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 has been estimated at approximately 1.5-2% of the general population in the developed world. Management of AF is aimed at symptom control and prevention of complications. These guidelines review current use of anticoagulation therapy in AF for stroke prevention.

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. The European Society of Cardiology (ESC) guidelines consider valvular AF to derive from rheumatic valvular disease or prosthetic heart valves and therefore all other types of AF would be classed as non-valvular.

Assessing the risk of stroke
The ESC Guidelines recommend the use of the CHA2DS2VASc score 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: CHA2DS2VASc scoring system

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

Anticoagulation should be considered for any patient with a CHA2DS2VASc of 1 and is highly recommended for any patient with a CHA2DS2VASc of 2 or more. However, a female, aged less than 65 years with lone AF has a low risk of stroke and therefore no anticoagulation therapy is recommended.

Assessing the risk of bleeding
Prior to initiation of anticoagulation therapy, the risk of bleeding should be considered. Calculating the HAS-BLED score may be useful to determine modifiable risk factors. Prescribing of anticoagulation must be carefully considered in patients with a recent history of active bleeding or previous spontaneous bleeding. The MHRA has previously provided advice on the use of the newer oral anticoagulants and bleeding risk. 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. 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). Patients with a CHA2DS2VASc score of 2 or more with contraindications to oral anticoagulation, may be candidates for percutaneous left atrial appendage occlusion and can be referred to the Cardiac Electrophysiology Team for assessment via the on-call Cardiology SpR (bleep 4205).

Oral Anticoagulation Therapy
There are a number of different anticoagulants available:

1. 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 are readily available. Before initiating treatment, consideration should be given to both medical and social patient 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. Concomitant LMWH cover is not required (thromboprophylaxis may be appropriate as per Trust VTE guidance). The recommended INR target is 2.5 (range 2.0 to 3.0).

2. Direct Oral Anticoagulants (‘DOACs’, formerly ‘NOACs’)
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. 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 fragmentidarucizumab (Praxbind®). There are currently no antidotes to reverse the effects of the factor Xa inhibitors. Local advice on the management of haemorrhage and overdose are available via the Anticoagulation and Thrombosis website.

Choice of anticoagulant therapy
Warfarin may be preferred by some patients on the basis that there are decades of experience and an antidote. It is preferred in patients with liver dysfunction or significant renal impairment. It can also be an advantage to have a monitored treatment in the poorly compliant.

There is no information on long-term safety of the newer agents. They may be deemed more convenient due to their quick onset of action, lack of monitoring and less drug interactions.

Compared with warfarin all have a reduced risk of intracranial haemorrhage. Dabigatran 150 mg bd and apixaban 5 mg bd have a reduced risk of stroke and systemic embolization and dabigatran 150 mg bd has a reduced risk of ischaemic stroke. Dabigatran 110 mg bd, apixaban 5 mg bd 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 bd, rivaroxaban and edoxaban 60mg od. Dabigatran would not be the optimum choice in those with a creatinine clearance less than 50 ml/min nor in those with ischaemic heart disease. Table 2 summarises these options.

Table 2: Guidance on choice of anticoagulant

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Preferred in liver dysfunction, in significant renal impairment and in the poorly compliant</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Compared to warfarin reduced risk of stroke and reduced major and clinically relevant non-major bleeding.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Compared to warfarin, reduced risk of stroke with 150 mg bd and only drug and dose which demonstrated reduced ischaemic stroke compared to warfarin. GI bleeding more common with 150mg bd than warfarin. Reduced major and minor bleeding with 110 mg bd. Not first choice if creatinine clearance less than 50 ml/min, in ischaemic heart disease or for patients with dyspepsia.</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Similar efficacy compared to warfarin. Overall, reduced risk of major and clinically relevant bleeding but GI bleeding more common when compared to warfarin. Once a day dosing.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Similar efficacy and safety to warfarin but GI bleeding more common. Once a day dosing.</td>
</tr>
</tbody>
</table>

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.
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 120 kg. 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.

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 creatinine clearance below 30ml/min because of a lack of outcome data for DOACs in this setting.

Pregnancy and Breastfeeding
Oral anticoagulation therapy is 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 take place.

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 non-steroidal anti-inflammatories significantly increases the patient’s risk of bleeding and combined use requires very careful consideration of the risks and benefits. The following provides some guidance on antiplatelets and anticoagulants:

- Stable coronary artery disease patients (more than 12 months away from ACS, NSTEMI, STEMI, CABG or stent): If warfarin, rivaroxaban apixaban or edoxaban 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. Until more data are available we would caution against the use of dabigatran in this setting.
- 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.

