JAPC Position Statement on Edoxaban (Lixiana®) prescribing for non-valvular atrial fibrillation only

The direct acting oral anticoagulants (DOACs) are currently the highest spend medicines category in primary care for the NHS in England. The recently updated NICE atrial fibrillation (AF) guideline\(^1\) recommends that DOACs are the preferred anticoagulant for patients with AF, unless contraindicated, not tolerated or not suitable. The NHS expects to spend more on DOACs in the future than today as more patients with AF are diagnosed and treated.

On 1\(^{\text{st}}\) December 2021, a letter received from NHS England and Improvement (NHSEI) confirmed the details of the national procurement agreement for DOACs. In summary, the Daiichi Sankyo (edoxaban) offer included significantly better prices, investment, and support than that offered individually or collectively by other suppliers. The national procurement was informed by and included the three national clinical directors for CVD Prevention, Stroke and Cardiovascular Disease, and the National Medical Director.

It aligns with work already underway to reduce stroke rates in line with the NHS Long Term Plan and the ‘Detect, Protect and Perfect’ pathway initiatives by:

- diagnosing patients with undiagnosed AF (the detect gap)
- ensuring patients diagnosed with AF are offered anticoagulation where appropriate (protect gap)
- optimising the anticoagulant pathway (time from referral to treatment, quality of anticoagulant management including regular reviews of treatment selection and dose; and promoting adherence, self-monitoring, and self-management) to ensure patient outcomes are optimised (perfect gap).

The results of the procurement provide a significant opportunity for the NHS to treat an additional 440,000 to 620,000 (50\% - 72\%) more patients. This level of uptake will help to prevent an estimated 21,700 strokes and save the lives of 5,400 patients from a fatal outcome over the next three years, while reducing current and future growth in spend. The savings will also allow other cardiovascular disease (CVD) to be diagnosed and treated.

The procurement process has resulted in an agreement of three of the four DOAC suppliers to provide apixaban, edoxaban and rivaroxaban under national framework agreements. A single discounted price per product (confidential), irrespective of the volume used, will be available across primary and secondary care. Boehringer Ingelheim (dabigatran) did not respond and therefore was not awarded a national framework agreement, but dabigatran will still be available at its list (BNF) price.

The commercial agreement went live from the 1\(^{\text{st}}\) January 2022 and Buckinghamshire, Oxfordshire and Berkshire West (BOB) CCGs have signed up to the national agreements. There are immediate savings to the CCGs and the potential for additional savings (which are then available to fund the increase in the use of DOACs) depending on the choice of DOAC.

On 19\(^{\text{th}}\) January 2022 the NHS England Commissioning recommendations for national procurement for DOACs\(^2\) was published to encourage further identification (Detect), treatment (Protect) and optimisation (Perfect) and where appropriate, greater use of lower priced DOACs. All four DOACs are licensed to treat AF and as per NICE AF guidance it is for the prescribing clinician, in conjunction with the patient, to determine which DOAC is the most clinically appropriate for an individual patient.

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The commissioning recommendations includes the following statement:

For patients commencing treatment for AF; subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should use edoxaban where this is clinically appropriate. If edoxaban is contraindicated or not clinically appropriate for the specific patient then, subject to the criteria specified in the relevant NICE technology appraisal guidance, clinicians should then consider rivaroxaban first, then apixaban or dabigatran.

For patients already prescribed a DOAC for the treatment of AF only (i.e., for no other indication): subject to the criteria specified in the relevant NICE technology appraisal guidance, commissioners may wish to consider developing local policy to review patients currently prescribed apixaban, rivaroxaban or dabigatran, where clinically appropriate.

