Anticoagulants, including 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 etexilate, 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.

- All anticoagulants are associated with several patient safety hazards. In 2007, the National Patient Safety Agency (NPSA), which is now part of NHS Improvement, issued a patient safety alert about anticoagulants. Although the alert pre-dates the widespread use of NOACs the principles within it are still applicable to practice.

- Review and, if appropriate, optimise prescribing and local policies relating to anticoagulants and antiplatelets, including NOACs, to ensure these are in line with NICE guidance and the principles of the NPSA safety alert.

- Several factors are likely to affect the choice of anticoagulant for an individual person. NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.
Evidence context

Place in therapy of non-vitamin K antagonist oral anticoagulants (NOACs)

The 4 non-vitamin K antagonist oral anticoagulants (NOACs) currently licensed in the UK are apixaban, dabigatran etexilate, 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Apixaban</th>
<th>Dabigatran etexilate</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of VTE after elective hip or knee replacement</td>
<td>Recommended as an option: TA245\textsuperscript{a}</td>
<td>Recommended as an option: TA157\textsuperscript{a}</td>
<td>Not licensed for this indication</td>
<td>Recommended as an option: TA170\textsuperscript{a}</td>
</tr>
<tr>
<td>Treatment and secondary prevention of DVT and/or PE</td>
<td>Recommended as an option: TA341\textsuperscript{a}</td>
<td>Recommended as an option: TA327\textsuperscript{a}</td>
<td>Recommended as an option: TA354\textsuperscript{a}</td>
<td>Recommended as an option: TA261\textsuperscript{a} and TA287\textsuperscript{a}</td>
</tr>
<tr>
<td>Prevention of stroke and systemic embolism in people with non-valvular AF</td>
<td>Recommended as an option in specified circumstances: TA275\textsuperscript{a}</td>
<td>Recommended as an option in specified circumstances: TA249\textsuperscript{a}</td>
<td>Recommended as an option in specified circumstances: TA355</td>
<td>Recommended as an option in specified circumstances: TA256\textsuperscript{a}</td>
</tr>
<tr>
<td>Prevention of adverse outcomes after acute management of ACS with raised biomarkers</td>
<td>Not licensed for this indication</td>
<td>Not licensed for this indication</td>
<td>Not licensed for this indication</td>
<td>Recommended as an option in specified circumstances: TA335\textsuperscript{a}</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; TA, technology appraisal; VTE, venous thromboembolism.

\textsuperscript{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** NICE guideline CG92 (which is being updated; publication expected January 2018)

- **Venous thromboembolic diseases: diagnosis, management and thrombophilia testing** NICE guideline CG144

- **Atrial fibrillation: management** NICE guideline CG180

- **Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease** NICE guideline CG172.

The NICE pathways on **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 in adults: reducing the risk in hospital** and **atrial fibrillation** 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. All 4 NOACs must be included in local formularies for use in line with NICE technology appraisal guidance, with no additional funding or formulary restrictions. Further information is available in the document 'Frequently asked questions about NICE compliance', published on the NICE website.

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. This discussion should aim to help the person to reach a fully informed decision. NICE has produced a **patient decision aid** to support discussions about anticoagulant options for people with atrial fibrillation. A **decision support tool** endorsed by NICE is also available. The tool supports the majority of NICE recommendations relating to the diagnosis and assessment of atrial fibrillation, assessment of stroke and bleeding risks and anticoagulation, and the NICE patient decision aid.

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 options, including the advantages and disadvantages of each as appropriate to the individual person's clinical circumstances, needs, values and preferences.

