Oral anticoagulants for stroke prevention in nonvalvular AF

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Warfarin and direct oral anticoagulants (DOACs) have been shown to reduce the risk of stroke in patients with atrial fibrillation, yet many patients are still not being anticoagulated. This article discusses the barriers to the initiation of oral anticoagulants, in particular DOACs, and how these can be overcome.

Atrial fibrillation (AF) is the most common arrhythmia with over one million people diagnosed in the UK.\textsuperscript{1,2} It can lead to ischaemic stroke, which is one of the biggest causes of death in England and has annual health and social care costs of £4.38 billion in the UK.\textsuperscript{4} Ischaemic strokes associated with AF have poorer outcomes with a higher mortality and greater disability,\textsuperscript{5} yet strokes associated with AF are mainly preventable. It is estimated that 7000 strokes and 2000 premature deaths each year in England could be prevented using oral anticoagulants.\textsuperscript{6} Warfarin can reduce the risk of stroke by 64\%\textsuperscript{7} and direct oral anticoagulants (DOACs) have been shown to be as effective as warfarin in the prevention of ischaemic stroke.\textsuperscript{8}

Stroke prevention in atrial fibrillation

Warfarin and DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) are recommended by NICE for stroke prevention in nonvalvular AF (SPAF). Aspirin monotherapy should not be used for SPAF as it is considerably less effective than warfarin or DOACs\textsuperscript{1,9} and possesses similar bleeding risks to warfarin.\textsuperscript{10} All patients with AF and a CHA\textsubscript{2}-DS\textsubscript{2}-VASc score of 2 or more should be offered oral anticoagulants unless there is an absolute contraindication. Anticoagulation is not indicated for patients with AF at very low risk of stroke, ie under 65 years of age and no risk factors other than their sex.\textsuperscript{9}

Nationally, 22\% of people with AF and a CHA\textsubscript{2}-DS\textsubscript{2}-VASc score of 2 or more are still not anticoagulated according to the latest Quality and Outcomes Framework (QOF) data\textsuperscript{2} and a third of patients are inadequately treated with aspirin monotherapy.\textsuperscript{6} There has been a gradual increase in the levels of anticoagulation of patients with AF in England, Wales and Northern Ireland over the past few years, which seems to have been unaffected by the removal of aspirin from the guidelines or the increase in therapeutic options available (see Figure 1).\textsuperscript{11-14} The latest national stroke audit data showed that only 54\% patients with AF admitted with stroke between August 2016 and November 2016 were taking oral anticoagulants. Almost one-fifth of
patients were taking antiplatelet therapy only, such as aspirin, despite it being removed from the NICE guideline and QOF more than a year ago. There is also a wide variability in the use of DOACs across CCGs in England (see Figure 2).

**Barriers to initiating oral anticoagulants for SPAF**

The perceptions of clinicians about risks associated with oral anticoagulants can be a barrier to the initiation of oral anticoagulation therapy. Clinicians, including GPs, have been shown to be reluctant to initiate oral anticoagulants in patients with advanced age, especially those older than 80 years, despite them being healthy and without contraindications to oral anticoagulation. Age on its own should not be a contraindication to anticoagulation as older patients (>75 years) are at higher risk of stroke and show greater benefit from the intervention. The reluctance to prescribe oral anticoagulants to patients with advanced age is a result of overestimation of the bleeding risk. Treatment is often withheld in elderly patients due to concerns over excessive bleeding risk, despite the net clinical benefit of oral anticoagulants increasing with age and being the highest among patients aged 85 years and older. There is no consensus among clinicians on what risk of bleeding is acceptable with oral anticoagulants. In a matched-pair analysis, clinicians were significantly less likely to prescribe oral anticoagulants to new patients after a previous patient had had a major bleeding adverse event associated with anticoagulation. Surprisingly, occurrence of ischaemic stroke in a non-anticoagulated patient with AF did not increase the use of oral anticoagulants in clinicians’ future patients. The perception of bleeding and stroke risks differs between physicians and patients. In an observational study, patients at high risk of developing AF were happy to accept a much higher risk of bleeding in order to avoid stroke compared with primary and secondary care clinicians. This means that patients should always be involved in shared decision-making about whether to prescribe or not (see below).

Falls with risk of intracranial bleeding were cited as a reason to withhold oral anticoagulants. Clinicians perceive that elderly patients will be at increased risk of falls and thus increased risk of bleeding and therefore oral anticoagulants are often not initiated. However, patients would need to fall around 300 times per year for the risk of intracranial bleeding to outweigh the benefits of oral anticoagulants. The reported annual sustained falls rate for elderly patients is only 1.81. The bleeding risk should be calculated using validated tools such as HAS-BLED. A high HAS-BLED score is not a reason to

**Figure 1.** Anticoagulation of patients with known atrial fibrillation on admission for stroke in England, Wales and Northern Ireland, 2013–2016

![Figure 1](image-url)
withhold treatment with oral anticoagulants; it should be used as a tool to correct modifiable bleed risks such as high blood pressure and co-prescribing of gastric irritant drugs such as corticosteroids and NSAIDs, and drugs with antiplatelet effects such as SSRIs, aspirin, ticagrelor, prasugrel and clopidogrel.

