Anticoagulation

This project reviews anticoagulation with warfarin and non-vitamin K antagonist oral anticoagulants (NOACs) in line with current national guidance. The project discusses the rationale for anticoagulation in atrial fibrillation, risk stratification for treatment, available agents, the appropriate implementation of these agents and additional, specific clinical considerations for treatment. NOACs have emerged as an alternative to vitamin K antagonists (VKA) for thrombo-embolic prevention in patients with non-valvular atrial fibrillation (AF). Some authors refer to these drugs as ‘direct oral anticoagulants’ (DOACs), but since the term NOAC is used by national guidance, this bulletin will continue to use the term NOAC.

Further PrescQIPP resources: briefing, slide set, warfarin prescriber decision aid, NOAC Comparisons, drug interactions, algorithm AF/VTE, clinical decision aid, NOAC counselling checklist, patient information leaflet, audit.

Recommendations

- Anticoagulation is the treatment of choice to reduce the risk of stroke.
- Aspirin is no longer recommended in atrial fibrillation (AF).¹
- Use CHA₂DS²-VASc score to assess stroke risk.¹
- Use HAS-BLED to assess bleeding risk.¹
- The decision about whether to start treatment with warfarin or a NOAC should be made after an informed discussion between the prescriber and the patient about the relative risks and benefits of each agent.²
- For patients on warfarin who have AF or heart valve disease and prefer to self monitor, ensure that the person or their carer is both physically and cognitively able to self-monitor effectively. Ensure that there is a process for appropriate quality control of the meter and for obtaining test strips, refer to appendix 1).³
- All four NOACs have a National Institute for Health and Care Excellence Technology Appraisal (NICE TA) and are an option for prescribing where appropriate.²
- There is no clear evidence for one NOAC being superior to another.⁴
- Use NOACS in line with algorithms or decision support tools. Take into account benefits, bleeding risks, reversibility, the person's values and preferences, renal and hepatic impairment, interacting drugs and attitudes towards once or twice daily dosing.²
- Ensure regular review of risks and benefits; ensure that baseline renal function is checked prior to starting a NOAC, then monitored on a regular basis. Ensure that dosage is adjusted accordingly.²
- For the prevention of Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE), ensure that NOACs are stopped after the defined period of anticoagulation stated by the hospital (usually at least three months). Take into account information that may help predict risk of recurrence and risk of bleeding in the individual patient.⁵-¹⁰
- For prevention of Venous Thromboembolism (VTE) after major elective orthopaedic surgery (i.e. knee or hip replacement) ensure that NOACs are stopped after the documented or licensed treatment period is reached.⁵-⁷ See PrescQIPP NOAC and LMWH deprescribing algorithm: https://www.prescqipp.info/resources/category/356-polypharmacy-practical-guide-to-deprescribing
Indications for oral anticoagulation

It is estimated that 1.4 million people in England have AF. This is equal to 2.4% of the population. AF increases the risk of stroke, which is a leading cause of death and disability worldwide. The use of oral anticoagulation in patients with atrial fibrillation at moderate or high risk of stroke, estimated by established criteria, improves outcomes. However, to ensure that the benefits exceed the risks of bleeding, appropriate patient selection is essential. Warfarin and other vitamin K antagonists have been the mainstay of treatment. They are highly effective treatments, reducing the relative risk of stroke by about two thirds, but their use is limited by a narrow therapeutic range, drug and food interactions, required monitoring, and risk of bleeding (see appendix 1. INR testing and monitoring). NOACs may be an alternative option.

Anticoagulation is prescribed in line with licensed indications for the treatment or prevention of thrombosis in the following conditions:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors.
- Treatment or recurrence of deep-vein thrombosis or pulmonary embolism.
- Cardioversion—target INR should be achieved at least three weeks before cardioversion and anticoagulation should continue for at least four weeks after the procedure (higher target values, such as an INR of 3, can be used for up to four weeks before the procedure to avoid cancellations due to low INR).
- Dilated cardiomyopathy.
- Mitral stenosis or regurgitation in patients with either atrial fibrillation, a history of systemic embolism, a left atrial thrombus, or an enlarged left atrium.
- Bioprosthetic heart valves in the mitral position (treat for three months), or in patients with a history of systemic embolism (treat for at least three months), or with a left atrial thrombus at surgery (treat until clot resolves), or with other risk factors (e.g. atrial fibrillation or a low ventricular ejection fraction).
- Acute arterial embolism requiring embolectomy (consider long-term treatment).
- Myocardial infarction.
- Mechanical prosthetic heart valves.

