

Anticoagulants, including direct-acting oral anticoagulants (DOACs)

Key therapeutic topic

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www.nice.org.uk/guidance/ktt16

Key points

- The use of anticoagulants is covered by many NICE guidelines and technology appraisals. Anticoagulant options may include vitamin K antagonists such as warfarin, or direct-acting oral anticoagulants (DOACs).
- NICE has issued technology appraisal guidance on the use of the 4 DOACs apixaban, dabigatran etexilate, edoxaban and rivaroxaban in several clinical settings.
- As relevant NICE guidelines are updated, the evidence for anticoagulant therapy will be reviewed to contextualise recommendations in the relevant NICE technology appraisal guidance.
- Several factors are likely to affect the choice of anticoagulant for an individual person. NICE has produced a [patient decision aid](#) and endorsed a [decision support tool](#) to support discussions about anticoagulant options for people with atrial fibrillation.
- NICE does not recommend [lead-I electrocardiogram \(ECG\) devices \(imPulse, Kardia Mobile, MyDiagnostick and Zenicor-ECG\) for detecting symptomatic atrial fibrillation using single time point testing in primary care](#) and has published advice on the [AliveCor Heart Monitor and AliveECG app \(Kardia Mobile\) for detecting atrial fibrillation](#). The National Screening Council does not recommend systematic population [screening for atrial fibrillation](#) as it is not clear that those identified as at risk through screening would benefit from early diagnosis.
- Be aware that all anticoagulants are associated with several patient safety issues. In 2007, the

- National Patient Safety Agency (NPSA), which is now part of NHS Improvement, issued a [patient safety alert about anticoagulants](#). The principles within this are still applicable to practice.
- Options for local implementation:
 - Review and, if appropriate, optimise prescribing and local policies relating to anticoagulants, including DOACs, to ensure these are in line with NICE and the National Screening Committee guidance and the principles of the NPSA safety alert.

Evidence context

Place in therapy of direct-acting oral anticoagulants (DOACs)

The 4 DOACs currently licensed in the UK are apixaban, dabigatran etexilate, edoxaban and rivaroxaban. NICE has issued technology appraisal guidance on the use of DOACs in several clinical settings. These are summarised in table 1.

Table 1 NICE technology appraisal guidance on DOACs

Indication	Apixaban	Dabigatran etexilate	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^a	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
<p>^aSee the technology appraisal for full details of NICE's recommendations.</p> <p>Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; TA, technology appraisal; VTE, venous thromboembolism.</p>				

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. In some instances, not all the DOACs 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 must be available for use if the prescriber and patient agree that they are the best course of action. Further information on [achieving and demonstrating compliance with NICE guidance](#) is available. As some guidelines are updated, the evidence for anticoagulant therapy will be reviewed to contextualise recommendations in the relevant NICE technology appraisal guidance. For example the updated NICE guideline on [reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism](#) contextualises technology appraisal guidance on DOAC use for people undergoing elective hip or knee replacement.

Preventing and treating venous thromboembolism

The NICE guideline on [reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism](#) (2018) is a major revision of NICE guidance. Risk assessment recommendations now emphasise the need to balance a person's individual risks of venous thromboembolism (VTE) against their risk of bleeding. NICE recommends:

- Assessing medical, surgery, trauma and psychiatric patients as soon as possible after admission or by the time of the first consultant review.
- Assessing pregnant women and women who gave birth or had a miscarriage or termination of pregnancy in the past 6 weeks on admission.

See the guidance for when to reassess the person's risk. The guideline provides population-specific recommendations on risk assessment tools and reassessment. There is an emphasis on giving people (and their family or carers) appropriate information for discharge and while in hospital, and

informing the person's GP.

Anti-embolism stockings are no longer routinely recommended as a possible option for medical patients in whom pharmacological VTE prophylaxis is contraindicated, although they remain an option in certain circumstances. Recommendations on VTE prophylaxis for people admitted to hospital after acute stroke have also been revised from previous guidance. The guideline makes recommendations on VTE prevention in a wide range of clinical conditions.

The guideline also optimises technology appraisal guidance on:

- [apixaban in elective hip and knee replacement \(TA245\)](#)
- [dabigatran in elective hip and knee replacement \(TA157\)](#)
- [rivaroxaban in elective hip and knee replacement \(TA170\)](#).

