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:
Medicines Management Pharmacist

Approver:
Medicine Guidelines and Policies Group

Signature:

Signature:

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Executive Sign-Off
This document has been endorsed by the Director of Pharmacy and Medicines Management

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

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Purpose/description: Direct Oral Anticoagulant (DOAC) prescribing guidance for the prevention of stroke and systemic embolism in adult patients with Non-Valvular Atrial Fibrillation (NVAF).

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: 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: Medicines Management Team

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: Pharmacy and Medicines Directorate

Job/group title of those who have control over this document: Medicines Management Team

Responsibilities for disseminating document as per distribution list: Medicines Management Team

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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<tbody>
<tr>
<td>April 2021</td>
<td>N/A</td>
<td>Removal of edoxaban as first line DOAC and replaced with apixaban. Addition of rivaroxaban as second line choice.</td>
<td>Page 1</td>
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<tr>
<td>April 2021</td>
<td></td>
<td>Amendment to recommendation to use adjusted body weight in patients with BMI ≥25 when calculating Creatinine Clearance (CrCl).</td>
<td>Page 1</td>
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<tr>
<td>April 2021</td>
<td></td>
<td>Clarity regarding use of GP clinical systems for calculating CrCl and risks of not using CrCl to calculate DOAC dose.</td>
<td>Page 1</td>
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<tr>
<td>April 2021</td>
<td></td>
<td>DOAC initiation guidance flowchart</td>
<td>Page 2</td>
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<tr>
<td></td>
<td></td>
<td>- Addition of SNRIs of medicines to review prior to initiation.</td>
<td></td>
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<tr>
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<td></td>
<td>- Addition of antiphospholipid syndrome in third box.</td>
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<td>- Amendment to azole antifungals as drug class.</td>
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<tr>
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<td></td>
<td>- Link to electronic CrCl calculator added to</td>
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<td></td>
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<td>Box A.</td>
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<td></td>
<td>- International Society on Thrombosis and Haemostasis reference added.</td>
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<tr>
<td>April 2021</td>
<td></td>
<td>Apixaban contraindications and additional cautions updated.</td>
<td>Page 3</td>
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<tr>
<td></td>
<td></td>
<td>Re-wording of switching advice.</td>
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<tr>
<td>April 2021</td>
<td></td>
<td>Rivaroxaban section added.</td>
<td>Page 6</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)

- Apixaban is the first line choice DOAC for NVAF in NHS Grampian.
- Rivaroxaban is the second line choice DOAC and should be considered where apixaban 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.

When calculating CrCl, it is recommended to use adjusted body weight in overweight patients BMI ≥25.

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. However, these tools are not suitable if the patient’s BMI is ≥25 as they do not use adjusted body weight.

Not using the Cockcroft-Gault equation to calculate CrCl may result in prescribing the incorrect DOAC dose. This may put patients at increased risk of embolic events/preventable strokes if a lower dose is prescribed or at increased risk of bleeding if a higher than indicated dose is prescribed.
Newly diagnosed patient. Assess CHA2DS-VASc score. Assess HAS-BLED score. Consider contraindications to anticoagulation (SmPCs)

If anticoagulation is indicated review concomitant medicines that increase bleeding risk, e.g. Antiplatelets, NSAIDs and SSRIs/SNRIs

Assess the patient for the following:
- Mitral stenosis
- Weight >120 Kg or BMI >40*
- Mechanical valve
- Antiphospholipid syndrome
- Prescribed azole antifungals or HIV protease inhibitors

Warfarin indicated

Any of the above apply?

No

DOAC Indicated

Apixaban first line choice
Refer to Apixaban prescribing information and flowchart for dosing recommendations

Box A - Cockcroft-Gault

\[ \text{CrCl} \, \text{mL/min} = (140 - \text{age}) \times (\text{actual weight (kg)}) \times (\text{constant}^*) \]
\[ \text{Cr} \, (\mu\text{mol/L}) \]
\[ ^*\text{constant} = 1.23 \text{ men}/1.04 \text{ woman} \]

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

\[ \text{ABW} = \text{Ideal Body Weight (IBW)} + 0.4 \times (\text{Actual Body Weight – IBW}) \]

\[ \text{IBW (men)} = 50\text{kg} + 2.3\text{kg (height [inches] – 60 [inches])} \]
\[ \text{IBW (women)} = 45.5\text{kg} + 2.3\text{kg (height [inches] – 60 [inches])} \]

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

* Guidance from the Scientific and Standardization Committee – International Society on Thrombosis and Haemostasis.
Apixaban Prescribing Information

Apixaban is the first line choice 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:

- Concomitant treatment with any other anticoagulant except when switching therapy or under specialist supervision.
- 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, azole antifungals.
- 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 (this list is not exhaustive – refer to individual SmPC)
  - CYP3A4 and P-gp inducers (e.g. rifampicin, St John’s Wort, carbamazepine, phenytoin, phenobarbital) – can reduce effect of apixaban, caution advised
  - CYP3A4 inhibitors (e.g. amiodarone) – can ↑ effect of apixaban, no dose adjustments necessary however ensure appropriate counselling
  - 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

