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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Atrial Fibrillation and Anticoagulation Management

Atrial fibrillation (AF) occurs when the normal rhythm of the heart is replaced by an irregular and chaotic atrial rhythm. Consequently, AF is associated with a five-fold risk of stroke. The prevalence of AF is ever increasing with an ageing population and improved detection. Management of AF is aimed at symptom control and prevention of complications. These guidelines review current use of anticoagulation for stroke prevention in AF.

Types of AF

Paroxysmal AF with a significant arrhythmia burden carries a similar stroke risk to permanent or persistent AF. AF may be further classified as valvular and non-valvular. Non-valvular AF is AF in the absence of moderate-to-severe mitral stenosis or mechanical heart valve.

Assessing the risk of stroke

The CHA_2DS_2VASc score is used to assess the risk of stroke in patients with AF (table 1). Risk factors are cumulative and the total score guides management (the annual risk of stroke is available through this link).

Table 1: CHA_2DS_2VASc scoring system

Stroke clinical risk factor	Score
Congestive heart failure/Left ventricular dysfunction	1
Hypertension	1
Age75 years and over	2
Diabetes mellitus	1
Stroke, TIA or thromboembolism	2
Vascular disease	1
Age 65 - 74 years	1
Sex: Female	1

Anticoagulation should be considered for any patient with a CHA_2DS_2VASc of 1 and is recommended for any patient with a CHA_2DS_2VASc of 2 or more. However, a female, aged less than 65 years with lone AF has a low risk of stroke; therefore no anticoagulation therapy is recommended.

Assessing the risk of bleeding

Prior to initiation of anticoagulation, the risk of bleeding should be considered. Calculating the HAS-BLED score can help determine modifiable risk factors. Prescribing of anticoagulation must be carefully considered in patients with a recent history of active bleeding or previous spontaneous bleeding. In some patients the net benefit of anticoagulation may outweigh the risks of bleeding; if unsure seek senior specialist advice from Cardiology (bleep 4205) or Haematology (bleep 5529). The risk of falls is not a contraindication to oral anticoagulation; a patient may need to fall approximately 300 times per year for the risk of intracranial haemorrhage to outweigh the benefit of oral anticoagulation. Patients with a CHA_2DS_2VASc score of 2 or more with contraindications to oral anticoagulation, or people with systemic thromboembolism despite anticoagulation are candidates for **percutaneous left atrial appendage occlusion** and can be referred to the Arrhythmia Clinic for assessment.

Oral anticoagulation therapy

There are several different anticoagulants available. Please note that DOACs are only licensed for use in non-valvular AF.

1. Direct Oral Anticoagulants (DOACs)

There are currently four DOACs licensed for use in **non-valvular AF**: dabigatran (a direct thrombin inhibitor), rivaroxaban, apixaban and edoxaban (direct factor Xa inhibitors). NICE has approved each drug for use in stroke prevention within their current licence. Specific patient criteria, as detailed in appendix 1 must be met. **Concomitant heparins or fondaparinux are contraindicated.**

Prior to starting treatment with a DOAC, a baseline coagulation screen, full blood count, U&Es (including renal function) and liver function must be performed. A measured weight should be recorded for the patient. No monitoring of the therapeutic effects of DOACs is required. Dabigatran and rivaroxaban should be taken with food. Dabigatran can be reversed using the monoclonal antibody fragment idarucizumab (Praxbind®). There are currently no antidotes available to reverse the effects of the factor Xa inhibitors. Local advice on the management of haemorrhage and overdose are available via the Anticoagulation Thrombosis website.

2. Vitamin K antagonists

Warfarin is a well-established drug. There is considerable experience with its use including significant long-term safety data and reversal agents (phytomenadione (vitamin K) or prothrombin complex concentrate) are readily available. Before initiating treatment, consideration should be given to both medical and social factors. Please refer to MIL volume 5, number 8 'Initiating oral anticoagulation with vitamin K antagonists in adult patients' for detailed information. Prior to starting a patient on warfarin, a baseline coagulation screen (prothrombin time (PT)/INR and activated partial thromboplastin time (APTT)) must be performed. A suggested slow induction regime of 3mg daily, with an INR check between days 4 and 7 is advised. Inpatients require concomitant prophylactic LMWH when being loaded on warfarin whilst INR is sub-therapeutic and may be considered for therapeutic LMWH. Patients can be discharged home whilst INR is sub-therapeutic and managed by the anticoagulation service. The recommended INR target is 2.5 (range 2 to 3).