Meta-analysis of DOAC trials showed significantly lower rates of intracranial bleeding, similar major bleeding but higher gastrointestinal bleeding rates when compared with warfarin. DOACs overcome some of the barriers reported with warfarin use (extensive food and drug interactions, frequent monitoring requirements) but some physicians have been shown to be reluctant to initiate them, citing the lack of a reversal agent in a major bleeding event. The rapid onset of DOACs diminishes the need for an antidote in most situations. However, in certain situations such as a life-threatening bleed or urgent surgery, a reversal agent could be beneficial. There is now a licensed specific reversal agent for dabigatran called idarucizumab and several others are in the pipeline.

Lack of experience is another key factor in preventing prescribing of oral anticoagulants for SPAF. A study interviewing GPs, practice managers and nurses observed that the majority of oral anticoagulation for SPAF was initiated in secondary care and hence primary care staff, including GPs, felt lacking in experience in starting anticoagulation. Inadequate communication between primary and secondary care was highlighted as another barrier.

The prescribing behaviour of GPs is also influenced by secondary care specialists, consultants, clinical investigators and peers. Organisational barriers to the use of oral anticoagulants, especially DOACs, are less well described in the literature. The cost of DOACs is also perceived to be a barrier to their use. However, NICE concluded that they are cost-effective and should be made available in line with local guidance without additional funding or formulary restrictions.

Locally, CCGs are responsible for medicines management in their area and can adapt medicines management processes to local area needs. CCGs should follow NICE recommendations, which state that warfarin or DOACs can be considered for newly diagnosed patients, patients inadequately managed with warfarin, and patients taking aspirin and thus should be made available locally.

Shared decision-making

Patient-centred care is at the heart of the NHS and patients should be fully informed about their treatment options. Patients with AF requiring anticoagulation wish to be involved in shared decision-making about oral anticoagulation, even in situations when they defer decisions to physicians. Patients also want to receive new information after making the decision and again, it is important for them to be able to discuss their options with the physician. This observation is important since four DOACs have been introduced for SPAF and patients already taking warfarin should be offered the choice to change oral anticoagulant, if appropriate. However, the literature shows that patients usually have little or no say in such decisions. NICE has produced a patient decision aid to help them to make informed decisions about taking oral anticoagulants.

Initiation and monitoring of DOACs

Historically some GPs have been reluctant to initiate DOACs as they did not consider themselves to have sufficient expertise. Currently, DOAC initiation is most often undertaken, or recommended, by specialists or GPs with a special interest. However, GPs are increasingly initiating DOACs, and as they are expected to continue the prescribing of DOACs started by others, they need to have the knowledge and skills to prescribe and monitor.

Initiation

NICE recommends that anticoagulation should be:

- Considered for men with a CHA₂DS₂-VASc score of 1, taking bleed risk into account
- Offered to people with a CHA₂DS₂-VASc score of 2 or above, taking bleed risk into account.

Firstly, patients with any absolute contraindications to anticoagulation should be identified, as these patients cannot be offered treatment. However, individual circumstances may change over time, so periodic reassessment is recommended. The number of absolute contraindications to DOACs is relatively
A significant risk of major bleeding such as:
- Current gastrointestinal ulcer
- Oesophageal varices
- Recent brain or spinal injury
- Recent brain, spine or ophthalmic surgery
- Recent intracranial haemorrhage
- Malignant neoplasm
- Vascular aneurysm
- A prosthetic heart valve
- Liver disease associated with coagulopathy and clinically relevant bleeding risk, or cirrhosis with Child-Pugh grade B (moderate impairment) or grade C (severe impairment)
- Significant thrombocytopenia (platelet count <50x10^9/L) – refer to haematologist
- Within 72 hours of major surgery with risk of severe bleeding – defer and reassess risk postoperatively
- Previously documented hypersensitivity to either the drug or excipients – consider cardiology opinion
- Acute clinically significant bleed – defer and reassess stroke versus bleeding risk within three months
- Pregnancy, breast feeding or within 48 hours postpartum – seek urgent haematological/obstetric/cardiology advice
- Certain co-prescribed medicines (see summary of product characteristics)
- Renal impairment
  - CrCl <30ml/min: avoid dabigatran
  - CrCl <15ml/min: avoid all DOACs
  - On dialysis