On 1st March 2022 the final General practice contract arrangements in 2022/23 letter\(^3\) details two new Investment and Impact Fund (IIF) indicators focused on DOAC prescribing, one specifically on the use of edoxaban, to ensure that a greater number of patients with AF receive anticoagulation therapy where clinically appropriate. The IIF forms part of the Primary Care Network (PCN) Direct Enhanced Services (DES) contract. As of 31st March 2022, the IIF indicator for DOACs\(^4\) is as follows:

<table>
<thead>
<tr>
<th>Area</th>
<th>Indicator</th>
<th>Thresholds</th>
<th>Valuation</th>
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<tbody>
<tr>
<td></td>
<td>CVD-12: Percentage of patients on the QOF Atrial Fibrillation register and with a CHA2DS2-VASc score of 2 or more (1 or more for patients that are not female), who were prescribed a direct-acting oral anticoagulant (DOAC), or, where a DOAC was declined or clinically unsuitable, a Vitamin K antagonist.</td>
<td>Upper Threshold: 95% Lower Threshold: 70%</td>
<td>£14.8m / 66 points</td>
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<tr>
<td></td>
<td>CVD-15: Number of patients that were prescribed Edoxaban, as a percentage of patients on the QOF Atrial Fibrillation register and with a CHA2DS2-VASc score of 1 or more for men or 2 or more for women and who were prescribed a direct-acting oral anticoagulant (DOAC).</td>
<td>Upper Threshold: 35% Lower Threshold: 25%</td>
<td>£14.8m / 66 points</td>
</tr>
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</table>

There is currently no specified preferred first choice DOAC in the BOB formularies\(^5,6,7\), however in practice apixaban is the most widely used and preferred DOAC throughout BOB. There are no head-to-head clinical trials to give definitive guidance on which DOAC is best for AF. However, there are multiple meta-analyses which provide information which contribute to decision making algorithms to tailor DOAC choice to an individual patient. All four DOACs are classified as ‘Green’ and available for prescribing in primary care. As a general principle when all considerations are equal, the most cost-effective DOAC should be the first choice.

- Due to the national procurement for DOACs scheme, the DOAC with the lowest acquisition cost is currently edoxaban. Having consulted with local cardiologists, stroke physicians, haematologists, general practitioners, and clinical pharmacists, the current DOAC prescribing decision support in AF guidance for Buckinghamshire/Oxfordshire/Berkshire West should continue to be followed to guide use of the clinically appropriate DOAC:
  - Buckinghamshire non-valvular AF prescribing guideline/decision support guide
  - Oxfordshire decision support guide
  - Berkshire West AF guideline/decision support guide

For NEW patients commencing treatment for non-valvular atrial fibrillation

A shared decision should be made and agreed with the patient/carer to start anticoagulation treatment as per NICE guidance. This should include an assessment and discussion on the benefits and risks of anticoagulation use, taking into account clinical features and personal preferences to guide treatment choices.
In addition to the above local AF guidelines and DOAC decision support guides for patients newly starting on a DOAC for AF, the following patient factors may suggest where edoxaban may be the preferred drug of choice or provide specific clinical reason not to use edoxaban. This list is not exhaustive and specialist advice should be sought where required:

### Where edoxaban may be preferred in new patients with AF

<table>
<thead>
<tr>
<th>Factor</th>
<th>Preference</th>
</tr>
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<tbody>
<tr>
<td>Once daily administration without the need to take with food</td>
<td>Edoxaban – if patient has no other specific clinical reason why edoxaban is not suitable</td>
</tr>
<tr>
<td>Lactose intolerant</td>
<td>Edoxaban is the only DOAC that does not contain lactose.</td>
</tr>
</tbody>
</table>
| Clinically significant drug interactions | Drug interactions with the P-glycoprotein (P-gp) and CYP450 3A4 enzymes are important considerations with DOACs. See: 
  - [European Society of Cardiology](#) practical guide on prescribing DOACs containing information on the effect of drug-to-drug interactions and clinical factors on DOAC drug levels
  - Individual DOAC summary product characteristics (SPC) on [EMC medicines website](#)
  - For patient on treatments for cancer see [https://cancer-druginteractions.org/checker](#)
  
**Important note:** If treated with a concurrent course of short term antibiotic, erythromycin or clarithromycin, a reduced dose of edoxaban 30mg once daily is needed. Once the antibiotic course is completed the patient should be put back on the higher dose edoxaban 60mg once daily if applicable.

