The intention of this information pack is to bring together resources from several areas to aid review, and where appropriate, switching of DOACs (apixaban, rivaroxaban or dabigatran) to edoxaban. Whilst new patients may be initiated on edoxaban, or switched from warfarin, the focus is entirely on switching patients with Non-valvular Atrial Fibrillation from an alternate DOAC to edoxaban.

Please familiarise yourself with all documents before proceeding as information may be covered in more detail in one of the accompanying documents.

Useful Resources and Links:

Electronic Medicines Compendium for DOAC SPCs **EMC**

Refer to local formulary and guidance, NICE, BNF etc. for further information

Appendix 1 - Monitoring required for DOACs

Appendix 2

- **CHA_2DS_2-VASc** risk factor **(EHRA 2020)**
- **HAS-BLED** – Assessment of bleeding risk in patients with atrial fibrillation **(EHRA 2020)**
- **ORBIT** – Simple bedside score to assess bleeding risk in AF **(NICE NG196)**
- Risk Categories and Bleeding Events of ORBIT and HAS-BLED

Appendix 3 – Table 6 – Prescribing parameters for all DOACS

Appendix 4 – Table 7 of interactions with DOACs

Appendix 5 – Checklist for patient/carer consultation

Disclaimer

This guideline is intended solely for use by healthcare professionals to aid the treatment of patients within L&SC. Clinical guidelines are for guidance only, their interpretation and application remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert.

Searches used to highlight patients, for review and switch to edoxaban, will be reliant on accurate coding within the clinical system. It is the reviewing clinician's responsibility to ensure the information identified by the search is accurate before deciding to proceed with a switch.

Clinicians are advised to refer to the manufacturer's current prescribing information before treating individual patients. The intention has been to compile accurate up-to-date information in this guideline, but it cannot be guaranteed that it is fully complete and correct at all times.

Hints & Tips:

- Ideally monitoring of U+E's, FBC, LFTs, BP*, HR* and actual body weight are within the preceding 3 months.
  ***NB: consider if HR >100 bpm, refer to GP for rate control. BP consistently above 140/90mmHg should be discussed with GP or reviewed according to local guidelines**

- If it appears a patient is currently taking a DOAC for an indication other than AF it is good practice to confirm the dose and duration of treatment is appropriate.

- Calculate and update the CHA2DS2-VASc score using the EMIS calculator:

  - patients with a CHA2DS2-VASc =1 in men or =2 in women should be *considered* for an OAC

  - patients with a CHA2DS2-VASc score >2 in men and >3 in women: it is recommended that these patients should be *prescribed* an OAC.

- NICE NG196 AF Guidelines recommends using the ORBIT score to calculate the risk of bleeding. Until this is embedded into EMIS it is acceptable to continue using the HAS- BLED score or calculate both scores to make an informed decision (see below).

- A high bleeding risk score should generally not result in withholding OAC. Rather, bleeding risk factors should be identified and treatable factors corrected, including:

  - uncontrolled hypertension (see NICE's guideline NG136 on hypertension in adults)

  - concurrent medication, including selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs)

  - concomitant anti-platelets, review if these are appropriate. Consider stopping if >1 year post-acute coronary syndrome (ACS) or stable coronary artery disease. Discuss with GP/Specialist if necessary. Consider gastro-protection with appropriate concomitant anti-platelets

  - harmful alcohol consumption (see NICE's guideline CG115 on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence)

  - reversible causes of anaemia.

- Use a suitable code such as 'Anticoagulant medication review' (8BT3.) and consider free typing *switched to edoxaban* if possible. Set an appropriate follow-up review date that considers the criteria in Appendix 1 below.