Choice of anticoagulant therapy

When appropriate, DOACS are deemed more convenient due to their quick onset of action, lack of required monitoring and fewer drug interactions. Warfarin is preferred in patients with liver dysfunction or significant renal impairment, a weight over 120kg and in poorly compliant patients (when it can be useful to have monitoring). All DOACs have a reduced risk of intracranial haemorrhage compared to warfarin (approximately 50%). Dabigatran 150 mg and apixaban 5 mg have a reduced risk of stroke and systemic embolisation and dabigatran 150 mg has a reduced risk of ischaemic stroke. Dabigatran 110mg, apixaban 5mg and edoxaban all have a reduced risk of major bleeding and clinically relevant non-major bleeding. When compared to warfarin, gastrointestinal bleeding was more common with dabigatran 150mg, rivaroxaban and edoxaban 60mg (table 2).

Table 2: Guidance on choice of anticoagulant

Anticoagulant	Comments
Warfarin	Preferred in liver dysfunction, in significant renal impairment, where weight is over 120kg and in the poorly compliant.
Apixaban	Compared to warfarin reduced risk of stroke and reduced major and clinically relevant non-major bleeding.
Dabigatran	Compared to warfarin, reduced risk of stroke with 150 mg and only drug and dose which demonstrated reduced ischaemic stroke compared to warfarin. GI bleeding more common with 150mg than warfarin. Reduced major and minor bleeding with 110 mg. Not first choice for patients with dyspepsia.
Edoxaban	Similar efficacy compared to warfarin. Overall, reduced risk of major and clinically relevant bleeding but GI bleeding more common when compared to warfarin.
Rivaroxaban	Similar efficacy and safety to warfarin but GI bleeding more common.
There are currently no head-to-head trials between different DOACs. It is advisable to discuss with the patient the advantages and disadvantages of each medicine in order to tailor appropriate therapy. A patient decision aid is available via the NICE website. Due to safety concerns over the availability of multiple DOAC options, if a patient is suitable for all 4 DOACs, apixaban would be our recommended first line option. However, it is accepted that there may be circumstances where another DOAC is preferred.	

It is advisable to re-evaluate the need for and choice of anticoagulant therapy at periodic intervals, considering the current stroke and bleeding risks.

DOACs and Body Weight

Although the Summary of Product Characteristics (SPCs) do not have an upper limit for body weight the International society on Thrombosis and Haemostasis (ISTH) suggest that DOACs should not be used in patients with a weight of **more than 120kg.** This is because there are limited clinical data available for patients at the extreme of weight, and the available pharmacokinetic/ pharmacodynamic evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under-dosing.

Patient aged over 75 years

Older patients with AF are at higher risk of thromboembolic events and oral anticoagulant related bleeding complications. A recent meta-analysis by Malik et al., reported that overall compared to warfarin DOACs were found to have superior efficacy in reducing stroke or systemic embolisation. The rate of major bleeding was similar between the two groups. Apixaban appeared to provide the best combination of efficacy and safety.

Renal impairment

The DOACs are renally excreted to variable extents and therefore should be used with caution in renal impairment (appendix 1). Apixaban is the least renally cleared DOAC. Warfarin is the preferred option in patients with a calculated creatinine clearance below 30ml/min because of a lack of outcome data for DOACs in this setting.

Pregnancy and Breastfeeding

Oral anticoagulants are contraindicated in pregnancy and therefore pregnancy should be excluded prior to starting treatment. Warfarin is a known teratogen and women of child-bearing potential should be counselled appropriately. Warfarin is excreted into breast milk in small amounts but is considered safe for use. DOACs should not be used in breastfeeding.

Medication Compliance

Patients with poor compliance need careful assessment. INR monitoring enables assessment of compliance with warfarin and therefore is the preferred option in such patients. Given no monitoring is required for DOACs, assessment and reinforcement of compliance do not routinely occur. Unlike warfarin, DOACs have a short half-life (approximately 12 hours). Non-compliance can lead to the patient not being adequately anticoagulated.

