NICE advice

Non-vitamin K antagonist oral anticoagulants (NOACs)

Key therapeutic topic
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nice.org.uk/guidance/ktt16

Options for local implementation

- NICE has issued technology appraisal guidance on the use of the 4 non-vitamin K antagonist oral anticoagulants (NOACs), apixaban, dabigatran, edoxaban and rivaroxaban, in several clinical settings. All 4 NOACs must be included in local formularies for use in line with this guidance, with no additional funding or formulary restrictions.
- Review and, if appropriate, revise prescribing and local policies relating to antithrombotics, including NOACs, to ensure these are in line with NICE guidance.
- Several factors are likely to affect the choice of antithrombotic for an individual. NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.

Evidence context

The 4 non-vitamin K antagonist oral anticoagulants (NOACs) currently licensed in the UK are apixaban, dabigatran, edoxaban and rivaroxaban. NICE has issued technology appraisal guidance on the use of NOACs in several clinical settings. These are summarised in table 1.

Table 1: NICE technology appraisal guidance on NOACs

Indication	Apixaban	Dabigatran	Edoxaban	Rivaroxaban

Prevention of VTE after elective hip or knee replacement	Recommended as an option: TA245[a]	Recommended as an option: TA157[a]	Not licensed for this indication	Recommended as an option: TA170[a]
Treatment and secondary prevention of DVT and/or PE	Recommended as an option: TA341[a]	Recommended as an option: TA327[a]	Recommended as an option: TA354[a]	Recommended as an option: TA261[a] and TA287[a]
Prevention of stroke and systemic embolism in people with non-valvular AF	Recommended as an option in specified circumstances: TA275[a]	Recommended as an option in specified circumstances: TA249[a]	Recommended as an option in specified circumstances: TA355	Recommended as an option in specified circumstances: TA256[a]
Prevention of adverse outcomes after acute management of ACS with raised biomarkers	Not licensed for this indication	Not licensed for this indication	Not licensed for this indication	Recommended as an option in specified circumstances: TA335[a]
Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; TA, technology appraisal; VTE, venous thromboembolism. [a] See the technology appraisal for full details of NICE's recommendations.				

The technology appraisal guidance summarised in table 1 should be read in the context of the relevant NICE guidelines, which set out the alternative treatments:

- Venous thromboembolism: reducing the risk for patients in hospital (2010) NICE guidance CG92
- Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (2012) NICE guidance CG144
- Atrial fibrillation: management (2014) NICE guidance CG180
- Myocardial infarction: cardiac rehabilitation and prevention of further MI (2013) NICE guidance CG172

The NICE pathways on venous thromboembolism: orthopaedic surgery, treating venous thromboembolism, atrial fibrillation and myocardial infarction: secondary prevention bring together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams. NICE has also published quality standards on venous thromboembolism prevention and atrial fibrillation: treatment and management which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas. It should be noted that, consistent with the NICE guideline, quality statement 2 for atrial fibrillation states: 'Adults with atrial fibrillation are not prescribed aspirin as monotherapy for stroke prevention.'

In some instances, not all the NOACs recommended as options in later technology appraisals are mentioned in the relevant NICE guideline. This is because they were not licensed for the indication at the time the guideline was published. Nevertheless, they should be considered as equal options alongside the NOAC(s) mentioned: see demonstrating compliance with NICE technology appraisal guidance.

As with all its recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions and the person's values and preferences. (NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.) This discussion should aim to help the person to reach a fully informed decision.

The absence of direct comparisons between different NOACs and differences in study populations, analyses and other factors in key studies raise difficulties when choosing among them for different indications. Several factors are likely to affect the choice for an individual. The discussion should therefore consider all the possible alternative antithrombotic options, including the advantages and disadvantages of each as appropriate to the individual person's clinical circumstances, needs, values and preferences. These are likely to include:

- the likely benefits from anticoagulation per se
- the risk of bleeding
- the likelihood that the person will be able to maintain consistent anticoagulation with the different options (that is, the need for a high proportion of time in therapeutic range for warfarin and the need for high adherence for NOACs)
- potentially interacting drugs
- renal and hepatic function

- the person's past experiences, attitudes towards blood testing and their preference for once or twice daily dosing
- the relative size of the capsules/tablets and their suitability for compliance aids (if relevant).