<table>
<thead>
<tr>
<th>BASELINE</th>
<th>U+Es (inc CrCl – calculate using Cockcroft-gault calculator/Box A), LFTs, FBC, HAS-BLED score, CHA2DS-VASc score.</th>
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</table>

| ONGOING | Review treatment annually as a minimum – include compliance assessment, side-effects, Over the Counter (OTC) medicines, risk factors (age, weight). Review full bloods (U+Es, CrCl, LFTs + FBC, serum creatinine) annually. (Note it is recommended if CrCl<60mL/min monitoring is more frequent than annually – EHRA guidance recommends monitoring CrCl/10 (in months) e.g. CrCl 50mL/min recommended monitoring every 5 months). If CrCl <15mL/min apixaban is no longer recommended, a review is required and consider switch to warfarin. If CrCl 15-29mL/min ensure appropriate apixaban dose is prescribed, 2.5mg twice daily. If two or more risk factors (≥80years, ≤60kg, serum creatinine ≥133micromol/L) ensure appropriate apixaban dose is prescribed, 2.5mg twice daily. |

Switching

<table>
<thead>
<tr>
<th>Warfarin → Apixaban</th>
<th>DOAC → Alternative DOAC (e.g. edoxaban to apixaban)</th>
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<tbody>
<tr>
<td>Check baseline INR. Discontinue Warfarin and re-check INR in 3 days if &gt;2; Start apixaban when INR &lt;2. Ensure very careful and robust counselling advice to ensure a safe switch.</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. apixaban twice 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 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.
- Advise patient must check with a pharmacist before taking any new medicine (including over the counter medicines and supplements) to ensure it is suitable to take alongside their DOAC.
- Suitable to go in a compliance aid (ensure communication with community pharmacy).
- Link to DOAC video for patients.
- Additional patient support materials can be found here.
In circumstances where apixaban is not suitable, rivaroxaban is the second line DOAC.

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

- Concomitant treatment with any other anticoagulant except when switching therapy or under specialist supervision.
- 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, azole antifungals, dronedarone.
- 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 (this list is not exhaustive – refer to individual SmPC)
  - CYP3A4 and P-gp inducers (e.g. rifampicin, St John’s Wort, carbamazepine, phenytoin, phenobarbital) – can reduce effect of rivaroxaban caution advised
  - CYP3A4 inhibitors (e.g. amiodarone) – can ↑ effect of rivaroxaban, no dose adjustments necessary however ensure appropriate counselling
  - Antibiotics – avoid erythromycin/clarithromycin. Consider appropriate alternatives e.g. doxycycline
  - Clopidogrel – only if following specialist cardiology advice.
Dosage – as per flow chart above, dependent on renal function, either 15mg or 20mg once daily with food. To note, other doses are not licensed for the prevention of stroke and systemic embolism in NVAF.

Monitoring Requirements

| BASELINE | U+Es (inc CrCl – calculate using Cockcroft-gault calculator/Box A), LFTs, FBC, HAS-BLED score, CHA2DS-VASc score |
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Switching

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<th>DOAC → Alternative DOAC (e.g. edoxaban to rivaroxaban)</th>
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<td>Check baseline INR. Discontinue Warfarin, Start rivaroxaban when INR ≤3.</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 and requirement to take with food.</td>
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- This is lifelong treatment with regular monitoring required (as outlined above).
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- Take with food.
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- Inform all healthcare professionals (including dentist, pharmacist) of DOAC treatment.
- Advise patient must check with a pharmacist before taking any new medicine (including over the counter medicines and supplements) to ensure it is suitable to take alongside their DOAC.
- Suitable to go in a compliance aid (ensure communication with community pharmacy).
- Link to DOAC video for patients.
- Additional patient support materials can be found here.
Original Consultation Group

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</tr>
<tr>
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<td>Clinical Pharmacist Cardiology</td>
</tr>
<tr>
<td>Claire Douglas</td>
<td>Practice Pharmacist Aberdeen City H&amp;SCP</td>
</tr>
<tr>
<td>Craig Rore</td>
<td>Lead Pharmacist NHS Grampian Medicines Information Centre</td>
</tr>
<tr>
<td>Lesley Coyle</td>
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<tr>
<td>Karen McKessack</td>
<td>Clinical Pharmacist ARI: Medical Team Lead</td>
</tr>
<tr>
<td>Sarah O’Beirne</td>
<td>Lead Pharmacist NHS Grampian Medicines Information Centre</td>
</tr>
<tr>
<td>Kirsty Neave</td>
<td>Medicines Management Pharmacist</td>
</tr>
<tr>
<td>Dr Karen Simpson</td>
<td>GP, Cluster Lead, Garioch Cluster</td>
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References

British National Formulary and British National Formulary for Children  
https://www.bnf.org  

Electronic Medicines Compendium  
http://www.medicines.org.uk Eliquis 5mg Film-Coated Tablets – Date of revision of text 11/01/2021.  

Electronic Medicines Compendium  
http://www.medicines.org.uk Xarelto 20mg Film-Coated Tablets – Date of revision of text 05/02/2021.  


Journal of Thrombosis and Haemostasis  
Use of the direct oral anticoagulants in obese patients: guidance from the SSX of the ISTH  
Accessed 02/04/2021.