Direct Oral Anticoagulant (DOAC) Prescribing Guidance For The Prevention Of Stroke And Systemic Embolism In Adult Patients With Non-Valvular Atrial Fibrillation (NVAF)

Co-ordinators:  
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Approver:  
Medicines Guideline and Polices Group

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Responsibilities for implementation:

Organisational: Chief Executive and Management Teams
Corporate: Senior Managers
Departmental: Heads of Service/Clinical Leads
Area: Line Managers
Hospital/Interface services: Assistant General Managers and Group Clinical Directors
Operational Management: Unit Operational Managers

Policy statement: It is the responsibility of all staff to ensure that they are working to the most up to date and relevant policies, protocols procedures.

Review: This policy will be reviewed in three years or sooner if current treatment recommendations change.
Responsibilities for review of this document: Consultant Haematologist

Responsibilities for ensuring registration of this document on the NHS Grampian Information Website/SharePoint: Pharmacy and Medicines Directorate

Physical location of the original of this document: Haematology Office, 3rd Floor Rotunda, ARI

Job/group title of those who have control over this document: Consultant Haematologist

Responsibilities for disseminating document as per distribution list: Consultant Haematologist

Revision History:

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Previous Revision Date</th>
<th>Summary of Changes (Descriptive summary of the changes made)</th>
<th>Changes Marked* (Identify page numbers and section heading)</th>
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<td>N/A – New Document</td>
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* Changes marked should detail the section(s) of the document that have been amended, i.e. page number and section heading.
Direct Oral Anticoagulant (DOAC) Prescribing Guidance For The Prevention Of Stroke And Systemic Embolism In Adult Patients With Non-Valvular Atrial Fibrillation (NVAF)

- Edoxaban 60mg daily is the first line choice DOAC for NVAF in NHS Grampian.
- Apixaban is the second line choice DOAC and should be considered where edoxaban 60mg daily is not suitable.
- Warfarin may still be the most appropriate anticoagulant for some patients.

Notes:

Definition of Non-Valvular Atrial Fibrillation (NVAF)

The term “Valvular AF” refers to patients with mitral stenosis (moderate or severe) or mechanical heart valves and such patients should be considered only for warfarin therapy for stroke prevention. The term “Non-valvular AF” therefore encompasses cases of AF in the absence of the above.

Biological valve replacements, or other valvular heart conditions, such as mitral regurgitation, aortic stenosis and aortic regurgitation, do not tend to result in conditions of low flow in the left atrium and therefore are not thought to further increase the risk of thromboembolism brought by AF. This group of patients, when it comes to choice of oral anticoagulation, can also be included under the term non-valvular AF and the choice of anticoagulant could include either warfarin or a DOAC.

Renal Monitoring for DOACs

All DOACs are renally excreted and may require dose adjustment according to renal function.

It is important to note that the choice of dosage is based on a calculation of creatinine clearance (CrCl) using the Cockcroft-Gault equation (Box A).

Creatinine clearance using the Cockcroft-Gault equation is not the same as the estimated glomerular filtration rate (eGFR). If the eGFR is used this may overestimate renal clearance particularly in elderly patients with low body weight/body mass index.

GP clinical systems have built in tools to calculate CrCl, when using these tools it is necessary to ensure up to date clinical parameters particularly weight and renal function. It is also recommended to use adjusted body weight in overweight patients BMI>25.

The risks of not using the Cockcroft-Gault equation to calculate CrCL may result in prescribing the incorrect DOAC dose. This may put patients at risk of increased embolic events/preventable strokes if a lower dose is prescribed or with elevated bleeding risks if a higher than indicated dose is prescribed.
DOAC/Anticoagulation Initiation Guidance (Non-Valvular Atrial Fibrillation)

**Apixaban Candidate**
Refer to Apixaban prescribing information and flowchart for dosing recommendations

**Warfarin indicated**

**Newly diagnosed patient.** Assess CHA2DS-VASc score. Assess HAS-BLED score. Consider contraindications to anticoagulation (SmPCs)

If anticoagulation is indicated review antiplatelets, NSAIDs and SSRIs due to increased bleeding risks

Assess the patient for the following:
- Mitral stenosis
- Weight >120Kg or BMI >40
- Mechanical valve
- Prescribed itraconazole, ketoconazole or HIV protease inhibitors

Any of the above apply?