Appendix 1

Blood monitoring required for DOACs (EHRA 2018)

Monitoring	
Interval	**Patient Cohort**
Yearly	Patients other than those specified below
6 – monthly	≥75 years (especially if on dabigatran) or frail
X - monthly	If renal function CrCl ≤60 mL/min: recheck interval = CrCl/10 (= X value)
If needed	Any intercurrent condition that may impact renal or hepatic function as identified by the GP/NMP

Appendix 2

CHA_2DS_2-VASc risk factor (ESC 2016)	
Congestive heart failure Signs/symptoms of HF or objective evidence of reduced left ventricular EF	+1
Hypertension Resting BP>140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age ≥75 years	+2
Diabetes mellitus Fasting glucose >125mg/dL (7mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism (arterial)	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65-74 years	+1
Sex (female=1)	+1
Score	

HAS-BLED – Assessment of bleeding risk in patients with AF (ESC 2016)	
Hypertension (Systolic >160mmHg)	1
Abnormal renal function - Dialysis, transplant, serum Cr >200 micromol/L	1
Abnormal liver function – cirrhosis, bilirubin> x 2 upper limit, AST/ALT/ALP X 3 upper limit	1
Stroke – previous ischaemic or haemorrhagic stroke	1
Bleeding tendency or predisposition – previous major haemorrhage or anaemia or severe thrombocytopenia	1
Labile INRs (if on warfarin/VKA) – TTR <60%	1
Elderly (e.g. age > 65 years or extreme frailty)	1
Drugs (e.g. concomitant aspirin, NSAID)	1
Alcohol intake at same time (>14 units per week)	1
Maximum score	9
A HAS-BLED score >3 suggests that caution is warranted when prescribing oral anticoagulation that regular review is recommended and that the reversible bleeding risk factors are addressed.	

ORBIT	
Selection Criteria	**Points**
Older age ≥75 years old	1
Reduced Haemoglobin /reduced Haematocrit/Anaemia Hb <130g/L Male; Hb <120g/L Hct: <40% Males, <30% Females History of anaemia	2
Bleeding history	2
Insufficient renal function eGFR<60mg/dL	1
Treatment with antiplatelet agents	1
Score (maximum score = 7 points)	

Risk categories and bleeding events in Validation Cohorts						
	Risk Categories			Bleeding Events in Validation Cohorts (Per 100 patient-years)		
	Low	Intermediate	High	Low	Intermediate	High
HAS-BLED	0-1	2	≥3	1.02-1.13	1.88	≥3.74
ORBIT	0-2	3	≥4	2.4	4.7	8.1

Appendix 3

Dosing for DOACs – see SPC for full details at emc.medicines.org.uk		
	Standard dose	**Reduce dose in the following patients**
Edoxaban	**60mg daily**	**30mg daily** . CrCl ≤50ml/min . Weight ≤60kg . On interacting medication (Ciclosporin, dronedarone, erythromycin, ketoconazole)
Apixaban	**5mg twice daily**	**2.5mg twice daily** If CrCl 15-29ml/min **OR** 2 of the following criteria: . ≥80yrs . Creatinine ≥133 . Weight ≤60kg
Rivaroxaban	**20mg daily**	**15mg daily** If CrCl <50ml/min
Dabigatran	**150mg twice daily**	**110mg twice daily** . ≥ 80 years . On concomitant verapamil Consider reduced dose based on individual assessment of the thromboembolic risk and risk of bleeding if: . 75-80yrs and high bleeding risk . Calc CrCl 30-50mls/min . Gastritis, oesophagitis or GI reflux . At increased risk of bleeding Close clinical surveillance is needed if patient weighs <50kg