Prevention of stroke and systemic embolism in people with non-valvular AF

NICE CG180 recommends to offer anticoagulation with a NOAC or a vitamin K antagonist in AF patients with a CHA2DS2-VASc score of 2 or above or consider offering anticoagulation in men with a CHA2DS2-VASc score of 1 or more, taking bleeding risk into account. NICE states that aspirin monotherapy should not be offered solely for stroke prevention to people with atrial fibrillation. Warfarin is licensed for use without additional risk factors present. All NOACs are licensed for prevention of stroke in non-valvular atrial fibrillation plus at least one additional risk factor.

Background to NOACs

NOACs are classified into two groups: direct thrombin inhibitor (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). Factor Xa catalyses the activation of prothrombin into thrombin so all NOACs exert an anti-thrombin effect and prevent activation of fibrinogen into fibrin. Warfarin inhibits the formation of active clotting factors II, VII, IX and X.

NICE has issued TAs on the use of the four NOACs, apixaban, dabigatran, edoxaban and rivaroxaban, in several clinical settings. Table 1 below (also documented in NICE) summarises the recommendations.
Table 1: Summary of licensed indications and NICE recommendations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of stroke and systemic embolism in people with non-valvular AF</td>
<td>Recommended NICE TA 249&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Recommended NICE TA 256&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Recommended NICE TA 275&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Recommended NICE TA 355&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treatment and secondary prevention of DVT and/or PE</td>
<td>Recommended NICE TA 327&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Recommended NICE TA 261&lt;sup&gt;18&lt;/sup&gt; and 287&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Recommended NICE TA 341&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Recommended NICE TA 354&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prevention of VTE after elective hip or knee replacement</td>
<td>Recommended NICE TA 157&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Recommended NICE TA 170&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Recommended NICE TA 245&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Not licensed</td>
</tr>
<tr>
<td>Prevention of adverse outcomes after acute management of ACS with raised biomarkers</td>
<td>Not licensed</td>
<td>Recommended as an option in specific circumstances (TA 355)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Not licensed</td>
<td>Not licensed</td>
</tr>
</tbody>
</table>

In the randomised controlled trials comparing NOACs with warfarin for stroke prevention in non-valvular AF, the NOACs all provide non-inferior or superior protection against stroke. Most importantly, the risk of intracranial haemorrhage is significantly reduced with the use of NOACs as compared with warfarin.<sup>26</sup> A recent meta-analysis of seven studies found an odds ratio of 0.46 (95% CI 0.36 to 0.57) for intracranial haemorrhage risk associated with NOAC use as compared with warfarin among patients with AF.<sup>27</sup> Both of these findings have largely been replicated in real-world studies, although they are limited primarily to analyses of dabigatran and rivaroxaban use.<sup>26</sup>

A further meta-analysis of 12 studies (with a study population of 77,011) compared the safety and efficacy of the four NOACs to warfarin in patients with AF; NOACs were found to be superior to warfarin for the prevention of the composite of stroke and systemic embolism in patients with AF and an additional risk factor for stroke. There was a significant 52% reduction in intracranial haemorrhage, which drives the finding of significantly lower mortality. Cessation of long-term NOAC use and switch to warfarin may be associated with an increase in the composite of ischaemic stroke and systemic embolic events as well as major bleeding in the 30 days after cessation, which most likely highlights the necessity of close clinical supervision during this time.<sup>4</sup>

A large retrospective US insurance based study evaluated the effectiveness and safety of dabigatran, rivaroxaban, and apixaban by comparing each agent with warfarin. In patients with nonvalvular AF (NVAF), apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin.<sup>28</sup>

For ischaemic stroke, a Danish meta-analysis found no significant difference between NOACs and warfarin when the analysis was restricted to ischaemic stroke.<sup>29</sup>

NOACs have more predictable pharmacokinetics, fewer food and drug interactions, shorter half-lives, and quicker onset of action than warfarin. With the net benefit of the NOACs established and the convenience of fixed dosing without routine coagulation monitoring, NOACs are replacing warfarin as anticoagulants of choice in many patients.<sup>2</sup>
Summary of NOAC studies in AF

Dabigatran

In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, dabigatran 150mg twice daily reduced the relative risk of stroke and systemic embolism by 34% compared with warfarin without a significant difference in major bleeding events.  

