Increasing prescribing of oral anticoagulants for stroke prevention in non-valvular atrial fibrillation

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Stroke prevention in atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia with over 1 million people diagnosed in the United Kingdom (UK).[1-3] It can lead to ischaemic stroke, which is one of the biggest causes of death in England and has annual health and social cares costs of £4.38billion in the UK.[4] Ischaemic strokes associated with AF have poorer outcomes with a higher mortality and greater disability[5], yet strokes associated with AF are mainly preventable. It is estimated that 7,000 strokes and 2,000 premature deaths each year could be prevented with oral anticoagulants in England.[6] Warfarin can reduce the risk of stroke by 64%[7] and direct oral anticoagulants (DOACs) were shown to be as effective as warfarin in the prevention of ischaemic stroke.[8]

Warfarin and DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are recommended by NICE for stroke prevention in non-valvular AF (SPAF). Aspirin monotherapy should not be used for SPAF as it is considerably less effective than warfarin or DOAC[7,9] and possesses similar bleeding risks to warfarin.[10] All patients with AF and CHA_2DS_2-VASc score of 2 or more should be offered oral anticoagulants unless there is an absolute contraindication. Anticoagulation is not indicated to very low risk of stroke patients with AF, i.e. under 65 years of age and no risk factors other than their sex.[9]

Nationally, 22% of people with AF and CHA_2DS_2-VASc score of 2 or more are still not anticoagulated according to the latest Quality Outcome Framework (QOF) data[11] and 1/3 of patients are inadequately treated with aspirin monotherapy.[6] There has been a gradual increase in the levels of anticoagulation which seems to be unaffected by the removal of aspirin from the guidelines or the increase in therapeutic options available (*Figure 1*).[12-15] The latest national stroke audit data shows that only 54% patients with AF admitted for stroke between August 2016 and November 2016 were taking oral anticoagulants. Almost one fifth of patients were taking antiplatelet only, such as aspirin, despite it being removed from the NICE guideline and QOF more than a year ago.[15]

Barriers for initiating oral anticoagulants for SPAF

The perceptions of clinicians about risks associated with oral anticoagulants can prevent the initiation of oral anticoagulation therapy. Clinicians, including general practitioners (GPs), have been shown to be reluctant to initiate oral anticoagulants in patients with advanced age, especially in older than 80 years, despite them being healthy and without contraindications to oral anticoagulation.[16,17] Age on its own should not be a contraindication to anticoagulation as older patients (>75 years) are at higher risk of stroke and have greater benefit from the intervention.[9,16,17] The reluctance to prescribe oral anticoagulants to patients with advanced age is followed by overestimation of the bleeding risk.[16] Treatment is often withheld in elderly due to concerns over excessive bleeding risk[17], despite the net clinical benefit of oral anticoagulants increasing with age and being the highest among 85 years and older patients.[18]

There is no consensus amongst clinicians what risk of bleeding is acceptable with oral anticoagulants.[16,19] Clinicians were significantly less likely to prescribe oral anticoagulants to new patients after their previous patient had a major bleeding adverse event associated with anticoagulation.[20] Surprisingly, occurrence of ischaemic stroke in non-anticoagulated patient with AF did not increase the use of oral anticoagulants in physician's future patients.[20] The perception of bleeding and stroke risks differs between physicians and patients. Patients at high risk of developing AF were happy to accept a much higher risk of bleeding in order to avoid stroke compared to primary and secondary care clinicians.[19] 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.[17] Clinicians perceive that elderly patients will be at the increased risk of falls and thus increased risk of bleeding and therefore oral anticoagulants are not initiated. However, patients would need to fall around 300 times per year for risks of intracranial bleeding to outweigh the benefits of oral anticoagulants.[21] The reported annual sustained falls rate for elderly patients is only 1.81.[22] The bleeding risk should be calculated using validated tools such as HAS-BLED.[9] A high HAS-BLED score is not a reason to withhold treatment with oral anticoagulants; it should be used as a tool to correct modifying bleed risks such as high blood pressure; co-prescribing of gastric irritant drugs such as corticosteroids and NSAIDs and drugs with antiplatelet effects such as SSRIs, aspirin, ticagrelor, prasugrel and clopidogrel for instance.

