagulants being tested, is expected to be completed in the second half of 2013.</p>	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
United Kingdom Clinical Pharmacy Association	Agree (but expressed caution in incorporating guidance wording verbatim)	<p>UKCPA support the NICE Guidance Executive proposal to incorporate the recommendations of TA249, TA256 and recommendations on apixaban into the ongoing update of clinical guideline 36 'Atrial Fibrillation'. However we note that the intention is to incorporate guidance verbatim, we consider that there is a need for caution with this approach due to the variation in wording of guidance on the advice regarding making a decision to start treatment with the new oral anticoagulants:</p> <ul style="list-style-type: none"> <li>• TA249 recommends that a decision to start dabigatran etexilate should be made after 'an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin'.</li> <li>• Similarly, TA256 recommends that a decision to start rivaroxaban should be made after 'an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin'.</li> <li>• However in the current draft of the apixaban guidance the proposed wording is as follows: 'The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban.'</li> </ul> <p>It would seem prudent for the updated AF guideline to consider addressing the difference of wording between the Technology appraisals within the guideline.</p>	Comment noted. The proposal is to incorporate the recommendations, verbatim, so as to preserve the funding direction of the individual technology appraisal guidance. However, the update of the clinical guideline can consider addressing the difference in wording between the published technology appraisals.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
		<p>As stated in the Guidance Executive's proposal although the ideal, it is unlikely that direct head to head comparisons of the new oral anticoagulants will be conducted. Further, whilst useful indirect comparisons and meta-analysis have been published these are unlikely to clearly and unequivocally differentiate the use of these agents for non valvular atrial fibrillation. UKCPA agree that an evidence based narrative to contextualise the use of specific novel oral anticoagulants over others in specific situations is appropriate.</p> <p>UKCPA are in favour of the Technology appraisal guidance for dabigatran, rivaroxaban and apixaban remaining extant to preserve the funding direction.</p> <p><b>Consideration of edoxaban</b></p> <p>We understand that if current timelines hold that edoxaban will have received a licence between the third and fourth quarter 2013. There is currently no indication that edoxaban is on NICE's work programme, therefore it is unclear when NICE guidance on edoxaban might be available and in what format. If edoxaban is included in the guideline without a prior Technology Appraisal, this will have a direct impact on the funding direction. NICE is asked to consider this in their proposal discussions.</p>	<p>Comment noted. Edoxaban will be considered for referral as part of the Technology Appraisal process as with any other technology.</p>

<b>Respondent</b>	<b>Response to proposal</b>	<b>Details</b>	<b>Comment from Technology Appraisals</b>
Atrial Fibrillation Association	Agree	We support the approach to review and provide collective information to support and guide the appropriate use of dabigatran and rivaroxaban and apixaban. We believe this will help to provide improved guidance and clarity to commissioners when deciding which treatment option would be the most appropriate to secure the best outcomes and quality of life for an AF patient considered at risk of AF-related stroke and so most likely to benefit from oral anticoagulation.	No action required.
South Asian Health Foundation	Agree	We are fully supportive of incorporating TA249 and TA256 into a clinical guideline and also would recommend NICE considers incorporating other novel oral anticoagulants such as apixaban into the same.	No action required.
AntiCoagulation Europe	Agree	We agree that the review of the NOACS - Rivaroxaban, Dabigatran and Apixaban for AF should be incorporated into the ongoing update of the AF Guidelines. We are unaware of any further evidence which may impact on the individual reviews of any of these technologies	No action required.
Arrhythmia Alliance	Agree	We support for the approach to review and provide collective information for the use of Dabigatran and Rivaroxaban and Apixaban. We feel that this will help to provide improved guidance and clarity to commissioners when deciding which treatment option may be most suitable for an arrhythmia patient. This will in turn contribute to improved quality of life and outcomes for the patient.	No action required.