Dabigatran 110mg twice daily was non-inferior to warfarin for prevention of stroke and systemic embolism, with 20% fewer major bleeding events. Both dabigatran doses significantly reduced haemorrhagic stroke and intracranial haemorrhage. Dabigatran 150mg twice daily significantly reduced ischaemic stroke by 24% and vascular mortality by 12%, while gastrointestinal bleeding was significantly increased by 50%. There was a non-significant numerical increase in the rate of myocardial infarction with both dabigatran doses, which has not been replicated in large post-authorization analyses. These observational data have also replicated the benefit of dabigatran over vitamin K antagonists found in the RE-LY trial in patients who were mainly treated with the higher 150mg twice daily dose.  

Rivaroxaban

In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, 14,264 patients were randomized to rivaroxaban 20mg once daily or vitamin K antagonist, with a dose adjustment to 15mg daily for those with estimated CrCl 30 – 49 mL/min. Rivaroxaban was non-inferior to warfarin for the prevention of stroke and systemic embolism in the intent-to-treat analysis, while the per-protocol on-treatment analysis achieved statistical superiority with a 21% relative risk reduction in stroke or systemic embolism compared with warfarin. Rivaroxaban did not reduce the rates of mortality, ischaemic stroke, or major bleeding events compared to vitamin K antagonists. There was an increase in gastrointestinal bleeding events, but a significant reduction in haemorrhagic stroke and intracranial haemorrhage with rivaroxaban compared with warfarin. A further real world observational new-user cohort study of 118,891 patients aged over 65 years concluded that treatments with rivaroxaban 20mg once daily was associated with statistically significant increases in intracranial haemorrhage and major extracranial bleeding, including major gastrointestinal bleeding, compared with dabigatran 150mg twice daily.  

Apixaban

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation) trial, apixaban 5mg twice daily reduced stroke or systemic embolism by 21% compared with warfarin, combined with a 31% reduction in major bleeding and an 11% reduction in all-cause mortality (all statistically significant). Rates of haemorrhagic stroke and intracranial haemorrhage, but not of ischaemic stroke, were lower on apixaban. Rates of gastrointestinal bleeding were similar between the two treatment arms.

Apixaban is the only NOAC that has been compared with aspirin in AF patients; apixaban significantly reduced stroke or systemic embolism by 55% compared with aspirin, with no or only a small difference in rates of major bleeding or intracranial haemorrhage.  

Edoxaban

In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48) trial, edoxaban 60mg once daily and edoxaban 30mg once daily were compared with adjusted-dose warfarin. Edoxaban 60mg once daily was non-inferior to warfarin. In an on-treatment analysis, edoxaban 60mg once daily significantly reduced stroke or systemic embolism by 21% and significantly reduced major bleeding events by 20% compared with warfarin, while edoxaban 30mg once daily was non-inferior to warfarin for prevention of stroke and systemic embolism but significantly reduced major bleeding events by 53%. Cardiovascular death was reduced in patients randomized to edoxaban 60mg once daily or edoxaban 30mg once daily compared with warfarin. Only the higher dose regimen has been approved for stroke prevention in AF.
Which NOAC do national guidelines recommend?

There are no randomized clinical trials comparing NOACs, and the few indirect comparisons suggest that NOACs are equally effective in the prevention of stroke.

NICE states that several factors are likely to affect the choice of antithrombotic for an individual. It recommends to review and, if appropriate, revise prescribing and local policies relating to antithrombotics, including NOACs, to ensure these are in line with NICE guidance. All four NOACs must be included in local formularies for use in line with this guidance, with no additional funding or formulary restrictions. 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.2

Certain clinical situations may favour one NOAC over another. For example, patients with severe renal function can be treated with apixaban, edoxaban or rivaroxaban.

Patients with AF with high stroke risk (e.g. CHA2DS2-VASc of 5 or 6) could be treated with dabigatran 150mg twice daily, as this was the only medication to show a significant reduction in ischaemic stroke risk as compared with warfarin in the randomised trials.26,30

For patients with AF at higher risk of bleeding, apixaban, edoxaban or dabigatran 110mg twice daily may be preferable given that each of these medications reduced the risk of bleeding as compared with warfarin.26 Among newly anticoagulated non-valvular atrial fibrillation (NVAF) patients in the real-world setting of 45,361 patients, apixaban and dabigatran initiation was associated with significantly lower risk of major bleeding compared to warfarin initiation. When compared to apixaban, rivaroxaban initiation was associated with significantly higher risk of major bleeding.36

