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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, atrial flutter 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. Atrial flutter is commonly associated with AF. The prevalence is ever increasing with an ageing population and improved detection. Management of both arrhythmias is aimed at symptom control and prevention of complications. These guidelines review current use of anticoagulation for stroke prevention in AF and atrial flutter.

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 and atrial flutter (table 1). Risk factors are cumulative and the total score guides management (calculator for annual risk of stroke)

Table 1: CHA_2DS_2VASc scoring system

Stroke clinical risk factor	Score
Congestive heart failure/Left ventricular dysfunction	1
Hypertension	1
Age 75 years and over	2
Diabetes mellitus	1
Stroke, TIA or thromboembolism	2
Vascular disease	1
Age 65 - 74 years	1
Sex: Female	1

Anticoagulation is recommended for any patient with a CHA_2DS_2VASc of 2 or more and should be considered for any male patient with a CHA_2DS_2VASc of 1.

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 these 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). A 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, where oral anticoagulation is not tolerated, or people with systemic thromboembolism despite optimal anticoagulation may be 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 and are considered first choice for most patients. If DOACs are contraindicated, not tolerated or not suitable, offer a vitamin K antagonist.

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, a baseline coagulation screen, full blood count, U&Es (including renal function) and liver function must be performed. A measured weight should be recorded. 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®). Andexanet alfa is an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding *only* if the bleed is in the gastrointestinal tract. As approval for use is pending, please follow local advice on the management of haemorrhage and overdose, refer to the Anticoagulation website or contact haematology.

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 more information. Prior to starting treatment, 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, minimal monitoring and fewer drug interactions. Warfarin is preferred in patients with liver dysfunction or significant renal impairment, a weight over 120kg and in non-adherent patients (when it can be useful to have monitoring). All DOACs have a reduced risk of intracranial haemorrhage compared to warfarin (approximately 50%). Dabigatran 110mg, apixaban 5mg and edoxaban 60mg all have a reduced risk of major bleeding and clinically relevant non-major bleeding. When compared to warfarin, gastrointestinal (GI) bleeding was more common with dabigatran 150mg, rivaroxaban and edoxaban 60mg. Therefore, if a patient has a high risk of GI bleeding e.g. high dose PPI, varices, previous GI bleeding and/or known active GI luminal malignancy, other options should be considered. 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 to tailor appropriate therapy. As a general principle when all considerations are equal, the most cost-effective DOAC should be the first choice; this is currently edoxaban. If a DOAC other than edoxaban is used for a patient with a new diagnosis of AF, it is useful for primary care to be informed of the rationale to avoid inappropriate switches. The need for and choice of anticoagulant therapy should be reviewed at periodic intervals, considering the current stroke and bleeding risks.

DOACs and body weight more than 120kg or with a BMI over 40kg/m^2

There are limited data available for patients at the extreme of weight, and the available pharmacokinetic and pharmacodynamics evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under-dosing. Our recommendation is that warfarin should be considered first line as there is more evidence and monitoring for therapeutic effect can be carried out. However, if warfarin is deemed unsuitable, careful consideration can be given to the use of a DOAC for patients up to 150kg. Beyond 150kg, extreme caution should be applied. A thorough consultation should be carried out by the prescriber with the patient to guide them about the possible treatment options and potential risks and uncertainties around using a DOAC. This should be documented in the medical notes.

Patients undergoing bariatric surgery or bowel resection or malabsorption

For patients undergoing procedures or surgery or those with underlying conditions that may affect absorption of fixed dose DOACs, warfarin should be

used as this can be monitored and adjusted. DOAC absorption will depend on site and type of surgery or disease, gastric pH and gut motility amongst other factors and this must be taken into account if a DOAC is being considered. Please discuss with haematology if this is the case.

Renal function

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 (CrCl) below 30ml/min. Apixaban, edoxaban and rivaroxaban can be used with caution in patients with CrCl of 15-29ml/min. Trough anti-Xa levels can be checked if there is concern about accumulation.

A trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin. Therefore, for patients with a CrCl over 95 ml/min, edoxaban should only be used after careful evaluation of the individual thromboembolic and bleeding risk.

Pregnancy and Breastfeeding

Oral anticoagulants are contraindicated in pregnancy and therefore pregnancy should be excluded prior to starting treatment. Advice should be given regarding contraception and patients should be advised to speak to their doctor if they fall pregnant or are considering pregnancy. Warfarin is excreted into breast milk in small amounts but is considered safe for use. DOACs should not be used in breastfeeding.

Medicines adherence

Patients with poor adherence need careful assessment. INR monitoring enables assessment of adherence with warfarin and therefore is the preferred option in such patients. Given no monitoring is required for DOACs, assessment and reinforcement of adherence do not routinely occur. Unlike warfarin, DOACs have a short half-life (approximately 12 hours). Non-adherence 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 cytochrome P4503A4. Edoxaban is only minimally eliminated via CYP4503A4. Appendix 1 details many of the currently known interactions. Notably, concurrent use of antiplatelets, NSAIDs and steroids significantly increases the patient's risk of bleeding, so combined use requires very careful assessment including consideration of a PPI (see safety message and MIL Vol 8, No 2). 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.

For patients on chemotherapy, interactions can be checked using the website https://cancer-druginteractions.org/checker. Risks and benefits should be considered on an individual patient basis.