Meta-analysis of DOACs studies showed significantly lower rates of intracranial bleeding, similar major bleeding but higher gastrointestinal bleeding rates when compared with warfarin.[23] DOACs overcome some of the barriers reported with warfarin use (extensive food and drug interactions, frequent monitoring requirements)[9,24] but some clinicians have been shown to be resilient to initiate them by citing the lack of a reversal agent in a major bleeding event.[24] The rapid onset of

DOACs diminishes the need of antidote in most situations. However, in certain situations such as life-threatening bleed or urgent surgery a reversal agent could be beneficial. There is currently a licensed reversal agent for dabigatran called idarucizumab[25] and several others are in the pipeline.[26]

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 majority of oral anticoagulation for SPAF was initiated in secondary care and hence primary care staff, including GPs, felt a lack of experience in starting anticoagulation.[27] Inadequate communication between primary and secondary care was highlighted as another barrier.[27]

Prescribing behaviour of GPs is also influenced by secondary care specialists, consultants, clinical investigators, and peers.[28-32] Organisational barriers to the use of oral anticoagulants, especially DOACs, are less well described in the literature. Cost of DOACs is perceived as a barrier for their use. However, NICE concluded that they are cost-effective and should be made available locally in line with their guidance without additional funding and formulary restrictions.[9] Locally, Clinical Commissioning Groups (CCGs) are responsible for the medicine management in their areas and can adapt medicine management processes to local area needs.[33] But 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.[9]

Shared-decision making

Patient-centred care is at the heart of the NHS and patients should be fully informed about their treatment options.[34] Patients with AF requiring anticoagulation wish to be involved in the shared decision-making about oral anticoagulation[35-38] even in situations when they defer decisions to clinicians.[35-37] Patients also want to receive new information after making the decision and it is important for them to be able to discuss their options again with the clincian.[35] This observation is important since four DOACs have been introduced for SPAF and patients already taking warfarin should be offered a choice of changing oral anticoagulant, if appropiate.[9] However, the literature shows that patients have little or no say in such decisions.[35,39,40] NICE has produced a patient decision aid to help patients to make informed decisions about taking oral anticoagulants.[41]

Initiation and monitoring of DOACs

Historically many GPs have been reluctant to initiate DOACs as they did not consider themselves to have sufficient expertise. Currently initiation is most often undertaken, or recommended, by specialists and 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 knowledge and skills to prescribe and monitor.

Initiation[9,42]

NICE recommend that anticoagulation should be:

- Considered for men with a CHA_2DS_2-VASc score of 1, taking the bleed risk into account
- Offered to people with a CHA_2DS_2-VASc score of 2 or above, taking bleed risk into account.

Firstly, 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 is relatively small (*Table 1*).

There are a number of relative contraindications to oral anticoagulants (*Table 2*) and the decision as to whether to offer treatment should take these into consideration.

Where treatment can be offered patients must be involved in the decision. Patients need to know that DOACs, like warfarin, are potent anticoagulants so the same risks of minor and major bleeding still apply. The anticoagulant effects of DOACs wear off quickly (next day). This means that if patients miss a dose then they will not have anticoagulant cover and will be at increased risk of a stroke.

Before starting treatment modifiable risk factors should be managed such as controlling systolic blood pressure to < 160mmHg and stopping gastric irritant medicines such as NSAIDS, and if possible antiplatelet and interacting drugs.

Before starting a DOAC necessary tests should be up to date (kidney function; liver function, full blood count and clotting screen). Life-style modifications should also be discussed with the patient such as reducing alcohol intake or moderating drinking, if applicable. Patient should be referred to the community pharmacist for a New Medicines Review and be given an anticoagulant warning card to carry at all times.

A checklist for initiation of anticoagulants is given in the *Table 3*:

Monitoring until patient stable

Monitoring is recommended to occur every 3 months to assess adherence and to reinforce advice regarding regular dosing schedule and also to enquire about adverse effects such as bleeding.[42] Patients should be assessed for the presence of thromboembolic events and enquiries made about other medicines the patient is taking, including OTC medicines.

Ongoing monitoring

Recall systems should be set up for monitoring of DOACs. Recalls can be set up on GP systems such as TPP SystmOne and EMIS, or software such as INR STARN3 can also be used.