<b>Respondent</b>	<b>Response to proposal</b>	<b>Details</b>	<b>Comment from Technology Appraisals</b>
British Association of Stroke Physicians	Agree	We entirely approve of NICE's decision to develop a guideline on this important topic.	No action required.
British Association of Stroke Physicians	Request change to matrix	The Association of British Neurologists should be included among the professional groups consultees for this proposed guideline	Comment noted. Stakeholder registration is available on the NICE web site.
Royal College of Physicians	Agree	The RCP is pleased to confirm that our experts in stroke medicine see no issue with the NICE proposal. We have also been copied to the comments submitted by the British Cardiovascular Society and would wish to support the valid comments raised within that submission.	No action required.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
British Cardiovascular Society	Agree	<p>The BCS is fully supportive of the NICE TAGs for dabigatran, rivaroxaban and apixaban, where these novel oral anticoagulants (OACs) should be an 'option' when stroke prevention is considered for patients with atrial fibrillation (AF).</p> <p>For the NICE AF guideline (CG36) being revised, the BCS is very strongly of the view that the stroke prevention section being revised should refer to the therapy in general, that is, "oral anticoagulants" as the option for stroke prevention, and this can be provided as one of the novel OACs or as very well controlled adjusted dose warfarin (an average time in therapeutic range of &gt;70% is recommended in a recent European position document, and the 2012 focused update of the European Society of Cardiology (ESC) guidelines on AF).</p> <p>Thus, there should not be focus on specific novel OACs in the CG36 update, but to OACs in general. In the absence of head to head trials, and notwithstanding the limitations of indirect comparisons, there are no profound differences between the different agents (dabigatran, rivaroxaban and apixaban) and clinicians should be allowed to match the patient profile to a particular drug regime.</p> <p>The BCS also fully supports the 2012 ESC guidelines where the initial decision-making step should be to identify 'truly low risk patients' who do not need any antithrombotic therapy. Such 'truly low risk patients' are those 'age &lt;65 and lone AF (male and female), or a CHA2DS2-VASc score=0'. After this initial step, all other patients with AF with <math>\geq 1</math> stroke risk factors can be considered for effective stroke prevention, which is essentially OAC therapy (whether as well controlled warfarin or one of the novel agents).</p>	<p>Comments noted. The scope relating to the update of clinical guideline 36 defines what the guideline will (and will not) examine, and what the guideline developers will consider.</p>

Respondent	Response to proposal	Details	Comment from Technology Appraisals
British Cardiovascular Society (continued)		<p>Antiplatelet therapy should only be reserved for the minority of patients who totally and absolutely refuse any form of OAC for stroke prevention. It should be emphasized that aspirin is pretty ineffective for stroke prevention in AF, and is not any safer compared to warfarin in terms of major bleeds and intracranial bleeding</p> <p>The BCS also endorses in the 2012 ESC guidelines in recommending the CHA2DS2-VASc and HAS-BLED scores for assessing stroke and bleeding risk, respectively.</p>	
Royal College of Nursing	No comment	Feedback received from nurses working in this area of health suggest that there is no additional evidence to submit on behalf of the RCN to inform on the review proposal for the development of this guidance, other than what can be found in systematic reviews.	No action required.
Bristol-Myers Squibb  Pfizer	Agree	<p>Bristol-Myers Squibb Pharmaceuticals Limited (BMS) and Pfizer Limited welcome NICE's suggestion of placing the three technology appraisals on the static list to preserve the funding direction and incorporating the appraisals into the update of clinical guideline 36.</p> <p>BMS and Pfizer are not aware of any new evidence that would change the recommendations for the Apixaban technology appraisal. We would encourage NICE to make it clear to the NHS that while the guideline is in development, the guidance from the three NOAC technology appraisals is in force.</p>	No action required.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
British Cardiovascular Intervention Society	Agree	We agree with the proposal to incorporate TA249 Dabigatran, TA256 Rivaroxaban, and the final guidance on apixaban into the ongoing update of CG36. We are not aware of any evidence which would suggest that a review would be beneficial.	No action required.
Boehringer Ingelheim	No explicit statement of agreement or disagreement	<p>Boehringer Ingelheim welcomes the opportunity to provide evidence to NICE as part of the review of dabigatran etexilate [dabigatran], apixaban and rivaroxaban in relation to stroke prevention in non-valvular atrial fibrillation [AF]. Although the Novel Oral Anticoagulants (NOACs) have been studied versus warfarin as a common comparator, there are differences across trial design and patient populations studied. However, there is a need to differentiate the NOACs as there are potential benefits in various patient subgroups. This is pertinent in the absence of any head-to-head randomised control trials.</p> <p><i>[Boehringer Ingelheim submitted a document, too large to be included here, describing some features relating specifically to dabigatran and a summary of the currently available evidence including some published indirect comparisons between dabigatran, rivaroxaban and apixaban.]</i></p>	The majority of consultees agreed that the current proposal was appropriate. If appropriate the guideline developers can consider whether there is evidence to support providing additional recommendations relating to subgroups.