Duration of therapy

Long term anticoagulation therapy is required. In patients with a diagnosis of AF, do not stop anticoagulation solely because AF is no longer detectable.

Cardioversion and ablation

Oral anticoagulation is required before and after cardioversion (for either atrial fibrillation or atrial flutter). It is recommended that patients receive at least 3 weeks of therapeutic anticoagulation before cardioversion, and at least 4 weeks after cardioversion, irrespective of their thromboembolic risk. It is possible that anticoagulation may have been started before the cardioversion, and/or be continued after the cardioversion for a longer period because the risk of the individual dictates long-term anticoagulation anyway. If a transoesophageal echocardiogram (TOE) is performed at the time of cardioversion to exclude left atrial/left atrial appendage thrombus then the duration of oral anticoagulation prior to cardioversion does not need to be 3 weeks. For patients undergoing catheter ablation for atrial fibrillation periprocedural anticoagulation is recommended irrespective of stroke risk and type of AF. Patients should either be on oral anticoagulation for 3 weeks prior to the ablation, or may have a TOE performed at the time of the ablation and take the oral anticoagulation for a shorter period of time. Oral anticoagulation must be continued without interruption for at least 8 weeks after the ablation. Subsequent longer-term continuation of oral anticoagulation will be based on the patient's thromboembolic risk profile. Similar guidance is applied to patients who have atrial flutter who are undergoing catheter ablation. The only variation is that if the patient has paroxysmal atrial flutter and is in sinus rhythm on the day of the ablation procedure then they may not require oral anticoagulation post procedure. Management of oral anticoagulation around the time of cardioversion or catheter ablation will be guided by the cardiology team performing the procedure.

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 by completing the EPR counselling form. 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 advised to carry this 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. Haemostasis SpR – bleep 5529
2. Cardiology SpR – bleep 4205
3. Anticoagulation pharmacist - bleep 4511 or 5036
4. Anticoagulation inpatient safety nurse - bleep 5035
5. Anticoagulation Service

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

Banbury - bleep 9614, ext. 29752 or email ac.service@nhs.net

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Reviewed and updated by:

Vicki McDonnell, Lead Anticoagulation and Thrombosis Pharmacist, Gurpreet Bahra Specialist Anticoagulation & Thrombosis Pharmacist, Dr Dalia Khan Haematology Consultant and Dr Rajappan Cardiology Consultant.

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

	Edoxaban (1st choice)	Apixaban	Rivaroxaban	Dabigatran
Criteria for use in non-valvular AF	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: -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: -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: -Previous stroke or transient ischemic attack -Age 75 years or older -Symptomatic heart failure (NYHA Class 2 or above) -Diabetes mellitus -Hypertension
Standard Dose	60mg od	5mg bd	20mg od (with food)	150mg bd (with food)
Reduced Dose	30mg od if **1 or more** of the following present: ✓ Body weight 60kg or below ✓ CrCl 15-50ml/min*[1] ✓ Concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole	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*[1]	15mg od where CrCl 15-49ml/min*[1]	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 75-79 years, moderate renal impairment (CrCl 30-50ml/min*[1]), patients with gastritis, oesophagitis or gastroesophageal reflux and other patients at increased risk of bleeding.
Renal function	Do not use if CrCl less than 15ml/min*[1] Use with caution if CrCl 15-29ml/min*[1] Use with caution if CrCl more than 95ml/min	Do not use if CrCl less than 15ml/min*[1] Use with caution if CrCl 15-29ml/min*[1]	Do not use if CrCl less than 15ml/min*[1] Use with caution if CrCl 15-29ml/min*[1]	Do not use if CrCl less than 30ml/min*[1] Consider dose reduction if CrCl 30-50ml/min*[1]
Liver impairment	No data on using in patients with ALT or AST more than twice ULN*[2] or total bilirubin greater or equal to 1.5 times ULN*[2] – advise avoiding	No data on using in patients with ALT or AST more than twice ULN*[2] or total bilirubin greater or equal to 1.5 times ULN – advise avoiding	Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C	No data on using in patients with liver enzymes more than twice ULN*[2] – advise avoiding
Drug interactions*[3]	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 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 and dronedarone, rifampicin, carbamazepine, phenytoin, phenobarbital, primidone and St John's Wort. **Caution:** Erythromycin and clarithromycin.	**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.
Pharmaceutical issues	May be crushed and dispersed in water / apple puree. Stable in dosette boxes	May be crushed and dispersed in water / apple juice or puree. Stable in dosette boxes	May be crushed and dispersed in water / apple 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
Switching from warfarin	Stop warfarin and start edoxaban once the INR is 2.5 or less	Stop warfarin and start apixaban once INR is less than 2	Stop warfarin and start rivaroxaban once INR 3 or less	Stop warfarin and start dabigatran once INR less than 2
Switching to warfarin	Co-administer edoxaban*[4] 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 apixaban and warfarin for 2 days. After 2 days, check INR prior to next apixaban dose and continue until INR 2 or greater	Co-administer rivaroxaban and warfarin until INR 2 or greater	Start warfarin 2 days (CrCl 30-49ml/min) or 3 days (CrCl 50ml/min or above) before stopping dabigatran

NB: *[1]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. *[2]ULN = Upper Limit of Normal *[3]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. *[4] 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.