Patients who prefer once-daily dosing will find both edoxaban and rivaroxaban to be more convenient than the twice-daily regimens for apixaban and dabigatran.26

Patients looking for single-drug treatment of VTE (especially outpatient treatment) will favour the use of apixaban or rivaroxaban, which do not require five to ten days of pre-treatment with low molecular weight heparin as is required for dabigatran and edoxaban.26

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.2

NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.37 This is available at https://www.nice.org.uk/guidance/cg180/resources/patient-decision-%20aid-243734797

Keele university has also formulated an on-line decision aid available at http://www.anticoagulation-dst.co.uk

With this set of resources:
- Attachment 1 provides a clinical decision aid to support prescribing decisions.
- Attachment 2 is a further decision aid containing patient information.
- Attachment 3 is a warfarin clinical decision aid
- Attachment 4 is a patient information leaflet on NOACs.

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 include:

- Benefits from anticoagulation
- Risk of bleeding
- Availability of antidotes
- 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
- Contra-indications
- Renal and hepatic function
- Past experiences and attitudes towards blood testing
- Preference for once or twice daily dosing
- Compliance
- Relative size of the capsules/tablets to ensure adherence
- Suitability for compliance aids (if relevant).

Also refer to PrescQIPP NOAC counselling checklist at available at: https://www.prescqipp.info/b183-anticoagulation/category/400-anticoagulation

Read codes can be incorporated into consultations to inform decision making i.e (EMIS Web)

8CI. Shared decision making
8CIO. Shared decision making with patient decision aid
8CII. Shared decision making without patient decision aid

Attachment 5 provides a tabulated comparison of the different NOACS. Attachment 6 provides further details on drug interactions. The European Heart Rhythm Association also provides practical guidance on the use of NOACs in patients with non-valvular AF.

**Assessing stroke risk and bleeding risk**

NICE recommends assessing stroke and bleeding risks using CHA2DS2-VASc and HAS-BLED scores.

The CHA2DS2-VASc stratifies stroke risk and is now integrated into practice systems. Refer to PrescQIPP anticoagulation clinical decision aid and algorithm. The recommendations in NICE CG180 are as follows:

- Score of 2 or more (men and women): offer anticoagulation, taking bleeding risk into account
- Score of 1 in men only: consider anticoagulants, taking bleeding risk into account

Of note is the strength of the recommendation, e.g. 'offer' is used for strong recommendations and 'consider' for weak recommendations by NICE.

Recommendations on the thresholds for recommending anticoagulation vary for other national guidelines. The European Society guidelines recommend anticoagulation in men only with a CHA2DS2-VASc score of 2 or more and in women with a CHA2DS2-VASc score of 3 or more. The SIGN 2014 guidelines recommend that all patients with AF who have a CHADS2 or CHA2DS2-VASc score of ≥1 (one or more clinically relevant risk factors) should be considered for warfarin at a target INR of 2.5 (range 2.0-3.0) or a newer anticoagulant. The balance of risks and benefits of anticoagulant therapy should be assessed and discussed annually with the patient, with consideration given to patient preference.
The HAS-BLED score identifies those at high risk of bleeding (score >=3). Refer to PrescQIPP AF anticoagulation clinical decision aid and algorithms (attachments 1-4).

A paper published in the BMJ in 2016 compared actual event rates of thromboembolism and bleeding risk to predicted risks using the CHA\(_2\)DS\(_{-2}\)-VASc or HAS-BLED score. The study used data from a commercial health claims data base of 21,934 adults with AF treated with dabigatran 150mg or warfarin. It was noted that the real and predicted risk of thromboembolism was similar at 1.7%/year. However the rates of major bleeding were underestimated.\(^{40}\)

**Other scores**

**Q stroke**

Q stroke was also derived from the UK population. It assesses stroke risk over the next ten years. It is used for primary prevention only. Q Stroke also shows some improvement on current risk scoring methods, CHADS\(_2\) and CHA\(_2\)DS\(_{-2}\)-VASc, for the subset of patients with atrial fibrillation for whom anticoagulation may be required. However the authors concluded that further research is needed to evaluate the cost effectiveness of using the Q stroke algorithms in primary care.\(^{41}\)

Refer to [http://www.qstroke.org/calculator](http://www.qstroke.org/calculator)