The recommendations reflect clinical and cost-effectiveness evidence. For people undergoing elective hip replacement NICE recommends offering 1 of 3 treatment options (in decreasing order of cost-effectiveness):

- low molecular weight heparin (LMWH) for 10 days followed by aspirin (75 mg or 150 mg) for a further 28 days
- LMWH for 28 days combined with anti-embolism stockings until discharge from hospital
- rivaroxaban (in preference to other DOACs).

Similarly, NICE recommends 1 of 3 options for people undergoing elective knee replacement (in decreasing order of cost-effectiveness):

- aspirin (75 mg or 150 mg) for 14 days
- LMWH for 14 days combined with anti-embolism stockings until discharge from hospital
- rivaroxaban.

For people undergoing elective hip or knee replacement, NICE recommends considering apixaban or dabigatran if none of the other recommended pharmacological options can be used and recommends further alternatives if pharmacological interventions are contraindicated.

Reducing the risk of stroke in people with atrial fibrillation

NICE's guideline on [atrial fibrillation: management](#) (which is being [updated](#)) aims to ensure that people receive the best management to help prevent harmful complications, in particular stroke and bleeding.

Aspirin monotherapy for stroke prevention alone is no longer recommended; this is reflected in [quality statement 2](#) of NICE's quality standard on [atrial fibrillation](#).

Following appropriate assessment, NICE recommends offering anticoagulation to people with a CHA₂DS₂-VASc score of 2 or above and considering anticoagulation for men with a CHA₂DS₂-VASc score of 1, taking bleeding risk into account. Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist. The [scope](#) for the update to the guideline states that the evidence for anticoagulant therapy will be reviewed with the aim of contextualising recommendations in NICE technology appraisal guidance TA249, TA256, TA275 and TA355.

Other indications for anticoagulation

Other relevant guidelines covering the use of anticoagulants include:

- [Venous thromboembolic diseases: diagnosis, management and thrombophilia testing](#) (NICE guideline CG144; which is being [updated](#)).
- [Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease](#) (NICE guideline CG172). This guideline along with NICE's guidelines on unstable angina and non-ST-segment-elevation myocardial infarction (NSTEMI): early management (NICE guideline CG94) and myocardial infarction with ST-segment elevation: acute management (NICE guideline CG167) are being combined and updated. The new guideline will be titled [acute coronary syndromes](#) when published.

NICE is developing technology appraisal guidance on [rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease](#) (expected publication date to be confirmed). NICE's medicines evidence commentary on [rivaroxaban with or without aspirin in people with stable peripheral or carotid artery disease](#) summarises the findings of the study which considered the effectiveness of rivaroxaban plus aspirin for this indication.

The NICE Pathways on [venous thromboembolism](#), [atrial fibrillation](#) and [myocardial infarction: rehabilitation and preventing further cardiovascular disease](#) bring together all related NICE

guidance and associated products on the conditions in a set of interactive flowcharts.

Implementation issues

NICE's quality standards on [venous thromboembolism in adults: reducing the risk in hospital and atrial fibrillation](#) are concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

VTE prophylaxis in acutely ill medical patients

NICE recommends offering pharmacological VTE prophylaxis for a minimum of 7 days to acutely ill medical patients whose risk of VTE outweighs their risk of bleeding. LMWH is recommended as first-line treatment or alternatively fondaparinux sodium if LMWH is contraindicated. This recommendation is a significant change from the 2010 guideline that has potential financial and logistical implications for hospitals. The [full guideline](#) (section 16.3) provides the context and validation for this approach.

Reducing the risk of stroke in people with atrial fibrillation

NICE's medicines evidence commentary on [thromboembolic disease: direct oral anticoagulants compared with warfarin in a real world setting](#) discusses a large UK prospective observational study in people with or without atrial fibrillation (AF) comparing the effectiveness of DOACs with warfarin in preventing ischaemic stroke, VTE and all-cause mortality. Apixaban reduced the risk of major bleeding compared with warfarin in both subgroups of patients, which was not seen with dabigatran or rivaroxaban. Both rivaroxaban and apixaban were associated with an increased risk of all-cause mortality compared with warfarin.

NICE's medicines evidence commentary on [primary prevention of stroke and transient ischaemic attack: UK observational study suggests under-prescribing of prevention medicines](#) summarised the results of a large UK observational study. This found that, in nearly 18,000 people with a first ever stroke or transient ischaemic attack, more than half had not been prescribed an anticoagulant before the event despite having had a clinical indication for primary prevention. The authors estimated that about 12,000 first strokes could be prevented each year in the UK by optimal prescribing of prevention medicine (including lipid-lowering and antihypertensive medicines as well as anticoagulants). However, the study did not assess how many people had a good reason for not having been prescribed an anticoagulant, such as those with a high risk of bleeding.