Monitoring parameters are shown in the *Table 4*. The frequency of monitoring is consensus based. This guidance is based on advice from manufacturers and Clinical Knowledge Summaries guidance.

Bleed risk needs to be managed both at initiation of a DOAC and on an on-going basis, e.g. BP needs to be managed, alcohol intake should be limited and all gastric irritant drugs such as SSRI and antidepressants need to be reviewed. A proton pump inhibitor can be offered on initiation of a DOAC if felt appropriate, especially if also prescribed gastric irritant drugs which can't be stopped.

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 and introduction of DOACs. The slow uptake of DOACs has been a result of a number of behaviour 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 like HAS-BLED can be used to calculate the risk of bleeding and identify modifiable factors for correction rather than used as a stop tool for oral anticoagulation. Patients may have different perspectives on bleeding risks and accept higher risk than clinicians in order to prevent disabling and debilitating strokes but their involvement is not always facilitated in the shared-decision making. The offered choice of oral anticoagulant should follow national guidelines. Identified patients at risk of AF related stroke and patients inadequately anticoagulated with aspirin should be prescribed warfarin or a DOAC after discussion with the patient and consideration of risk and benefits. Education

of both patients and prescribers continue to be a vital aspect in overcoming barriers to oral anticoagulants for SPAF. GPs need to be provided with tools and support to confidentially and safely prescribe and monitor DOACs.

2007 words

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- A significant risk of major bleeding such as:
    - Current gastrointestinal ulcer.
    - 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, as well as people who have cirrhosis with Child-Pugh grade B (moderate impairment) or grade C (severe impairment).
- Significant thrombocytopenia (platelet count < 50 x 109/L) - refer to haematologist.
- Within 72 hours of major surgery with risk of severe bleeding - defer & reassess risk postoperatively.
- Previously documented hypersensitivity to either the drug or excipients – consider cardiology opinion.
- Acute clinically significant bleed - defer & re-assess stroke versus bleeding risk within 3 months.
- Pregnancy, breast feeding or within 48hours post-partum - seek urgent haematological/obstetric/cardiology advice.
- Certain co-prescribed medicines (see summary of product characteristics)
- Severe renal impairment
    - CrCl <30ml/min avoid dabigatran
    - CrCl<15ml/min: avoid all DOACs
    - On dialysis

Table 1. Absolute contraindications to DOACs.[42-47]

- Recent history of recurrent iatrogenic falls in patient at higher bleeding risk.

  A patient at higher bleeding risk is assessed by having 3 or more of the following risk factors:-
    - Age > 65 years
    - Previous history bleed or predisposition to bleeding (e.g. diverticulitis)
    - Uncontrolled hypertension
    - Severe renal impairment (i.e. serum creatinine > 200umol/L, GFR < 30 mL/min/1.73m^2 or on dialysis)
    - Acute hepatic impairment (e.g. bilirubin > 2xULN + LFTS > 3x ULN), chronic liver disease (e.g. cirrhosis)
    - Low platelet count < 80 x 10^9/L or a thrombocytopenia or anaemia of undiagnosed cause
    - On concomitant drugs associated with an increased bleeding risk, e.g. SSRIs, oral steroids, NSAIDs, methotrexate or other immune-suppressant agents.
- Previous history intracranial haemorrhage - as some AF patients especially

those considered at higher stroke risk may benefit from anti-thrombotic therapy, seek the opinion of a stroke specialist.

- Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated – decision for oral anti-thrombotic therapy should be deferred.
- Recent documented peptic ulcer (PU) within last 3 months– decision for oral anti-thrombotic therapy should be deferred until treatment for PU completed. In all cases with history PU give PPI cover whilst on anti-thrombotic.
- Dementia or marked cognitive impairment with poor medicines compliance and no access to carer support.
- Chronic alcohol abuse – especially if associated with binge drinking.