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 patients with a diagnosis of atrial flutter. It is recognised that there is no data for using DOACs in this setting, but they be an appropriate choice for some 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 or carer education
It is vital that all patients newly started on anticoagulation therapy receive written and verbal information. Any patient initiated on warfarin should be given the yellow warfarin booklet. Patient booklets are available from pharmacy for
each DOAC and alert cards are supplied in the original boxes. Patients should be encouraged to carry the alert cards with them at all times.

**Discharge arrangements**
Any warfarin patient must be referred to the Oxford Anticoagulation clinic (bleep 1857) for follow up at discharge. This includes both new and existing patients. Additionally, please inform the Oxford Anticoagulation clinic if you are switching one of their patients from warfarin to a DOAC. 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.
## Appendix 1: DOAC drug comparison table for use in AF

<table>
<thead>
<tr>
<th>Criteria for use in non-valvular AF</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
</table>
| 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 ischemic 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 ischemic attack |

### Standard Dose

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>5mg bd</td>
<td>150mg bd (with food)</td>
<td>60mg od</td>
<td>20mg od (with food)</td>
</tr>
</tbody>
</table>

### Reduced Dose

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5mg bd if 2 or more of the following present: age 80 years or older, body weight 60 kg or less or serum creatinine 133 micromole/L or gr eater OR 2.5mg bd where CrCl 15-29ml/min*</td>
<td>110mg bd age 80 years or older 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 gastrooesophageal reflux and other patients at increased risk of bleeding</td>
<td>30mg od if 1 or more of the following present: body weight 60kg or less, CrCl 15-50ml/min* or concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole</td>
<td>15mg od where CrCl 15-49ml/min*</td>
</tr>
</tbody>
</table>

### Renal impairment

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not use if CrCl &lt;15ml/min* Use with caution if CrCl 15-29ml/min*</td>
<td>Do not use if CrCl less than 30ml/min* Consider dose reduction if CrCl 30-50ml/min*</td>
<td>Do not use if CrCl less than 15ml/min* Use with caution if CrCl 15-29ml/min*</td>
<td>Do not use if CrCl less than 15ml/min* Use with caution if CrCl 15-29ml/min*</td>
</tr>
</tbody>
</table>

### Drug interactions**

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John’s Wort, erythromycin and clarithromycin.</td>
<td>Avoid with HIV protease inhibitors, rifampicin, carbamazepine, phenytoin, phenobarbital, St John’s Wort, dronedarone, ciclosporin, tacrolimus, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with amiodarone, verapamil, erythromycin and clarithromycin.</td>
<td>No data on co-administration with HIV protease inhibitors. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John’s Wort and clarithromycin. Dose reduce with ciclosporin, dronedarone, erythromycin or ketoconazole (see information above).</td>
<td>Avoid with HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole and dronedarone. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St John’s Wort, erythromycin and clarithromycin.</td>
</tr>
</tbody>
</table>

### Pharmaceutical issues

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be dispensed in water Stable in dosette boxes</td>
<td>Capsules can only be stored in original packaging thus not suitable for dosette boxes</td>
<td>Stable in dosette boxes</td>
<td>May be dispensed in water Stable in dosette boxes</td>
</tr>
</tbody>
</table>

### Switching from warfarin

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop warfarin and start apixaban once INR is less than 2</td>
<td>Stop warfarin and start dabigatran once INR less than 2</td>
<td>Stop warfarin and start edoxaban once the INR is 2.5 or less</td>
<td>Stop warfarin and start rivaroxaban once INR 3 or less</td>
</tr>
</tbody>
</table>

### Switching to warfarin

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Start warfarin 2 days (CrCl 30-49ml/min) or 3 days (CrCl 50ml/min or above) before stopping dabigatran</td>
<td>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.</td>
<td>Co-administer rivaroxaban and warfarin until INR 2 or greater</td>
</tr>
</tbody>
</table>

**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](http://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 SPC for further details.*

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**Medicines Management and Therapeutics Committee**

**Oxford University Hospitals**
References
1. European Society of Cardiology. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Euro Heart J 2012 33; 2719-45
4. European Society of Cardiology. Guidelines for the management of atrial fibrillation Euro Heart J 2012 31; 2369-2429

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