The study also didn't assess how many people had made an informed decision not to take an anticoagulant after considering the possible benefits and harms. Such practice is in line with NICE

guidance which notes that it is expected that there is discussion with the person about the risks and benefits of all the interventions it recommends, taking account of the person's values and preferences, so as to help the person to reach a fully informed decision. [Quality statement 3](#) in NICE's quality standard on [atrial fibrillation](#) states that people with AF who are prescribed anticoagulation should have the opportunity to discuss the options with their healthcare professional at least once a year. NICE has produced a [patient decision aid](#) to support discussions about anticoagulant options for people with AF. 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 AF, assessment of stroke and bleeding risks and anticoagulation, and the NICE patient decision aid.

Identifying people with atrial fibrillation

The National Screening Council does not recommend systematic population [screening for atrial fibrillation](#) because it is not clear that those identified through screening would benefit from early diagnosis. NICE's guideline on [atrial fibrillation](#) currently recommends performing manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying AF in people presenting with symptoms. NICE also recommends performing an ECG in all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected.

NICE diagnostics guidance on [lead-I electrocardiogram \(ECG\) devices \(imPulse, Kardia Mobile, MyDiagnostick and Zenicor-ECG\) for detecting symptomatic atrial fibrillation using single time point testing in primary care](#) covers devices that are used to record and analyse a single time point lead-I ECG for people with signs and symptoms of AF and an irregular pulse. NICE concluded that there is not enough evidence to recommend the routine adoption of lead-I ECG devices to detect AF in this situation. Using the devices for taking ECGs other than a single time point lead-I ECG reading, or for screening for AF in people without symptoms, was outside the scope of the assessment, as were wearable devices for detecting irregular heart rhythms available to the general public.

NICE's medtech innovation briefing on the [AliveCor Heart Monitor and AliveECG app \(Kardia Mobile\) for detecting atrial fibrillation](#) reviewed the best available evidence for this pocket-sized ECG recorder and an associated mobile device application providing analysis and communication of the results. The aim of the device is to identify paroxysmal AF. One of the studies included in the review ([Lowres et al. 2014](#)) was a community-based, opportunistic screening programme of 1,000 people aged 65 years and over in 10 pharmacies in Sydney, Australia. The AliveECG app was used to retrospectively interpret the original AliveCor Heart Monitor readings to identify AF. These interpretations were compared with a cardiologist's diagnosis from the AliveCor Heart

Monitor readings. The AliveECG app had 98.5% sensitivity (95% confidence interval [CI] 92.1 to 100) and 91.4% specificity (95% CI 89.4 to 93.1). Using these values the positive predictive value (PPV) and the negative predictive value (NPV) can be calculated. According to the National Cardiovascular Intelligence Network (February 2017), the expected prevalence of AF in England is 2.45%. In a population with that pre-test probability of AF, the sensitivity and specificity data from Lowres et al. (2014) indicate a PPV of 22.31% and an NPV of 99.96%. That is, for every 10,000 people in that population who test negative, only 4 people would actually have undetected AF. However, for every 10,000 people in that population who test positive 7,769 will be found not to have AF on further testing (false positive rate). The higher the pre-test probability, the lower the false positive rate. This illustrates the importance of informed consent for screening or case finding, in line with the principles of shared decision making.

Safety issues with anticoagulants

In 2007, the NPSA, (now part of NHS Improvement) issued a patient safety alert about anticoagulants. The alert pre-dates the widespread use of DOACs (for which international normalised ratio [INR] monitoring is not appropriate) but the principles within it are still relevant to practice, after suitable interpretation and application. Although all components of the NPSA safety alert should be considered, there are 3 safety issues relating to the use of anticoagulants which are particularly important:

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 (currently being updated).

It is also very important that health and social care practitioners are aware that DOACs 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 (NHS Improvement: personal communication 2016).

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 DOACs being omitted or delayed (NHS Improvement: personal communication 2016). High adherence to all anticoagulants is important, particularly for DOACs because their half-lives are much shorter

than that of warfarin. NICE's clinical knowledge summary on [oral anticoagulation](#) states that the anticoagulant effect of DOACs diminishes 12 to 24 hours after the last dose is taken. Omitting or delaying doses could therefore lead to a reduction in anticoagulant effect, resulting in thrombosis (see individual 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).