**Q bleed**

The Q Bleed algorithm was developed from a 1.4 million UK patient population. It provides valid measures of absolute risk of gastrointestinal and intracranial bleed in patients with and without anticoagulation. Further research is needed to evaluate the clinical outcomes and the cost effectiveness of using these algorithms in primary care.\(^{42}\)

Refer to [http://qbleed.org/](http://qbleed.org/)

Refer to Q bleed and Q stroke calculator [http://qbleed.org/plus-qstroke/](http://qbleed.org/plus-qstroke/)

**Bleeding**

Bleeding is a risk common to all anticoagulants. The 2016 MHRA update re-iterated advice on the risk of haemorrhage for the three NOACs licensed at the time (apixaban, dabigatran and rivaroxaban), and these have also been incorporated into the SPC for edoxaban. Care should be taken when considering prescribing a NOAC to a person with other conditions, procedures or concomitant treatments (e.g. non-steroidal anti-inflammatory drugs, antiplatelets) that may increase the risk of major bleeding.\(^{43}\)

It has been estimated that 1-4% of patients treated with NOACs may experience major bleeding and around 1% may require emergency surgery or rapid reversal of the anticoagulant effect for other reasons.\(^{44}\) The bleeding risk is summarised in table 1.

**Table 1: Bleeding risk of NOACs compared to warfarin**

<table>
<thead>
<tr>
<th>Bleeding risk compared to warfarin/Study</th>
<th>Dabigatran RE-LY(^{30})</th>
<th>Rivaroxaban ROCKET(^{32})</th>
<th>Apixaban ARISTOTLE(^{34})</th>
<th>Edoxaban ENGAGE AF-TIMI 48(^{35})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed and non-major clinically significant bleeding</td>
<td>Similar risk – 150mg bd Significant reduced risk 110mg bd</td>
<td>Similar risk</td>
<td>Reduced risk</td>
<td>Reduced risk</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>Reduced risk</td>
<td>Reduced risk</td>
<td>Reduced risk</td>
<td>Reduced risk</td>
</tr>
<tr>
<td>Major GI bleed</td>
<td>Significantly increased risk with 150mg twice daily. Similar risk with 110mg twice daily</td>
<td>Significantly increased risk</td>
<td>Similar risk</td>
<td>Significantly increased risk with 60mg</td>
</tr>
</tbody>
</table>
The European Heart Rhythm Association has produced a universal NOAC anticoagulation card. Specific alerts for the individual NOACs are listed in the PrescQIPP NOAC counselling checklist available at [https://www.prescqipp.info/b183-anticoagulation/category/400-anticoagulation](https://www.prescqipp.info/b183-anticoagulation/category/400-anticoagulation)

Monitoring requirements are listed in the AF decision aid (attachment 1).

**Renal function**

The MHRA advises that impaired renal function may be a contraindication or recommendation not to use an anticoagulant medicine, or may require a dose reduction: see manufacturers' SPCs for more information and attachment 5 – table of NOAC comparisons for more information.

It is important to note that all major trials of NOACs versus warfarin for stroke prevention in AF used the Cockcroft-Gault equation to estimate renal function. The SPC of each NOAC recommends that ‘Cockcroft and Gault’ formula is used for dosing and monitoring, i.e.

\[
\text{CrCl} = \frac{[140 - \text{age(yrs)}]}{\text{ideal body weight or actual if less (kg)}} \times 1.23 \text{ for males (1.04 in women)}
\]

Serum creatinine (micromole/l)

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/1.73m² and non-valvular atrial fibrillation who have one 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. 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/1.73m²) 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.

**Antidotes**

Specific antidotes to NOACs have recently been developed or are in current development. The London Medicines Evaluation Network has summarised these:

- **Idarucizumab** is currently available to reverse the anticoagulant effects of dabigatran.
- **Andexanet alfa** is being developed (for potential launch in 2017) to reverse the anticoagulant effects of rivaroxaban, apixaban and potentially edoxaban.
- **Aripazine (PER977)** is being developed (currently in phase 2 studies) as a universal antidote to reverse the anticoagulant effect of NOACs, oral factor Xa inhibitors, fondaparinux, LMWHs and unfractionated heparins.

Currently, in the event of life-threatening haemorrhage in patients taking NOACs, off-label use of prothrombin complex concentrate, activated prothrombin complex concentrate or recombinant-activated factor VIIa may be considered. However, their effectiveness is not demonstrated in clinical trials and conflicting data means that no consensus is available for treatment protocols. It is feared that an inability to rapidly reverse the anticoagulant effects of NOACs with unvalidated reversal strategies may seriously compromise the clinical outcome and even render the situation unsalvageable.

