Direct Oral Anticoagulant (DOAC) Guideline

Background

Apixaban, dabigatran, edoxaban and rivaroxaban are all approved by NICE for stroke prevention in non-valvular atrial fibrillation. Following a national NHS procurement exercise, edoxaban has become significantly less expensive than the other DOACs.

Increasing the use of edoxaban in place of the other DOACs will release substantial savings which can be reinvested in identifying and treating additional patients with atrial fibrillation (AF); thereby avoiding 5,400 deaths, 21,700 AF-related strokes and a significant amount of AF-stroke related health and care costs, over the term of the national framework.

The One Gloucestershire Medicines Optimisation Group supports the promotion of edoxaban and has provided the following guidance for prescribers:

<table>
<thead>
<tr>
<th>Indication for Anticoagulation</th>
<th>DOAC of choice</th>
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</thead>
<tbody>
<tr>
<td><strong>Venous Thromboembolism (VTE) Treatment</strong></td>
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<tr>
<td>Acute treatment of VTE</td>
<td>Apixaban or rivaroxaban</td>
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<td>Cancer-associated thrombosis</td>
<td>Apixaban</td>
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<tr>
<td><strong>Non-valvular AF / flutter</strong></td>
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<tr>
<td>Previous or high risk of gastrointestinal (GI) bleeding (e.g. HAS-BLED ≥3 or ORBIT ≥4)?</td>
<td>No Edoxaban</td>
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<tr>
<td></td>
<td>Yes Apixaban</td>
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<tr>
<td>Concomitant antiplatelet (e.g. ‘triple therapy’ post PCI)?</td>
<td>No Edoxaban</td>
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<tr>
<td></td>
<td>Yes Apixaban</td>
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<tr>
<td><strong>Other conditions</strong></td>
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<tr>
<td>High-risk acute coronary syndrome (in combination with aspirin +/- clopidogrel)</td>
<td>Rivaroxaban 2.5mg bd (Consultant Cardiologist only)</td>
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<tr>
<td>Combined coronary artery disease / peripheral artery disease (CAD/PAD) – in combination with aspirin</td>
<td>Rivaroxaban 2.5mg bd</td>
</tr>
<tr>
<td>VTE prophylaxis following orthopaedic surgery</td>
<td>Rivaroxaban or dabigatran</td>
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<tr>
<td>Moderate to severe mitral stenosis</td>
<td>DOAC not suitable</td>
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<tr>
<td>Mechanical prosthetic heart valve</td>
<td>DOAC not suitable</td>
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<tr>
<td>Antiphospholipid syndrome</td>
<td>DOAC not suitable</td>
</tr>
</tbody>
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**Edoxaban Dosing Information[1]**

Edoxaban 60mg od

Reduce to 30mg od if any of the following apply:

- CrCl <50ml/min
- body weight ≤60kg
- concomitant ciclosporin, dronedarone, erythromycin, or ketoconazole.

When switching to edoxaban from a different anticoagulant, please refer to the switching guideline for timings.

**Non-valvular AF Definition**: AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin).
Additional Notes

Acute Treatment of VTE

When used to treat VTE, edoxaban (and dabigatran) must be preceded by 5 days of ‘treatment dose’ low molecular weight heparin (LMWH) treatment.[1,2] Apixaban and rivaroxaban do not require prior LMWH treatment[3,4] and are therefore preferred for acute treatment.

Cancer-Associated Thrombosis (CAT)

In the CARAVAGGIO study, apixaban was shown to be non-inferior to LMWH for CAT and had a similar rate of bleeding.[5] In the Hokusai VTE Cancer study, edoxaban was non-inferior to LMWH but the rate of major bleeding was higher.[6]

Previous or High Risk of GI Bleeding

The RE-LY trial demonstrated that dabigatran 110mg bd showed superiority over warfarin for overall major bleeding. However both doses of dabigatran (150mg and 110mg) had a higher incidence of major GI bleeding in comparison to warfarin.[7] In addition, dabigatran capsules contain tartaric acid, which can contribute to dyspepsia and are therefore best avoided in patients with GI disorders.[2]

In the ROCKET-AF trial there was no significant difference in major bleeding, fewer fatal bleeds but more GI bleeds with rivaroxaban compared with warfarin.[8] Dyspepsia is an established side effect of rivaroxaban, therefore should be used with caution in patients with GI disease even without active ulceration.[4]

The ARISTOTLE trial demonstrated a lower risk of overall major bleeding with apixaban versus warfarin and a comparable rate of GI bleeding.[9]

The ENGAGE-AF TIMI 48 study demonstrated a lower risk of overall major bleeding with edoxaban versus warfarin but an increased risk of GI bleeding with edoxaban 60mg versus warfarin.[10]

The prescribing of an anticoagulant for patients with a high GI bleed risk score should be based on consideration of any options to reduce bleed risk factors, the individual patient’s stroke risk and shared patient decision making.