**DOAC Indicated**

Is the patient currently prescribed ciclosporin, dronedarone or erythromycin?

Calculate Creatinine Clearance (Box A)

Is CrCl either <50 or >95mL/min?

Weight <60kg?

Edoxaban 60mg once daily. Confirm no other contra-indications or interactions in SmPC

**Box A - Cockcroft-Gault**

\[
CrCl \text{ mL/min} = \frac{(140-\text{age}) \times (\text{actual weight kg}) \times (\text{constant}^*)}{(\text{Cr } \mu\text{mol/L})}
\]

^constant = 1.23 men/1.04 woman

N.B. Need to use adjusted body weight (ABW) if overweight, BMI ≥25

ABW = Ideal Body Weight (IBW) + 0.4 (Actual Body Weight – IBW)

IBW (men)=50kg+2.3kg(height inches - 60)

IBW(woman)=45.5kg+2.3kg(height inches - 60)

If using calculator refer to Creatinine Clearance Modified for Overweight Patients result.
Edoxaban Prescribing Information

Contra-indications – Edoxaban is NOT recommended in the following situations:

- Allergy or hypersensitivity to active ingredient or excipients
- Active bleeding/Major bleeding risks – unless under specialist recommendation and review
- CrCl<50mL/min, CrCl>95mL/min or on dialysis
- Weight <60kg or >120kg or BMI >40
- Severe liver impairment
- Pregnancy/Breastfeeding
- Uncontrolled severe hypertension
- Concomitant treatment with HIV protease inhibitors, itraconazole, ketoconazole, ciclosporin, dronedarone, erythromycin
- Conditions where warfarin is indicated, i.e. mitral stenosis or mechanical valve.

Additional Cautions

- Surgery please refer to [EHRA guidance](#) ‘Practical Guide on the use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation' (section 12).
- Drug therapy:
  - P-gp inducers, e.g. St John’s Wort, carbamazepine, phenytoin, can reduce effect of edoxaban caution advised
  - Antibiotics – avoid erythromycin/clarithromycin, consider appropriate alternatives, e.g. doxycycline
  - Clopidogrel – only if following specialist cardiology advice.

Dosage - Edoxaban 60mg once daily

Monitoring Requirements

<table>
<thead>
<tr>
<th>Baseline</th>
<th>U+Es (inc CrCl – calculate using <a href="#">Cockcroft-gault calculator</a>/Box A), LFTs, FBC, HAS-BLED score, Weight, <a href="#">CHA2DS2VASC</a> score.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Review treatment annually as a minimum – include compliance assessment, side-effects, Over The Counter (OTC) medicines</td>
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<tr>
<td></td>
<td>Review full bloods (U+Es, CrCl, LFTs + FBC) annually - if CrCl &lt;50 or &gt;95mL/min edoxaban no longer recommended, a review is required and consider switch to apixaban</td>
</tr>
<tr>
<td></td>
<td>(Note it is recommended if CrCl&lt;60mL/min monitoring is more frequent than annually – EHRA guidance recommends monitoring CrCl/10 (in months) e.g. CrCl 60mL/min recommended monitoring every 6 months)</td>
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<tr>
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<td>Review weight annually, if &lt;60kg or &gt;120kg or BMI&gt;40 edoxaban no longer recommended, a review is required and consider warfarin or apixaban.</td>
</tr>
</tbody>
</table>
Switching

<table>
<thead>
<tr>
<th>Warfarin → DOAC</th>
<th>DOAC → Alternative DOAC (e.g. rivaroxaban to edoxaban)</th>
</tr>
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<tbody>
<tr>
<td>Check baseline INR. Discontinue Warfarin and re-check INR in 3 days if &gt; 2; Start DOAC when INR &lt; 2</td>
<td>Agree designated switch day to allow the patient to use up supplies of current DOAC. The designated switch day should be the day following completion of the current DOAC supplies and the new DOAC should be taken when the next dose of the previous DOAC was due. Ensure the patient is aware of the dosing schedule for the new DOAC, i.e. edoxaban once daily.</td>
</tr>
</tbody>
</table>

Counselling Points

- Advise patient to carry alert card at all times.
- This is lifelong treatment with regular monitoring required (as outlined above).
- Take as directed, regularly, do not stop without speaking to a healthcare professional.
- Ensure patient is aware of signs of bleeding and what action to take.
- Ensure patient is aware of what to do if a dose is missed.
- Inform all healthcare professionals (including dentist, pharmacist) of DOAC treatment.
- Suitable to go in a compliance aid (ensure communication with community pharmacy).
- Provide link to DOAC video for patients.
Apixaban Prescribing Information

In circumstances where edoxaban is not suitable, apixaban is the second line DOAC.