Table 2. Relative Contraindications to DOACs.[42-47]

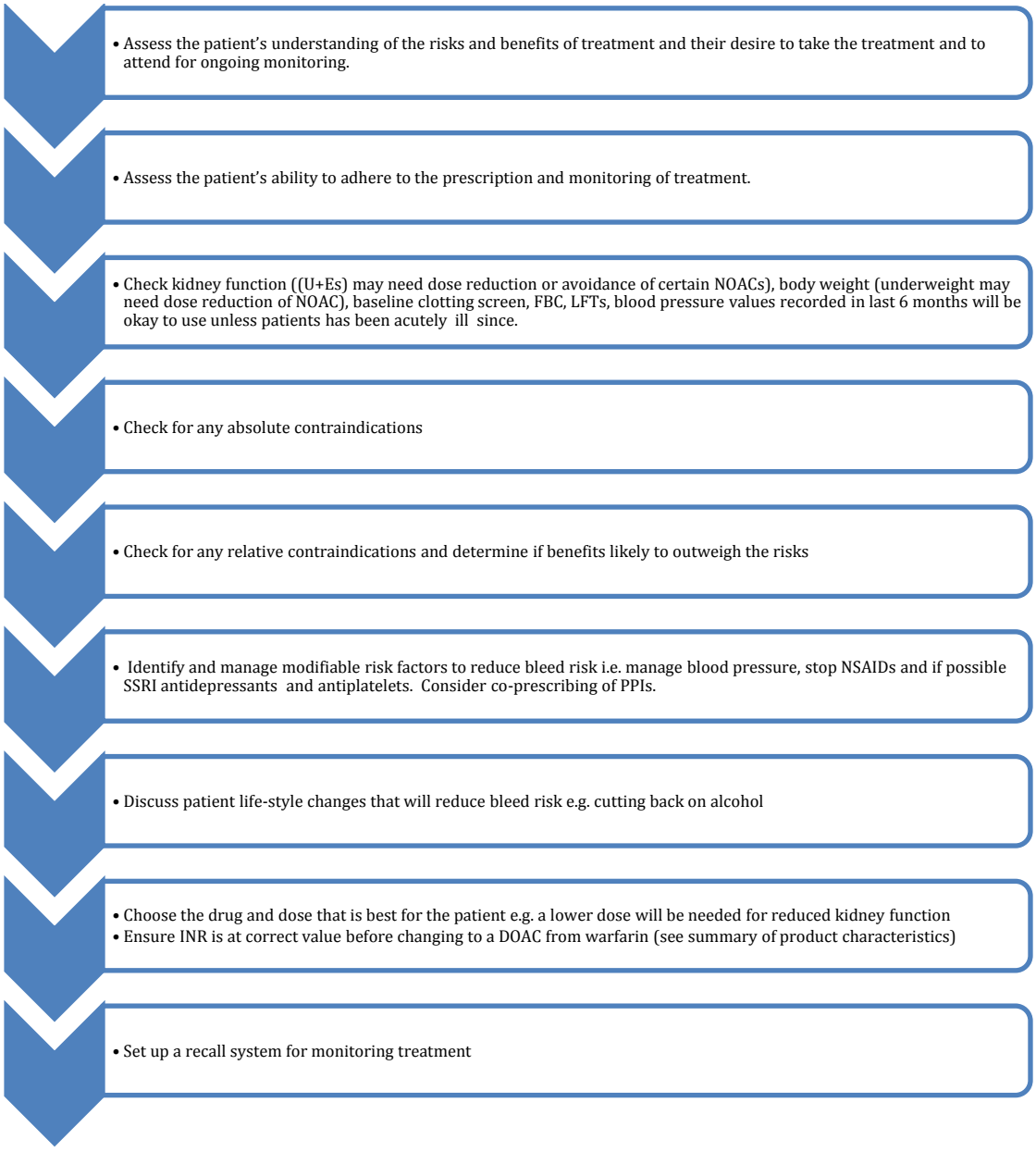

Table 3. Checklist before starting a DOAC.

Adherence	Ideally 3 monthly (otherwise 6 monthly)
Bleed risk	Ideally 3 monthly (otherwise 6 monthly)
Liver function tests	Annually
Full blood count	Annually
Kidney function	CrCl >60ml/min annually CrCl 30-60ml/min 6 monthly CrCl 15-30ml/min 3 monthly*

Table 4. Guidance on ongoing monitoring of DOACs.[42-45]

*Dabigatran treatment is contraindicated if CrCl < 30ml/min. Monitor U&E's/LFTs more frequently if inter-current illness

European guidance states that creatinine clearance, calculated using the Cockcroft & Gault equation, needs to be used when checking for correct dosing when monitoring DOACs.