**Table 1. Absolute contraindications to direct oral anticoagulants (DOACs)¹⁴⁻⁶**

![Small(tables)](image)

**Table 2. Relative contraindications to direct oral anticoagulants (DOACs)¹⁴⁻⁶**

- Recent history of recurrent iatrogenic falls in patients at higher bleeding risk. A patient is assessed to be at higher bleeding risk if they have three or more of the following risk factors:
  - Age >65 years
  - Previous history of bleeding or predisposition to bleeding (eg diverticulitis)
  - Uncontrolled hypertension
  - Severe renal impairment (ie serum creatinine >200µmol/L, CrCl <30ml/min or on dialysis)
  - Acute hepatic impairment (eg bilirubin >2xULN + LFTS >3xULN) or chronic liver disease (eg cirrhosis)
  - Low platelet count <80x10^9/L or a thrombocytopenia or anaemia of undiagnosed cause
  - On concomitant drugs associated with an increased bleeding risk, eg SSRIs, oral steroids, NSAIDs, methotrexate or other immunosuppressant agents
  - Previous history of intracranial haemorrhage – as some AF patients, especially those considered at higher stroke risk, may benefit from antithrombotic therapy; seek the opinion of a stroke specialist
  - Recent major extracranial bleed within the last six months where the cause has not been identified or treated – decision for oral antithrombotic therapy should be deferred
  - Recent documented peptic ulcer within last three months – decision for oral antithrombotic therapy should be deferred until peptic ulcer treatment completed; in all cases with a history of peptic ulcer, give proton pump inhibitor cover while on antithrombotic
  - Dementia or marked cognitive impairment with poor medicines compliance and no access to carer support
  - Chronic alcohol abuse – especially if associated with binge drinking

**Ongoing monitoring**
Recall systems should be set up for monitoring of DOACs. Recalls can be set up on GP systems such as TPP SystmOne or EMIS, or anticoagulation software such as INRstar N3 can be used.

Monitoring parameters are shown in Table 3. The frequency of monitoring is consensus based. This guidance is based on advice from drug companies and NiCE clinical knowledge summary guidance.

Bleed risk needs to be managed both at initiation of DOAC treatment and on an ongoing basis, eg BP needs to be managed, alcohol intake should be limited and all gastric irritant drugs such as SSRIs and antidepressants need to be reviewed. A proton pump inhibitor can be offered on initiation of a DOAC if necessary test result characteristics.

**Prescriber**

September 2017

prescriber.co.uk
**Table 3. Guidance on ongoing monitoring of direct oral anticoagulants (DOACs)**

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Adherence</td>
<td>Ideally every three months (otherwise every six months)</td>
</tr>
<tr>
<td>Bleed risk</td>
<td>Ideally every three months (otherwise every six months)</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Annually</td>
</tr>
<tr>
<td>Full blood count</td>
<td>Annually</td>
</tr>
<tr>
<td>Kidney function</td>
<td>CrCl &gt;60mL/min annually</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-60mL/min every six months</td>
</tr>
<tr>
<td></td>
<td>CrCl 15-30mL/min every three months*</td>
</tr>
</tbody>
</table>

*Dabigatran treatment is contraindicated if creatinine clearance (CrCl) <30mL/min. Monitor urea and electrolytes/liver function tests more frequently if intercurrent illness. European guidance states that CrCl, calculated using the Cockcroft-Gault equation, needs to be used when checking for correct dosing when monitoring DOACs.

**Summary**

Strokes due to AF are effectively prevented with warfarin or DOACs. Anticoagulation in AF is still underused and one-third of patients are inadequately treated with aspirin, despite the strong evidence for oral anticoagulants and introduction of DOACs. The slow uptake of DOACs has been a result of a number of behaviours and organisation barriers. The net clinical benefit of oral anticoagulants increases with age and is the highest among older patients perceived to be at high risk of bleeding and falls. Tools such as HAS-BLED can be used to calculate the risk of bleeding and modifiable factors identified for correction rather than used as a stop tool for oral anticoagulation. Patients may have different perspectives on bleeding risks and accept a higher risk than clinicians in order to prevent disabling and debilitating strokes but their involvement is not always facilitated with shared decision making. The choice of oral anticoagulant offered should follow national guidelines. Patients identified to be at risk of AF-related stroke and patients inadequately anticoagulated with aspirin should be prescribed warfarin or a DOAC after discussion with them and consideration of risk and benefits. Education of both patients and prescribers continues to be a vital factor in overcoming barriers to use of oral anticoagulants for SPAF. GPs need to be provided with tools and support to confidentially and safely prescribe and monitor DOACs.

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Declaration of interests
Duncan Petty has received a fee from Bayer for presenting at a conference.

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