Apixaban candidate
(Refer to DOAC Initiation Flowchart)
Confirm no other contra-indications/interactions in SmPC

Calculate Creatinine Clearance
(Box A Cockcroft-Gault)

- CrCl < 15mL/min
  - DOAC Contra-indicated
  - Warfarin should be considered

- CrCl 15 - 29mL/min
  - Apixaban 2.5mg twice daily

- CrCl ≥ 30mL/min
  - If the patient has at least two of the following risk factors:
    - Age 80 years or more
    - Weight 60kg or less
    - Serum creatinine 133micromol/L or more
  - Prescribe Apixaban 2.5mg twice daily
  - If the patient has one or less of the risk factors, prescribe Apixaban 5mg twice daily

Contra-indications – Apixaban is NOT recommended in the following situations:

- Allergy or hypersensitivity to active ingredient or excipients
- Active bleeding/Major bleeding risks – unless under specialist recommendation and review
- CrCl<15mL/min, or on dialysis
- Weight >120kg or BMI >40
- Severe liver impairment
- Pregnancy/Breastfeeding
- Uncontrolled severe hypertension
- Concomitant treatment with HIV protease inhibitors, itraconazole, ketoconazole
- Conditions where warfarin is preferred, i.e. mitral stenosis, mechanical valve.
Additional Cautions

- Surgery please refer to **EHRA guidance** ‘Practical Guide on the use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation’ (section 12).
- Drug therapy
  - CYP3A4 and P-gp inducers (e.g. rifampicin, St John’s Wort, carbamazepine) – can reduce effect of apixaban caution advised
  - CYP3A4 inhibitors (e.g. clarithromycin, diltiazem) – can ↑ effect of apixaban no dose adjustments necessary however consider appropriate alternative antibiotic therapy
  - Antibiotics – avoid erythromycin/clarithromycin. Consider appropriate alternatives e.g. doxycycline
  - Clopidogrel – only if following specialist cardiology advice.

**Dosage** – as per flow chart above, dependant on risk factors either apixaban 2.5mg or 5mg twice daily.

**Monitoring Requirements**

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<td>ONGOING</td>
<td>Review treatment annually as a minimum – include compliance assessment, side-effects, Over the Counter (OTC) medicines, risk factors (age, weight).</td>
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<td>Review full bloods (U+Es, CrCl, LFTs + FBC, serum creatinine) annually.</td>
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<td>- If CrCl&lt;15mL/min apixaban is no longer recommended a review is required and consider switch to warfarin.</td>
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<td>- If CrCl 15-29mL/min ensure appropriate apixaban dose is prescribed, 2.5mg twice daily.</td>
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<td>- If two or more risk factors (&gt;80years, &lt;60kg, serum creatinine ≥133micromol/L) ensure appropriate apixaban dose is prescribed, 2.5mg twice daily.</td>
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**Switching**

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Counselling Points

✓ Advise patient to carry alert card at all times.
✓ This is lifelong treatment with regular monitoring required (as outlined above).
✓ Take as directed, regularly, do not stop without speaking to a healthcare professional.
✓ Ensure patient aware of signs of bleeding and what action to take.
✓ Ensure patient aware of what to do if a dose is missed.
✓ Inform all healthcare professionals (including dentist, pharmacist) of DOAC treatment.
✓ Suitable to go in a compliance aid (ensure communication with community pharmacy).
✓ Link to DOAC video for patients.

Consultation Group

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
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References


Electronic Medicines Compendium http://www.medicines.org.uk Lixiana 60mg Film-Coated Tablets – Date of revision of text 3/8/18, accessed 1/12/18

Electronic Medicines Compendium http://www.medicines.org.uk Eliquis 5mg Film-Coated Tablets – Date of revision of text 1/2/19. accessed 1/4/19