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Guidance on the choice of Direct Oral Anticoagulants (DOACs) for patients with Non- Valvular Atrial Fibrillation (NVAF)

Introduction

The aim of guidance is to support prescribers with the choice of DOAC anticoagulant for the treatment of Non-valvular AF (NVAF) as there are several treatment options available. There has been a significant increase in cost of prescribing these drugs to the local health economy. The gross annual cost of DOACs across the Lincolnshire STP was £8,630,342 in 2018/19 compared to £4,864,574 in 2016/17.

NVAF is currently the most common heart rhythm disturbance, it affects at least 1.8% of the population, and prevalence rises to over 6% in people aged 65 years or older and greater than 15% in people aged 75 years or older. Untreated AF is a significant risk factor for stroke and thromboembolic events.

NICE have not distinguished between any of the four DOACs with UK marketing authorisation. There are no published head to head trials comparing one DOAC to another that can be used to confer superiority between the DOACs. The population differences between the trials comparing each DOAC to warfarin were large making it difficult to draw any conclusions between any inferred advantages. The choice of anticoagulant in AF should be made with the patient and is dependent upon clinical features and preferences.

There are currently four DOACs licensed in the UK for the prevention of stroke and systemic embolism in atrial fibrillation. These are: apixaban (Eliquis®), rivaroxaban (Xarelto®), dabigatran etexilate (Pradaxa®) and edoxaban (Lixiana®). All have been recommended by National Institute of Clinical Excellence (NICE) within their marketing authorisations as treatment options.

Key Recommendation for all new patients with NVAF:

Edoxaban (Lixiana®) is the preferred DOAC of choice in primary care for patients with NVAF (unless it is contraindicated) as it has the lowest acquisition cost to the local health economy.

Standard dose	Edoxaban 60mg once daily
Dose reduction	30mg once daily in • CrCl 15-50ml/min • Body weight ≤60kg • Concomitant P-glycoprotein inhibitors e.g. ciclosporin, dronedarone, erythromycin, ketoconazole
Administration	Take with or without food
Contraindications	Severe hepatic impairment. Prosthetic heart valves, moderate to severe mitral stenosis. End stage renal disease or dialysis. See the summary of product characteristics for full details: https://www.medicines.org.uk/emc/product/6905/smpc#CONTRAINDICATIONS

Rationale

Edoxaban is accepted on the Lincolnshire Joint formulary for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).
Edoxaban, the most recent DOAC to market, was studied in the largest number of patients, including a high proportion of high risk patients, and has received a positive recommendation from NICE technology appraisal (NICE TA 355).
Healthcare Improvement in Scotland published a review in June 2017 which summarised published evidence on the clinical effectiveness of DOACs for the prevention of stroke and systemic embolism in adult patients with non-valvular AF[6]. The Scottish Health Boards considered the key findings of the report and concluded that edoxaban is similarly effective to other DOACs, but costs considerably less.
Based on comparable efficacy and its low acquisition cost edoxaban is now recommended as the DOAC of choice by a growing number of Clinical Commissioning Groups and formulary committees.
Edoxaban is administered once daily and therefore may aid compliance, and reduce the tablet burden for patients compared to twice daily DOACs such as apixaban and dabigatran.
Edoxaban's availability does not alter with food, therefore unlike rivaroxaban it does not need to be taken with food.
Clinical experts in Lincolnshire are supporting the use of Edoxaban where appropriate.

Considerations when choosing oral anticoagulant

NICE recommends that the decision to start treatment should be made after an informed discussion between the patient and clinician on the risks and benefits of treatment selected. The patient decision aids which can be used to support such discussions are available via: https://www.nice.org.uk/guidance/cg180/resources

Patient factors	Outcome	Preferred treatment options
Does patient prefer a once daily formulation	Y	**Edoxaban** – can be given as once daily dose **Warfarin** – given as a single dose, but may be necessary to give several tablets dependent on dose. **Rivaroxaban** - can be given as a single dose.
Does the patient require medication in a compliance aid	Y	**Edoxaban** – no special storage requirement. Stable outside of original packaging for 3 months. **Warfarin** - can be used in compliance aid of risk assessment has been undertaken and a management plan in place to manage dose changes. **Apixaban** – no special storage requirement can be used in compliance aid. **Rivaroxaban** – no special storage requirement can be used in compliance aid.
Does the patient have swallowing difficulties	Y	**Edoxaban** - tablets can be crushed and administered either via a nasogastric tube or orally mixed in apple puree in patients who are unable to swallow solid oral dose formulations **Rivaroxaban –** Swallowing difficulties Can be crushed and mixed with water or apple puree immediately before use and administered orally. Gastric tube May be given through a nasogastric tube after confirmation of the correct placement of the tube. The crushed tablet should be administered with a small amount of water via a gastric tube after which it should be flushed with water. (Rivaroxaban **should not be** administered through feeding tubes that do not terminate in the stomach. This includes NJ, PEJ ,and PEGJ tubes) **Apixaban** Swallowing difficulties Tablets can be crushed and mixed with water, glucose 55, apple juice or apple puree. Take care to ensure the whole dose is administered. Enteral tubes Tablets can be crushed and dispersed in water or in glucose 5% for administration. Licensed for administration through nasogastric tubes. Take care to ensure the whole dose is administered and flush well after each dose. **Please note** **Dabigatran capsules must not be opened as it results in a substantial increase in drug bioavailability (+75%)**