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 NICE's evidence summary on [reversal of the anticoagulant effect of dabigatran: idarucizumab](#)). In April 2019, another reversal agent: andexanet alfa received [conditional authorisation](#) from the European Medicines Agency for stopping life-threatening or uncontrolled bleeding in adults taking the anticoagulant medicines apixaban or rivaroxaban. NICE is producing technology appraisal guidance on [andexanet alfa for reversing anticoagulation](#) (publication expected March 2020).

Analysis of adverse incidents involving inappropriate continuation of DOACs or omitted or delayed dosing suggests that failure to recognise the DOAC as an anticoagulant may have been a contributing factor in some cases (NHS Improvement: personal communication 2016).

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. DOACs also have drug–drug interactions that healthcare professionals should be aware of (see SPCs for details). In the [July 2019 edition of Drug Safety Update](#), the Medicines and Healthcare products Regulatory Agency (MHRA) advised healthcare professionals to remind patients that the 15 mg and 20 mg strength tablets of rivaroxaban should be taken with food. This is because of a small number of reports suggesting lack of efficacy (thromboembolic events) in people taking these strengths of rivaroxaban on an empty stomach.

People 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 DOACs as anticoagulants may have been a contributing factor in some cases where there was inadvertent co-prescribing of a DOAC with an antiplatelet, heparin or warfarin (NHS Improvement: personal communication 2016).

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 DOACs 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 DOAC, 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 AF, 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 AF 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](#) (currently being [updated](#)) 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 AF who have 1 or more specified risk factors for stroke.

In the [October 2018 edition of Drug Safety Update](#), the MHRA warned that rivaroxaban should not be used for thromboprophylaxis in people with prosthetic heart valves, including people who have undergone transcatheter aortic valve replacement. The MHRA also advised that apixaban and edoxaban should not be used in people with prosthetic heart valves; dabigatran is contraindicated in people with prosthetic heart valves requiring anticoagulant treatment. In the [June 2019 edition of Drug Safety Update](#), the MHRA advised that DOACs are not recommended in people with antiphospholipid syndrome, particularly high-risk patients because of an associated increased risk of recurrent thrombotic events. SPCs have been updated accordingly to incorporate this recent MHRA safety guidance.

Practice examples and shared learning

The NICE impact reports on [cardiovascular prevention](#) and [stroke](#) review how NICE guidance is used to improve people's health and care. These reports are based on data showing the uptake of NICE guidance and quality statement measures from national audits, reports, surveys and indicator frameworks.

There are several NICE [shared learning examples](#) relating to this key therapeutic topic showing how NICE guidance and standards have been put into practice by some health and care organisations:

- [Utilising the skills of the clinical pharmacist within the MDT for improved medicines optimisation](#)
- [Overprescribing of rivaroxaban in non-atrial fibrillation patients in primary care](#)
- [Atrial fibrillation \(AF\) Holistic Care Pathway](#)
- [Safe and effective management of stroke prevention in atrial fibrillation](#)
- [Improving Medicines Optimisation for Care Home Residents and Providing Medicines Management Support to Care Homes - The Wigan Borough CCG Approach](#)
- [Reducing the risk of stroke in AF: using the NICE PDA with patients not currently treated with anticoagulants.](#)

Prescribing data, metrics or supporting resources

At this point, the following metrics and resources have been identified to support this topic.

Several cardiovascular and coronary heart disease metrics related to this key therapeutic topic are included in the [Medicines optimisation dashboard](#), which brings together a range of medicines-related metrics from across sectors. These include:

- Atrial fibrillation (AF007) % achieving upper threshold or above, which is the percentage of practices in a clinical commissioning group (CCG) that achieve upper threshold or above (70% or more inclusive of exceptions) for quality and outcomes framework (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.

The [Sentinel Stroke National Audit Programme \(SSNAP\)](#) also provides stroke data for England, Wales and Northern Ireland under clinical audit, acute organisational audit, and post-acute organisational audit.

DOACs are also one of the medicines groupings 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

September 2019: This topic was removed from the retired list and included in the 2019 rapid update of medicines optimisation: key therapeutic topics. Editorial amendments have been made, links to new and updated NICE guidance, links to medicines evidence commentaries, MHRA safety warnings and a section on implementation issues have been added. We have also updated the title of this topic.

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.**

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