**Safety issues with anticoagulants**

In 2007, the National Patient Safety Agency (NPSA), which is now part of NHS Improvement, issued a patient safety alert about anticoagulants. This recommended that healthcare organisations in England and Wales should:

- Ensure staff are properly trained.
- Review and update written procedures and clinical protocols to ensure they reflect safe practice.
- Audit anticoagulant services using British Society of Haematology (BSH)/NPSA safety indicators as part of the annual medicines management audit programme.
- Ensure that patients prescribed anticoagulants receive appropriate information.
- Promote safe practice for prescribers and pharmacists to check that patients' blood clotting (International Normalised Ratio, INR) is monitored regularly and that the INR level is safe before issuing or dispensing repeat prescriptions for oral anticoagulants.
- Promote safe practice for prescribers co-prescribing one or more clinically significant interacting medicines for patients already on oral anticoagulants: arrange for additional INR blood tests and inform the anticoagulant service that an interacting medicine has been prescribed.
- Ensure dental practitioners manage patients on anticoagulants according to evidence-based therapeutic guidelines.
- Amend local policies to standardise the range of anticoagulant products used, incorporating characteristics which promote safer use.
- Promote the use of written safe practice procedures for the administration of anticoagulants in social care settings.

The alert pre-dates the widespread use of NOACs (for which INR monitoring is not appropriate) but the principles within it are still relevant to practice, after suitable interpretation and application. This key therapeutic topic highlights 3 important safety issues relating to the use of anticoagulants (although all components of the NPSA safety alert should be considered):
• Information and awareness.

• Dosing and administration errors, including omitted or delayed doses or inappropriately continued prescribing.

• Interactions (including concomitant use of additional anticoagulant or antiplatelet drugs), contraindications and warnings.

Information and awareness

It is important that people prescribed anticoagulants, and the health and social care practitioners looking after them, have sufficient information to use these medicines safely and effectively. The type of information to be provided to patients is described in the NICE guideline on venous thromboembolic diseases:

• how to use anticoagulants

• duration of anticoagulation treatment

• possible side effects of anticoagulant treatment and what to do if these occur

• the effects of other medications, foods and alcohol on oral anticoagulation treatment

• monitoring their anticoagulant treatment

• how anticoagulants may affect their dental treatment

• taking anticoagulants if they are planning pregnancy or become pregnant

• how anticoagulants may affect activities such as sports and travel

• when and how to seek medical help.

It is also very important that health and social care practitioners are aware that NOACs are anticoagulants: reports to the National Reporting and Learning System (NRLS) suggest that unawareness and lack of recognition of generic and brand names may be a contributing factor to safety issues (personal communication, NHS Improvement, July 2016).

The patient-held yellow booklet 'Oral anticoagulant therapy: important information for patients' includes an alert card designed to be carried at all times by a person taking warfarin, as recommended in the NICE guideline on venous thromboembolic diseases. The card informs health and social care practitioners that the person is taking oral anticoagulants, and provides a contact
telephone number. The booklet also contains general information about the safe use of warfarin and has space for a written record of the latest INR test results, dosage information and the next clinic appointment. People prescribed NOACs should be directed to the manufacturer's patient information leaflets and be advised to carry an alert card, and show it to all health and social care practitioners who care for them (including community pharmacists and optometrists as well as doctors, nurses, dentists and social care practitioners). The card might be one provided by the manufacturer and specific to that particular NOAC, or a generic card such as that produced by the Atrial Fibrillation Association.

Dosing and administration errors, including omitted or delayed doses or inappropriately continued prescribing

Several instances of patient harm have been reported to the NRLS that involved doses of NOACs being omitted or delayed (personal communication, NHS Improvement). High adherence to all anticoagulants is important, particularly for NOACs because their half-lives are much shorter than that of warfarin. The clinical knowledge summary on oral anticoagulation states that the anticoagulant effect of NOACs fades 12–24 hours after the last dose is taken. Omitting or delaying doses could therefore lead to a reduction in anticoagulant effect, resulting in thrombosis. Apixaban has twice-daily dosing for all indications whereas dabigatran etexilate and rivaroxaban have twice-daily dosing for some indications and once-daily dosing for others. Edoxaban has once-daily dosing for all indications (see summaries of product characteristics [SPCs] for details). It is important that patients and health and social care staff realise the importance of adherence, and that prescribers select the correct dose and dosing interval for the indication (taking into account any need for dose reduction, for example in people with renal impairment).