Patient factors	Outcome	Preferred treatment options
Is the patient likely to miss doses	Y	Preferred option warfarin unless compliance aid assists compliance (see above) **Warfarin -**. Patients with poor concordance may be at greater risk of thromboembolic complications with DOACs as the shorter half-lives of these agents compared to warfarin will potentially result in more time without any degree of anticoagulation is a dose is missed.
Is the patient needle phobic	Y	**DOACs - Edoxaban (preferred choice)** Although there is no need for regular blood tests to monitor INR , people taking DOACs still require regular follow-up. When initiating treatment baseline tests will be needed to be performed and patients monitored on a regular basis at least annually, however less than warfarin. **Warfarin –** requires frequent monitoring , at least every 3 months.(near patient testing only requires capillary blood – finger prick)
Does the patient have a BMI >40 or weight > 120kg.	Y	**Warfarin -** No dose adjustment on weight **DOACs –** The International Society of Thrombosis and Haemostasis (ISTH) does not recommend using DOACs in patients above 120Kg unless levels are measured – which would need to be in secondary care setting
Is it important to have 24 hour coverage	Y	**DOACs – Apixaban** twice daily dosing is considered more favourable in this situation **Edoxaban** a single dose administered as per the SmPC would also provide over 24 hour anticoagulation

Adapted from Derbyshire JAPC guidance

Reviewing current patients on anticoagulant therapy

Please do not switch the DOAC of any patient who is currently under active care of the cardiology service without prior discussion with the parent consultant.

Data shows that there may be some patients with NVAF on DOACs that would benefit from a clinical review:

- May be inappropriately dosed (including either over or under dosed).
- May have contraindications to treatment with DOACs.
- May not have a clear indication for treatment
- May have a CHA2DS2-VASc score = 0 (or CHA2DS2-VASc score = 1 only because they are female)
- May have a CHA2DS2-VASc score > 2 and are not anticoagulated.
- May not be adequately monitored.
- Have poor concordance to therapy, would prefer once daily administration/ reduced tablet burden.
- Are taking a high cost once daily preparation
- Are unable to take their medication with food

These patients should be identified and clinically reviewed to ensure they are adequately treated with the most appropriate cost effective DOAC. For further advice/support with these reviews please contact the MMO team ohs.mmo.sharedservices.nhs.net

References

1. NICE Clinical Guidance 180 July 2014
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7. Management of non-valvular AF. Derbyshire Joint Area Prescribing Committee (JAPC)
8. MIMS and Drug Tariff- accessed online 2019
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Prescribing Information for DOACs				
	EDOXABAN	**APIXABAN**	**RIVAROXABAN**	**DABIGATRAN**
Licensed Indication	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation NVAF (with at least one additional risk factor)			
Standard dose	60mg once daily	5mg twice daily	20mg once daily	150mg twice a day
Dose reduction	30mg once daily in • CrCl 15-50ml/min • Body weight ≤60kg • Concomitant P-glycoprotein inhibitors – ciclosporin, dronedarone, erythromycin, ketoconazole	2.5mg twice daily in • CrCl 15-29mL/min 2 or more of the following: • age >80 yrs • body weight ≤60kg • serum Cr >133micromole/l	15mg once daily in • CrCl 30-49 ml/min • CrCl 15-29mL/min (use with caution)	110mg twice daily in • Age ≥ 80 years or taking verapamil Consider if: thromboembolic risk is low & bleeding risk is high • Age 75-80 years patients with gastroesophageal reflux, oesophagitis or gastritis • CrCl 30-50mL/min
Administration	Take with or without food. Tablets can be crushed and administered either via a nasogastric tube or orally mixed in apple puree	Take with or without food may be crushed and put through NG tube if required	Take with food to increase absorption. Maybe crushed and put through NG tube if required	Swallow whole - opening capsules may increase risk of bleeding (results in a substantial increase in drug bioavailability (+75%)
Interactions	• Concomitant use with P-gp inhibitor (e.g. ciclosporin, dronedarone, erythromycin, or ketoconazole) requires dose reduction to 30mg once daily. • Use with caution when coadministered with P-gp inducers (e.g. phenytoin, carbamazepine, St. John's	• Avoid concomitant use with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors • Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort as they may lead to reduced apixaban	• Avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors • Concomitant administration of a	• Avoid concomitant use with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors • Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort as they may lead to reduced apixaban concentrations

	Wort or phenobarbital)	concentrations	strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) should be avoided unless the patient is closely observed for signs and symptoms of thrombosis. Caution with dronedarone	
Monitoring	Baseline monitoring: clotting screening; renal and liver function tests; FBC Every 3 months assess: • Compliance and reinforce advice regarding the importance of a regular dosing schedule. • Adverse effects (e.g. bleeding) • Thromboembolic events (e.g. symptoms of stroke or breathlessness) Repeat renal and liver function tests and FBC at least annually, and more frequently if the patient has: • Renal impairment. Check renal function: every 6 month if CrCl 30-60ml/min, every 3 month if CrCl 15-30ml/min (Dabigatran contraindicated in CrCl<30ml/min) • Acute illness that may impact on renal/hepatic function e.g. infections, acute heart failure. Patients need to be alerted that in such situations they should seek contact with their healthcare provider. • Dabigatran/ Edoxaban: check renal function every 6 months if patient has additional risk factors e.g. frail, multiple co-morbidities or age ≥75 years If renal function has declined review treatment, as DOAC may need to be stopped or a lower dose may be required- see below			

Adapted from Derbyshire JAPC guidance