### Where edoxaban may NOT be suitable for new patients with AF

<table>
<thead>
<tr>
<th>Factor</th>
<th>Precautions</th>
</tr>
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</table>
| Severe renal impairment (CrCl 15-30mL/min, Cockcroft-Gault formula) | –Use with caution in severe renal impairment as DOACs are predominantly eliminated by the renal route. Apixaban is the least renally cleared DOAC.
  - The Cockroft-Gault method should be used to calculate estimated creatinine clearance (CrCl), NOT eGFR which may overestimate renal clearance in some patient groups or clinical situations (See MHRA advice link).
  - Use **ACTUAL** body weight, not ideal body weight, when calculating CrCl, ideally taken within last 6 - 12 months or more recently if frail or likely to have been a change in weight.
  - Embedded clinical calculators in GP clinical systems or web-based application, e.g., MDCalc link, should be used to calculate estimated creatinine clearance. **Note:** Embedded clinical calculators automatically use ideal bodyweight, if the patient’s height is removed then it will use actual bodyweight.
  - Be mindful of the limitations of Cockcroft and Gault in estimating CrCl at extremes of bodyweight, especially in obese patients (see [Specialist Pharmacy Services guidance on dosing DOACs in renal impairment](#)).

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High creatinine clearance (>95 ml/min – Cockroft-Gault formula) | NOT edoxaban – a trend towards decreased efficacy at high creatinine clearance has been observed. If eGFR > 90mls/min renal function should be assessed using the Cockroft-Gault formula (see above).

| Where edoxaban may NOT be suitable for new patients with AF (continued) |
|-----------------------------|---------------------------------------------------------------------------------|
| Higher risk of gastrointestinal (GI) bleeding | High-risk patient would include those with previous GI haemorrhage, known varices, on high dose proton pump inhibitor therapy, known luminal GI malignancy. See local DOAC decision support guides for further guidance. |
| Obesity (BMI >40 kg/m2 or weight >120 kg) | Although the Summary of Product Characteristics (SPCs) does not have an upper limit for body weight, it is recommended that DOACs should not be used in patients with a weight of more than 120 kg. Note: Where clinically appropriate secondary care specialists may recommend a specified DOAC, apixaban or rivaroxaban, in obese patients, for which currently there is more real-world evidence with their use. |
| Other clinical indication for anticoagulation treatment | Where there is another pre-existing indication for anticoagulation with a DOAC: edoxaban should not be considered unless specifically started by specialists |

Patients ALREADY ESTABLISHED on apixaban, rivaroxaban or dabigatran for non-valvular atrial fibrillation only

Existing patients on a DOAC for non-valvular AF MUST NOT be BATCH SWITCHED to edoxaban, and consideration for a switch must be made on an individual patient basis.

In addition to the above information regarding edoxaban suitability see DOAC prescribing decision support in AF guidance for Buckinghamshire/Oxfordshire/Berkshire West.

A shared decision should be made and agreed with the patient/carer to switch anticoagulation treatment to edoxaban, where clinically appropriate, as per NICE commissioning guidance.

Where clinically appropriate and shared agreement with patient to switch:
- Discontinue DOAC (apixaban, dabigatran or rivaroxaban) and start edoxaban at the time of the next dose of the oral anticoagulant
  - Standard dose edoxaban 60mg once daily
  - Reduced dose edoxaban 30mg once daily if one or more of the following factors:
    - Creatinine clearance 15-50mL/min
    - Low body weight (≤60kg/ 132 lbs)
    - On dronedarone, erythromycin, clarithromycin, ketoconazole, ciclosporin
- Patient/carer should be suitably counselled on edoxaban (suggested counselling checklist p.21) and patient information AF booklet/leaflet provided. See healthcare professional guide here.

Where not clinically appropriate to switch:
- See above information regarding edoxaban suitability and document in patient notes.
- Previous stroke/systemic embolism with a once daily DOAC: If there is a specific concern from stroke physicians of further embolic event and they have specified a twice daily DOAC to be used.
- Patient previously on edoxaban and switched to an alternative DOAC due to intolerable side-effects.
• Patient declined switch – record in patient notes and review at next medication review.

Caution with switching:
• See above information regarding edoxaban suitability
• Age > 75 years
• Using in low body weight – caution if 50-60kg and extreme caution if < 50kg.

References