The risk of bleeding associated with surgery (including dental surgery) is increased if a person is taking an anticoagulant. As with warfarin, there are recommendations around whether NOACs need to be stopped before planned surgery, and at what interval beforehand (see SPCs for drug-specific recommendations). However, instances of patient harm have been reported to the NRLS that involved NOACs not being stopped before surgery, or not being restarted at an appropriate time after surgery (personal communication, NHS Improvement).

A specific reversal agent for dabigatran etexilate is available: idarucizumab. This is licensed for use in adults treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding (see the evidence summary: new medicine publication on reversal of the anticoagulant effect of dabigatran: idarucizumab). There are currently no other licensed agents to reverse the anticoagulant effect of dabigatran etexilate or any other NOAC.
Analysis of adverse incidents involving inappropriate continuation of NOACs or omitted or delayed dosing suggests that failure to recognise the NOAC as an anticoagulant may have been a contributing factor in some cases (personal communication, NHS Improvement).

**Interactions (including concomitant use of additional anticoagulant or antiplatelet drugs), contraindications and warnings**

Warfarin is well-known to have a large number of drug–drug and drug–food interactions. These include interactions with medicines available over the counter. For example, the *June 2016 edition of Drug Safety Update* reminded healthcare professionals of the potential for serious interactions between warfarin and miconazole, including miconazole gel. This highlights the need for awareness that the person is taking an anticoagulant. NOACs also have drug–drug interactions that healthcare professionals should be aware of (see SPCs for details).

Patients may be placed at increased risk of bleeding if multiple anticoagulants are prescribed, or anticoagulants are co-prescribed with other drugs that increase the risk of bleeding. Examples include antiplatelets and non-steroidal anti-inflammatory drugs. Analysis of adverse incidents reported to NRLS suggests that failure to recognise NOACs as anticoagulants may have been a contributing factor in some cases where there was inadvertent co-prescribing of a NOAC with an antiplatelet, heparin or warfarin (personal communication, NHS Improvement).

Care should be taken when considering prescribing any anticoagulant to a person with other conditions, procedures or concomitant treatments that may increase the risk of major bleeding. 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 etexilate and rivaroxaban), and these have also been incorporated into the *SPC for edoxaban*. In addition to other warnings, the MHRA highlighted the need to pay attention to the person's renal function. The BNF states that warfarin should be used with caution in people with mild to moderate renal impairment and, in people with severe renal impairment, INR monitoring should be conducted more frequently. Impaired renal function may be a contraindication to using a NOAC, or may require a dose reduction: see individual SPCs for more information. Note that 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.
The NICE guideline on chronic kidney disease in adults recommends that healthcare professionals should consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m² 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 m²) had the greatest reduction in major bleeding with apixaban compared with warfarin.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of prescribing comparators to support this key therapeutic topic is currently being explored by the NHS England Medicines Optimisation Intelligence Group[1].

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

- Atrial fibrillation (AF007) % 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 AF007.
- Atrial fibrillation (AF007) % underlying achievement, which is the percentage underlying achievement at CCG level for QOF indicator AF007 inclusive of exceptions.
- Oral anticoagulants % items, which is the number of prescription items for apixaban, dabigatran etexilate, edoxaban and rivaroxaban as a percentage of the total number of prescription items for apixaban, dabigatran etexilate, edoxaban, rivaroxaban and warfarin sodium.

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 etexilate, edoxaban and rivaroxaban are also included in the Innovation Scorecard, published by NHS Digital. 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.


Update information

January 2017: This topic was retained for the 2017 update of medicines optimisation: key therapeutic topics. The topic has been broadened to include information on anticoagulants more generally, and the evidence context has been updated in the light of new guidance and important new evidence.

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.