During an acute admission INRs may not accurately reflect long term control. The Time in Therapeutic Range (TTR) is a measure of warfarin control over a minimum of 6 months. A patient with a TTR less than 65% is considered to be poorly controlled. If the team wishes to review choice of anticoagulant, the anticoagulation team can be contacted for advice. Alternatively, consider highlighting to the GP for non-urgent review following discharge.

Drug interactions

Warfarin is well-known to interact with a large range of drugs and foods and therefore concurrent use of any other medicine should be carefully checked. All four DOACs are substrates for the P-glycoprotein transporter. Additionally, both rivaroxaban and apixaban are metabolised via the cytochrome P4503A4 system. Edoxaban is only minimally eliminated via P4503A4. Appendix 1 details many of the currently known interactions. Notably, concurrent use of antiplatelets and NSAIDs significantly increases the patient's risk of bleeding, so combined use requires very careful consideration. The following provides some guidance on antiplatelets and anticoagulants:

- Patients with stable coronary artery disease (more than 12 months since ACS, NSTEMI, STEMI, CABG or stent): If oral anticoagulation is started, antiplatelet therapy can be stopped, unless high risk of future coronary events (prior stenting of the left main, proximal left anterior descending, proximal bifurcation, recurrent MIs), in which case Cardiology advice should be sought (bleep 4205).
- Anyone who develops an ACS or undergoes coronary intervention whilst on an oral anticoagulant for AF or is diagnosed with AF within 12 months of a coronary event or procedure, should have their antiplatelet and anticoagulant regimen discussed with the relevant interventional cardiologist.

The choice of oral anticoagulation should be considered carefully in patients with a malignancy. There is limited evidence from DOAC clinical trials in

this setting. Possible interactions with chemotherapy agents must be assessed. Risks and benefits should be considered on an individual patient basis.

Duration of therapy
Long term anticoagulation therapy is required.

Cardioversion and ablation
Separate guidelines on the short-term use of DOACs in patients undergoing ablation and cardioversion are available (discuss with the Cardiac Electrophysiology team).

Atrial flutter
These guidelines are also applicable to the management of these patients.

The role of aspirin in AF
Monotherapy with aspirin solely for stroke prevention is not recommended due to significantly reduced efficacy but similar bleeding risks when compared to warfarin.

Patient and/or carer education
It is vital that all patients newly started on anticoagulation therapy receive written and verbal information. Counselling on initiation of oral anticoagulation should be documented during admission and/or on discharge. Patient counselling guides are available here.

Warfarin:
- Patients initiated on warfarin should be given the yellow booklet 'Important information about anticoagulation with vitamin K antagonists'.
- An anticoagulation alert card will be provided by the anticoagulation clinic. Patients should always be advised to carry this with them.

DOAC:
- Patient information booklets are available from pharmacy for each DOAC. These are tailored to specific indications.
- Alert cards are supplied within the medication box; patients should always be encouraged to carry the alert card with them.

Discharge arrangements
All warfarin patients (new and existing) must be referred to the Oxford anticoagulation clinic for follow up at discharge. Additionally, the Oxford anticoagulation clinic should be informed if a patient is converted from warfarin to a DOAC. This will ensure the patient's warfarin record is closed and DNA letters are not sent. For patients who are not covered by the Oxford anticoagulation service, a referral must be made to the patients' GP or local anticoagulation service. For further information, please refer to MIL Vol 5 No. 8.

Anticoagulation team contact details
1. Anticoagulation inpatient safety nurse - bleep 5035
2. Anticoagulation pharmacist - bleep 4511 or 5036
3. Anticoagulation Service

Oxford - bleep 1857, ext. 23729 or email ac.service@nhs.net

Banbury - bleep 614, ext. 29224 or email orh-tr.achgh@nhs.net

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Appendix 1: DOAC comparison table for use in non-valvular AF