Development of specific antidotes designed to reverse the anticoagulant activity of NOACs may provide an important treatment option for patients who experience a major bleeding event or require emergency surgery. The availability of antidotes to NOACs may help provide clinicians and patients with reassurance about the safety of using NOACs, in case an emergency were to occur.
The manufacturer of idarucizumab estimates that between 0.3% to 2.87% of patients using dabigatran will experience a major bleed and around 1.2% of patients using dabigatran would be eligible for therapy with idarucizumab. However it is not yet clear how frequently NOAC antidotes will actually be required to manage bleeding emergencies in patients taking NOACs. The anticoagulant effect of warfarin can be effectively and rapidly reversed by giving phytomenadione (vitamin K) or in severe cases by using prothrombin complexes or fresh frozen plasma to manage bleeding.45

Duration of anticoagulation

**Atrial Fibrillation:** Review the need for anticoagulation and the quality of anticoagulation at least annually, or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk.1

**Venous thrombo-embolism (VTE):** Should generally be treated for either three months or indefinitely. The decision to stop anticoagulants at three months or to treat indefinitely is dominated by the long term risk of recurrence, and secondarily influenced by the risk of bleeding and by patient preference.9,10,46

VTE provoked by a reversible risk factor, or a first unprovoked isolated distal (calf) deep vein thrombosis (DVT), has a low risk of recurrence and is usually treated for three months.9,10,46

VTE associated with active cancer, or a second unprovoked VTE, has a high risk of recurrence and is usually treated indefinitely. Indefinite anticoagulation is often chosen if there is a low risk of bleeding, whereas anticoagulation is usually stopped at three months if there is a high risk of bleeding.9,10,46

For prevention of VTE after major elective orthopaedic surgery (i.e. knee or hip replacement) ensure NOACs are stopped after the documented (as in discharge) or licensed duration of treatment period is reached, see attachment 5 in table of comparisons for licensed durations of therapy.5,6,7 A VTE algorithm is available in attachment 8.

**Elderly**

- Ensure changes in renal function are monitored and the dose adjusted accordingly.
- Good data are available to support the use of anticoagulants in older patients including from BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study).47
- Check for expired indications, e.g. temporary loss of mobility that has now resolved).
- Caution: Avoid increased risk of bleeding through co-prescribing of anticoagulants, antiplatelets and NSAIDs.12

Analysis and costs

Analysis of usage in AF can be obtained through QoF indicators. Table 2 states these for 2016/17.48

**Table 2: QoF indicators for atrial fibrillation**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Points</th>
<th>Achievement thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Records</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF001. The contractor establishes and maintains a register of patients with atrial fibrillation</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ongoing management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF006. The percentage of patients with atrial fibrillation in whom stroke risk has been assessed using the CHA2DS2-VASc score risk stratification scoring system in the preceding 12 months (excluding those patients with a previous CHADS2 or CHA2DS2-VASc score of 2 or more) NICE 2014 menu ID: NM81</td>
<td>12</td>
<td>40-90%</td>
</tr>
<tr>
<td>AF007. In those patients with atrial fibrillation with a record of a CHA2DS2-VASc score of 2 or more, the percentage of patients who are currently treated with anti-coagulation drug therapy NICE 2014 menu ID: NM82</td>
<td>12</td>
<td>40-70%</td>
</tr>
</tbody>
</table>
In England and Wales, almost £323.1 million is spent on oral anticoagulants annually (ePACT March to May 2017). This equates to £13,256 per 1,000 patients. A further breakdown of individual drugs is tabulated in table 3. Efficiencies may be achieved through ensuring appropriate managed use of NOACs across secondary and primary care and ensuring that duration of treatment (as stated above) is appropriate and in line with licensed indications. An audit to ensure appropriate monitoring and duration of treatment is available in attachment 7.

Table 3: Usage and costs of NOACs across England (ePACT March to May 2017)

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of 28 days treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and any monitoring costs</td>
<td>3mg - £0.79</td>
<td>£47.60</td>
<td>£50.40</td>
<td>£53.20</td>
<td>£49.00</td>
</tr>
<tr>
<td>Total spend in England and Wales (ePACT March to May 2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>£3.7 million</td>
<td>£5.2 million</td>
<td>£37.4 million</td>
<td>£32.9 million</td>
<td>£707,000</td>
<td></td>
</tr>
<tr>
<td>Total items England and Wales (ePACT March to May 2017)</td>
<td>2.7 million</td>
<td>120,332</td>
<td>832,680</td>
<td>730,521</td>
<td>15,316</td>
</tr>
</tbody>
</table>

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Additional PrescQIPP resources

Briefing

Implementation resources

Available here: https://www.prescqipp.info/b183-anticoagulation/category/400-anticoagulation

Data pack

Available here: https://pdata.uk/#/views/B183_Anticoagulation/FrontPage?iid=1

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Contact help@prescqipp.info with any queries or comments related to the content of this document.