The NICE guideline on MI: cardiac rehabilitation and prevention of further MI advises against using a NOAC in combination with dual antiplatelet therapy in people who have had an MI. It recommends considering using warfarin and discontinuing treatment with a NOAC in such people, unless there is a specific clinical indication to continue it. This relates to people who have an indication for anticoagulation, such as atrial fibrillation which may or may not be related to their MI. The full guideline explains that the recommendation arises from the limited evidence for the use of NOACs in this context, and the likely increased risk of bleeding. This is a different scenario from that considered in the NICE technology appraisal guidance on rivaroxaban after acute coronary syndrome. The licensed dose of rivaroxaban for preventing adverse outcomes after acute coronary syndrome is 2.5 mg twice a day; this is lower than the licensed dose for other indications (10–20 mg once a day). The risk of bleeding is therefore also likely to be lower.

Bleeding is a risk common to all anticoagulants. In the October 2013 edition of Drug Safety Update, the MHRA issued advice on the contraindications and warnings for the 3 NOACs licensed at the time (apixaban, dabigatran and rivaroxaban), and these have also been incorporated into the summary of product characteristics (SPC) for edoxaban. Care should be taken when considering prescribing a NOAC to a person with other conditions, procedures or concomitant treatments that may increase the risk of major bleeding. The MHRA advises that impaired renal function may be a contraindication for using an anticoagulant medicine, or may require a dose reduction: see manufacturers' SPCs for more information.

The NICE guideline on chronic kidney disease recommends that healthcare professionals should consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more specified risk factors for stroke. The full guideline explains that this recommendation is based on a pre-specified subgroup analysis of the ARISTOTLE study (Granger et al. 2011). This found that, compared with warfarin, apixaban reduced the rate of stroke, death, and major bleeding, and people with impaired kidney function (eGFR 25–50 ml/min/1.73 m^2) had the greatest reduction in major bleeding with apixaban compared with warfarin.

The SPC for edoxaban states that, when edoxaban was used for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation, a trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared with well-managed warfarin. Therefore, edoxaban should be used in people with non-valvular atrial fibrillation and high

creatinine clearance only after a careful evaluation of the individual thromboembolic and bleeding risk.

Demonstrating compliance with NICE technology appraisal guidance

Commissioners have a statutory responsibility to make funding available for a medicine recommended by a NICE technology appraisal, usually within 3 months of its publication. Under the NHS Constitution, patients have a right to receive all medicines recommended by NICE if they and their healthcare professional think that the medicine is right for them. In practical terms, this means that all 4 NOACs must be included in local formularies for use in line with the technology appraisal guidance, with no additional funding or formulary restrictions. For example, providers or commissioners cannot recommend that any individual NOAC (or any other medicine, such as warfarin) is used **routinely** in preference to the others, or say that a particular medicine is available only if the formulary first choice is contraindicated or not tolerated. However, providers or commissioners can advise clinicians on the factors that should be considered when selecting a NOAC, and also that a particular medicine is preferred locally if an individual patient and clinician have agreed that they have no special reason for preferring one of the medicines over another. This is a subtle but important distinction. Further information is available in the document 'Frequently asked questions about NICE compliance', published on the NICE website.

Prescribing data

There are currently no prescribing comparators for this topic. The development of new prescribing comparators to support this key therapeutic topic will be explored by the NHS England Medicines Optimisation Intelligence Group[1].

The medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, does however include several cardiovascular and coronary heart disease metrics related to this key therapeutic topic. These include:

- Atrial fibrillation: access to audit tool, which is the number of downloads of the software that supports audit of patients prescribed anticoagulants for atrial fibrillation in relation to the number of practices within the CCG. Note: this can currently only measure practices who are engaged with the GRASP tool.
- Atrial fibrillation (AF004) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (70% or more inclusive of exceptions) for QOF indicator AF004.

- Atrial fibrillation (AF004) % underlying achievement, which is the number of patients with atrial fibrillation whose latest record of a CHADS2 score is greater than 1 who are currently treated with anticoagulation therapy.
- Oral anticoagulants % items, which is the proportion of prescription items for apixaban, dabigatran and rivaroxaban and the proportion of prescription items for warfarin as a percentage of the total number of prescription items for oral anticoagulants.

The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Apixaban, dabigatran and rivaroxaban are also included in the Innovation Scorecard, published by the Health and Social Care Information Centre. The Innovation Scorecard aims to improve transparency within the NHS of what treatments recommended by NICE are available within Trusts and CCGs and at National and Area Team level. It is intended to support monitoring of compliance with NICE Technology Appraisal recommendations and to assist the NHS in the identification of variation, which can be explained, challenged or acted upon. It is not intended to be used for performance management.

[1] For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.

About this key therapeutic topic

This document summarises the evidence base on this key therapeutic topic which has been identified to support Medicines Optimisation. **It is not formal NICE guidance.**

For information about the process used to develop the Key therapeutic topics, see the integrated process statement.

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