Concomitant Antiplatelet Treatment

Concomitant antiplatelet treatment with all oral anticoagulants increases patients’ risk of bleeding; however, combination therapy may be required in patients with a need for anticoagulation and ischaemic heart disease – notably acute coronary syndrome or those treated with percutaneous coronary intervention (PCI).

The following trials have tested different oral anticoagulant / antiplatelet combinations:

TheWOEST study compared the use of triple therapy (aspirin + clopidogrel + oral anticoagulant) versus double therapy (clopidogrel + oral anticoagulant) in patients undergoing PCI who also had an indication for anticoagulation (e.g. AF). The study showed a significant reduction in bleeding with double therapy compared with triple therapy and no increase in the rate of thrombotic events (although it wasn’t powered to compare thrombotic events).[11]

The PIONEER-AF PCI study compared 2 rivaroxaban based regimens (rivaroxaban 15mg od + clopidogrel; rivaroxaban 2.5mg bd + clopidogrel + aspirin) with warfarin-based triple therapy in patients with AF undergoing PCI. Significantly lower rates of bleeding were seen in both rivaroxaban groups versus warfarin. The groups had similar efficacy rates however the study wasn’t powered to prove this.[12]
In the REDUAL study, significantly lower bleeding rates were seen with dabigatran-based double therapy than warfarin-based triple therapy. Numerically higher rates of coronary ischaemic events were seen with dabigatran 110mg double therapy versus warfarin triple therapy.[13]

The AUGUSTUS trial compared apixaban-based double therapy, apixaban-based triple therapy, warfarin-based double therapy, and warfarin-based triple therapy. Both apixaban regimens were found to be superior to warfarin in terms of bleeding rates and, predictably, the double therapy regimens were associated with less bleeding than the triple therapy regimens. Although not statistically significant, there were numerically more coronary ischaemic events with double therapy versus triple therapy.[14]

In the ENTRUST-AF PCI trial, edoxaban-based double therapy was found to be non-inferior to warfarin-based triple therapy in terms of bleeding events (all other DOACs have shown superiority versus warfarin for bleeding). The study wasn’t powered to compare ischaemic events.[15]

In the absence of definitive evidence showing the best antiplatelet/anticoagulation regimen for patients with AF undergoing PCI, the European Cardiology Society makes the following recommendations[16]:

**General Recommendations for oral anticoagulant in combination with antiplatelet therapy:**

- DOAC preferred to warfarin (in patients eligible for DOAC)
- Clopidogrel is the P2Y12 inhibitor of choice (avoid prasugrel or ticagrelor in combination with DOAC)
- HAS-BLED ≥3: use rivaroxaban 15mg od in preference to rivaroxaban 20mg od for the duration of concomitant single or dual antiplatelet therapy (DAPT)
- HAS-BLED ≥3: use dabigatran 110mg bd in preference to dabigatran 150mg bd for the duration of concomitant single or DAPT
- The treatment plan should be clearly specified at hospital discharge
- In patients at potential risk of gastrointestinal bleeding, concomitant use of proton-pump inhibitors is reasonable

**Low risk of stent thrombosis (or concerns about bleeding risk prevail over risk of stent thrombosis):**

- Triple therapy (aspirin + clopidogrel + DOAC) for ≤ 1 week, followed by
- Dual therapy (clopidogrel + DOAC) for up to 6 months (in chronic coronary syndrome) or up to 12 months (in acute coronary syndrome), followed by
- DOAC monotherapy

**Risk of stent thrombosis outweighs bleeding risk:**

- Triple therapy (aspirin + clopidogrel + DOAC) for ≤ 1 month, followed by
- Dual therapy (clopidogrel + DOAC) for up to 6 months (in chronic coronary syndrome) or up to 12 months (in acute coronary syndrome), followed by
- DOAC monotherapy

**Renal Impairment**

It is essential to calculate patients’ creatinine clearance (CrCl) using the Cockroft-Gault equation before DOAC initiation and annually thereafter. Estimated glomerular filtration rate (eGFR) can overestimate renal function and increase the risk of bleeding events (see Drug Safety Update). There is risk of DOAC accumulation and subsequent bleeding in renal impairment. Dose reductions are recommended in mild-moderate renal impairment, refer to individual SPCs for dosing advice. Dose adjustment may be necessary if renal function significantly changes during treatment. All DOACs are unlicensed in severe renal impairment CrCl <15ml/min (with the exception of dabigatran which should be avoided in CrCl <30ml/min). Consider discussion with renal team if CrCl <15.
Obesity

The International Society on Thrombosis and Haemostasis recommends that DOACs should not be used in patients with a BMI of > 40kg m\(^2\) or a weight of > 120kg.[19]

References:

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