This document represents the view of PrescQIPP CIC at the time of publication, which was arrived at after careful consideration of the referenced evidence, and in accordance with PrescQIPP’s quality assurance framework.

The use and application of this guidance does not override the individual responsibility of health and social care professionals to make decisions appropriate to local need and the circumstances of individual patients (in consultation with the patient and/or guardian or carer). Terms and conditions
Appendix 1: International normalised ratio (INR) testing and monitoring

The NICE anticoagulation commissioning guide states that anticoagulation therapy services can be delivered in a number of different ways, and that mixed models of provision may be needed across a local health region. This could include full service provision in secondary or primary care, shared provision, domiciliary provision and selfmanagement. A report by the anti-coagulant self-monitoring alliance, states that a wide variety of mechanisms are used to commission and fund the service: block contract, payment by results (PbR), local enhanced services, local tariffs, cost per case, any qualified provider, or a combination of these. Services may be managed by a range of healthcare professionals including nurses, pharmacists and general practitioners. The most common arrangement made by CCGs is to have a mixture of commissioning provision.

INR monitoring

Healthcare organisations need to take steps to manage the risks associated with the prescribing, dispensing and administering of anticoagulants in line with NPSA alert 2007. Practices should ensure that patients' records clearly indicate the location of monitoring. The following read-codes apply:

- Anticoagulation monitoring – secondary care (66QC)
- Anticoagulation monitoring – primary care (66QD)
- Self-monitoring of INR (66QE)

The need for continuation of therapy is reviewed regularly with an annual risk assessment. The following read-code applies:

- Annual risk assessment (66Q2)

INR target

Guidelines on oral anticoagulation with warfarin, published by the British Committee for Standards in Haematology outline the process for INR monitoring for those receiving warfarin. Table 1 documents the INR targets.

Table 1: Target INRs

<table>
<thead>
<tr>
<th>Target INR</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>DVT or PE</td>
</tr>
<tr>
<td></td>
<td>AF</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td></td>
<td>Cardioversion</td>
</tr>
<tr>
<td></td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Mitral stenosis or regurgitation</td>
</tr>
<tr>
<td></td>
<td>Bioprosthesis in the mitral position should receive three months of anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Bioprosthetic valve and a history of systemic embolism should have at least three months of anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Bioprosthetic valve and left atrial thrombus at surgery should receive warfarin until the clot has resolved</td>
</tr>
<tr>
<td></td>
<td>Bioprosthetic valves and other prothrombotic risk factors, such as atrial fibrillation and low ventricular ejection fraction</td>
</tr>
<tr>
<td></td>
<td>Acute arterial embolism requiring embolectomy</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Target INR</td>
<td>Condition</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>3.5</td>
<td>Recurrent VTE whilst anticoagulated and within the therapeutic range</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prosthesis thrombogenicity</th>
<th>INR target</th>
<th>INR target</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patient risk factors</td>
<td>Patient related risk factors</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Medium</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>High</td>
<td>3.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

The NICE clinical knowledge summary for oral anticoagulation states that the INR can be most accurately measured in venous blood samples, but that capillary blood samples are also used because they are more convenient. People being tested should receive a written copy of their INR result including any necessary dose adjustments and a date for the next check.\(^5\)

The summary states that the INR should be measured daily, or on alternate days, until it is within the therapeutic range (usually between 2.0 and 3.0, ideally 2.5) on two consecutive occasions then twice weekly for 1–2 weeks, followed by weekly measurements until the INR is stable within the therapeutic range thereafter, depending on the stability of the INR, at longer intervals (for example, up to every 12 weeks, if agreed locally).