**No response received from:**

<u>Patient/carer groups</u> <ul style="list-style-type: none"> <li>Action Heart</li> <li>Afiya Trust</li> <li>Black Health Agency</li> </ul>	<u>General</u> <ul style="list-style-type: none"> <li>Allied Health Professionals Federation</li> <li>Board of Community Health Councils in Wales</li> <li>British Cardiovascular Industry Association</li> </ul>
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- Blood Pressure Association
- British Cardiac Patients Association
- Counsel and Care
- Different Strokes
- Equalities National Council
- Heart Care Partnership
- HEART UK
- Muslim Council of Britain
- Muslim Health Network
- Network of Sikh Organisations
- Specialised Healthcare Alliance
- The Somerville Foundation (formerly known as Grown Up Congenital Heart Patients Association)
- The Stroke Association

Professional groups

- Anticoagulation Specialist Association
- British Association for Nursing in Cardiovascular Care
- British Association for Service to the Elderly
- British Atherosclerosis Society
- British Geriatrics Society
- British Heart Foundation
- British Nuclear Cardiology Society
- British Society for Haemostasis and Thrombosis
- British Society for Heart Failure
- British Society of Cardiovascular Imaging
- Clinical Leaders of Thrombosis
- Heart Rhythm UK
- National Heart Forum (UK)
- Primary Care Cardiovascular Society

- British National Formulary
- Care Quality Commission
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Association of Primary Care
- National Pharmacy Association
- NHS Alliance
- NHS Commercial Medicines Unit
- NHS Confederation
- Public Health Wales NHS Trust
- Scottish Medicines Consortium

Possible Comparator manufacturer(s)

- Actavis UK (aspirin)
- Alliance Pharma (aspirin)
- Aspar Pharmaceuticals (aspirin)
- Bayer (aspirin)
- Bristol Laboratories (warfarin)
- Crescent Pharma (warfarin)
- Dexcel–Pharma (aspirin)
- Focus Pharmaceuticals (aspirin)
- Galpharm International (aspirin)
- Genus Pharmaceuticals (aspirin)
- Mercury Pharma (warfarin)
- Rosemont Pharmaceuticals (warfarin)
- Sandoz (aspirin, warfarin)
- Taro Pharmaceuticals (warfarin)
- Teva UK (aspirin, warfarin)

- Royal College of General Practitioners
- Royal Pharmaceutical Society
- Royal Society of Medicine
- Society for Cardiological Science and Technology
- Society for Vascular Technology
- Society of Vascular Nurses
- The British Society for Haematology
- Vascular Society

Others

- Arden PCT Cluster
- Birmingham and Solihull PCT Cluster
- Department of Health
- Welsh Government

- Thornton & Ross (aspirin)
- Wockhardt UK (aspirin)
- Zentiva UK (warfarin, aspirin)

Relevant research groups

- Antithrombotic Trialists' Collaboration
- British Society for Cardiovascular Research
- Cardiac and Cardiology Research Dept, Barts
- Central Cardiac Audit Database
- Cochrane Heart Group
- Cochrane Stroke Group
- CODA
- European Council for Cardiovascular Research
- MRC Clinical Trials Unit
- National Heart Research Fund
- National Institute for Health Research
- Research Institute for the Care of Older People
- Wellcome Trust - Cardiovascular Research Initiative

Assessment Group

- Assessment Group tbc
- National Institute for Health Research Health Technology Assessment Programme

Associated Guideline Groups

- National Clinical Guideline Centre

Associated Public Health Groups

- None

**GE paper sign-off:** Janet Robertson, Associate Director – Technology Appraisals Programme

**Contributors to this paper:**

Technical Lead: Christian Griffiths

Project Manager: Andrew Kenyon

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