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Criteria for use in non-valvular AF	Presence of **one or more** of the following risk factors: -Prior stroke or transient ischaemic attack -Age 75 years or older -Hypertension -Diabetes mellitus -Symptomatic heart failure (NYHA Class 2 or above)	Presence of **one or more** of the following risk factors: -Previous stroke, transient ischemic attack or systemic embolism -Left ventricular ejection fraction less than 40 % -Symptomatic heart failure (NYHA Class 2 or above) -Age 75 years or older -Age 65-74 years with one of the following: diabetes mellitus, coronary artery disease or hypertension	Presence of **one or more** of the following risk factors: -Congestive heart failure -Hypertension -Age 75 years or older -Diabetes mellitus -Prior stroke or transient ischaemic attack	Presence of **one or more** of the following risk factors: -Congestive heart failure -Hypertension -Age 75 years or older -Diabetes mellitus -Prior stroke or transient ischaemic attack
Standard Dose	5mg bd	150mg bd (with food)	60mg od	20mg od (with food)
Reduced Dose	2.5mg bd if **2 or more** of the following present: ✓ Age 80 years or over ✓ Body weight 60 kg or below ✓ Serum creatinine 133 µmol/L or greater OR 2.5mg bd where CrCl 15-29ml/min*	110mg bd where age 80 years or over or concomitant use of verapamil. ***Consider*** dose reduction from 150mg bd to 110mg bd in the following: age 75-80 years, moderate renal impairment (CrCl 30-50ml/min*), patients with gastritis, oesophagitis or gastroesophageal reflux and other patients at increased risk of bleeding.	30mg od if **1 or more** of the following present: ✓ Body weight 60kg or below ✓ CrCl 15-50ml/min* ✓ Concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole	15mg od where CrCl 15-49ml/min*
Renal impairment	Do not use if CrCl <15ml/min* Use with caution if CrCl 15-29ml/min*	Do not use if CrCl less than 30ml/min* Consider dose reduction if CrCl 30-50ml/min*	Do not use if CrCl less than 15ml/min* Use with caution if CrCl 15-29ml/min*	Do not use if CrCl less than 15ml/min* Use with caution if CrCl 15-29ml/min*
Drug interactions**	**Avoid**: HIV protease inhibitors, ketoconazole, itraconazole, voriconazole and posaconazole, rifampicin, carbamazepine, phenytoin, phenobarbital, primidone and St John's Wort. **Caution**: Erythromycin and clarithromycin, diltiazem, amiodarone and quinidine.	**Avoid:** HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole, rifampicin, carbamazepine, phenytoin, phenobarbital, primidone, St John's Wort, dronedarone, ciclosporin and tacrolimus. **Caution:** Amiodarone, verapamil, erythromycin, clarithromycin and quinidine.	No data on co-administration with HIV protease inhibitors. **Caution (limited data):** Rifampicin, carbamazepine, phenytoin, phenobarbital, primidone, St John's Wort and clarithromycin. **Dose reduction:** Ciclosporin, dronedarone, erythromycin or ketoconazole.	**Avoid:** HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole and dronedarone, rifampicin, carbamazepine, phenytoin, phenobarbital, primidone and St John's Wort. **Caution:** Erythromycin and clarithromycin.
Pharmaceutical issues	May be crushed and dispersed in water / apple juice or puree. Stable in dosette boxes	Capsules can only be stored in original packaging and so are not suitable for dosette boxes. Capsules cannot be opened before administration	Stable in dosette boxes	May be crushed and dispersed in water / apple puree. Stable in dosette boxes
Switching from warfarin	Stop warfarin and start apixaban once INR is less than 2	Stop warfarin and start dabigatran once INR less than 2	Stop warfarin and start edoxaban once the INR is 2.5 or less	Stop warfarin and start rivaroxaban once INR 3 or less
Switching to warfarin	Co-administer apixaban and warfarin for 2 days. After 2 days, check INR prior to next apixaban dose and continue until INR 2 or greater	Start warfarin 2 days (CrCl 30-49ml/min) or 3 days (CrCl 50ml/min or above) before stopping dabigatran	Co-administer edoxaban*** and warfarin until INR 2 or greater, for up to a maximum of 14 days. During this time, frequently check INR immediately prior to edoxaban dose.	Co-administer rivaroxaban and warfarin until INR 2 or greater

NB: *Warfarin is the preferred option in those with a creatinine clearance below 30ml/min because of a lack of outcome data for DOACs in this setting.
**This list is not exhaustive and only gives some common examples. Please check the data sheet (www.medicines.org.uk) or contact Pharmacy for advice at the point of prescribing.
*** For patients on 60mg daily reduce to 30mg daily and for patients on 30mg daily reduce to 15mg daily - refer to data sheet for further details.