More frequent monitoring of the INR is recommended for patients:
- At risk of overcoagulation or bleeding, or
- Those having problems adhering to treatment
- Increased risk of bleeding
- People on high intensity anticoagulation (INR > 4.0)
- Age 65 years or over; highly variable INRs
- History of gastrointestinal bleeding
- Uncontrolled hypertension
- Cerebrovascular disease
- Serious heart disease
- Risk of falling
- Thrombocytopenia
- Anaemia, or coagulation disorders
- Malignancy
- Trauma
- Renal insufficiency
- Morbidity changes (such as intercurrent illness, or exacerbations of chronic conditions)
- Have changed their medication (for example, when starting or stopping prescribed or over-the-counter medicines).

Intravenous drug users, and people with hepatitis B, hepatitis C, or HIV, may be referred to a specialist clinic according to local arrangements.\(^5\)
Self-monitoring

Self-monitoring refers to monitoring by two different methods of care: self-testing and self-managing. Both methods are based on the INR.

- Self-testing refers to the user doing the INR test themselves and then contacting their healthcare professional with the reading for advice on any change to the dosage of the anticoagulant that may be needed.
- Self-managing refers to the user doing the INR test themselves and then self-adjusting the dosage of their anticoagulant medication by following an agreed care protocol.¹

NICE has developed diagnostics guidance on self-monitoring coagulation status in people on long term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease using point-of-care coagulometers. After an extensive review of the available evidence NICE have determined that point-of-care INR monitors (CoaguCheck XS system and INRatio2 PT/INR monitor) are safe to use. Evidence indicates that the precision and accuracy of both monitors are comparable to laboratory-based INR testing.¹

Currently, only CoaguCheck XS system (test strips) is available; the INRatio2 PT/INR monitor is no longer available on the NHS.¹

The CoaguChek XS system is recommended if:

- The person prefers this form of testing.
- The person or their carer is both physically and cognitively able to self-monitor effectively.
- Patients and carers should be trained on the effective use of the CoaguChek XS system and clinicians involved in their care should regularly review their ability to self-monitor.
- Equipment for self-monitoring should be regularly checked using reliable quality control procedures, and by testing patients' equipment against a healthcare professional's coagulometer which is checked in line with an external quality assurance scheme. Ensure accurate patient records are kept and shared appropriately.
- For people who may have difficulty with or who are unable to self-monitor, such as children or people with disabilities, their carers should be considered to help with self-monitoring.¹

NICE states that the use of these coagulometers may reduce the frequency of visits to hospital or clinics for patients and enable them to be monitored more regularly. This may improve health outcomes by enabling the dose of therapy to be adjusted more accurately, thereby avoiding adverse events that can result from an over or underdose of long term vitamin K antagonist therapy, such as stroke and major haemorrhage. In 2012, the anticoagulation alliance stated that here are more than 1.2 million people in the UK on warfarin therapy, of whom fewer than two per cent benefit from self-monitoring of their International Normalised Ratio (INR) level.²

Coagulometers are not currently available on the NHS but may be self-funded or donated by charities. Documented agreements between the patient and the anticoagulant service/relevant clinician should be considered. Box 1 gives an example.
Box 1: Example agreement for using coagulometer

Agreement
- Initial training in use.
- Ability to calibrate the device.
- Ability of patient or carer to use the meter and finger pricking device; consider vision and dexterity.
- Responsibility for ensuring correct use and correlation of results with those from the laboratory/near patient testing devices in practices.
- Agreement in advance what happens if test results don’t correlate, e.g. revert to practice testing.
- Reporting of results and responsibility for dosing.
- Recording of results and sharing as appropriate.
- Clinical responsibility remains with the clinician prescribing the vitamin K antagonist treatment, e.g. warfarin, even though the patient is self-testing.
- If patients are using more than a pre-set quantity of test strips per year, ensure review as they may not be suitable for self-testing.

One of the recent problems identified for self-monitoring, has been in obtaining the testing strips on prescription. If the patient is deemed suitable to self-monitor, there needs to be a process for obtaining test strips in sufficient quantity to ensure appropriate clinical monitoring whilst ensuring that waste is minimised. Processes for obtaining test strips and quantities may vary with different CCGs, e.g. test strips may be obtained via the provider, via prescription or directly through the manufacturer. The cost of test strips on FP10 is highlighted in table 2.

Table 2: Cost of INR testing strips

<table>
<thead>
<tr>
<th>INR testing strips</th>
<th>Quantity</th>
<th>Cost £</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoaguCheck XS PT</td>
<td>24</td>
<td>69.40</td>
</tr>
<tr>
<td>CoaguCheck XS PT</td>
<td>48</td>
<td>135.67</td>
</tr>
</tbody>
</table>

References (Appendix 1)