Appendix 4

Table 7: Interactions with DOACs – see SPC for full details at emc.medicines.org.uk			
Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Ketoconazole, ciclosporin, itraconazole, tacrolimus, dronedarone, ritinovir and combinations - **CONTRAINDICATED**	Azole antimycotics (e.g.ketoconazole, voriconazole, itraconazole) **– NOT RECOMMENDED**	Azole antimycotics (e.g.ketoconazole, voriconazole, itraconazole) **–NOT RECOMMENDED**	Erythromycin, ketoconazole, ciclosporin and dronedarone – **reduce to 30mg**
Amiodarone and quinidine increase dabigatran levels – clinical surveillance. Patient with mild-mod renal impairment are at higher risk of bleeding	Rifampicin, phenytoin, carbamazepine, phenobarbital or St.Johns Wort – significant reduction in efficacy of rivaroxaban – **best AVOIDED**	Rifampicin, phenytoin, carbamazepine, phenobarbital or St.Johns Wort – 50% reduction in serum apixaban level- **CAUTION**	Quinidine, verapamil + amiodarone can increase edoxaban – **no dose change**
Verapamil – increases dabigatran levels. **Reduce dose to 110mg BD** and monitor. Take dabigatran and verapamil at the same time.	HIV protease inhibitors e.g. ritonavir – **NOT RECOMMENDED**	Aspirin, clopidogrel, antiplatelets and NSAIDS – increased bleeding risk	Aspirin and antiplatelets – increased bleeding risk Chronic NSAID use – **CAUTION: REVIEW ADVISED**
Ticagrelor, clopidogrel, prasugrel, aspirin etc. consider dose reduction	NSAIDS/antiplatelets: Ticagrelor, clopidogrel, prasugrel, aspirin etc. increased bleeding risk	HIV protease inhibitors e.g. ritonavir – **NOT RECOMMENDED**	Rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort – reduces edoxaban levels, reducing effect - **CAUTION**
Rifampicin, carbamazepine, phenytoin, St. John's Wort – **NOT RECOMMENDED**	Dronedarone – inadequate data - **AVOID**	Diltiazem, amiodarone, verapamil and quinidine increase apixaban level **- no dose adjustment necessary**	HIV protease inhibitors – studies not done
Posaconazole – no experience - CAUTION	MHRA warning for potential interaction with erythromycin resulting in increased risk of bleeding when combined		

Appendix 5 – Patient/Carer Contacted - Consultation Checklist:

DOACs - Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®), Rivaroxaban (Xarelto®).

NB: the information below covers ALL DOACs but edoxaban is the DOAC of choice where possible

Counselling point **before** starting review
Explain that all patients with non- valvular Atrial Fibrillation who are prescribed a DOAC for stroke prevention are being reviewed to ensure it is appropriate and the correct dose. No need for alarm or concern

Cover these key questions and counselling points with the patient and/or carer **BEFORE** considering changes to DOAC treatment

Question\Counselling Point	
Check adherence with DOAC treatment	This includes taking Rivaroxaban 15mg or 20mg with food. Ensure the patient is aware of the importance of adherence with these medications
Check if the patient has experienced any ADRs or side effects	Report via yellow card scheme where necessary and update the clinical record. Seek advice from GP or specialist if needed
"Do you suffer with any symptoms such as: acid reflux, heartburn, stomach pains etc.?"	Is the patient taking gastro protection medication regularly? Refer to the GP for gastro protection if not already prescribed or if already prescribed gastro protection and still symptomatic
"Any current symptoms of bleeding?"	Ensure patient knows the signs to be aware of and to contact their GP or, if severe, to go straight to hospital or call an ambulance. Bruising or bleeding under the skin • Blood in the urine • Coughing up blood • Vomiting blood or material that looks like ground coffee • Nose bleeds or cuts that take a long time to stop bleeding • Tar-coloured stools • Dizziness or sudden headache • Unexplained tiredness • Abnormal vaginal bleeding, including heavier or prolonged menses •new confusion
"Any swallowing problems with tablets?"	Dabigatran **must not** be crushed so is not suitable for patients with swallowing problems
"Are you taking any other medication (e.g. from the hospital), OTC or herbal medicines?"	For example, Aspirin, NSAIDS, St. John's Wort etc. ensure the patient is aware to always check with a pharmacist before using any OTC or herbal meds due to risk of interactions with anticoagulants
Check on alcohol consumption - Re-calculate HASBLED score as needed	If appropriate, remind patient of current government guidelines; no more than 14 units of alcohol per week for men and women spread over at least 3 days with several alcohol-free days per week
"Have you ever had a blood clot? Or been told you have a blood clotting problem?"	This is to check any history of DVT or PE (including any unusual clots such as LV thrombus or portal vein thrombosis) or any thrombophilia that may not have been recorded on the PMR. This would highlight if the patient is on a DOAC for an off license use (LV thrombus) or requires a different dose e.g. DVT/PE Note: only arterial clots are considered as a thromboembolism when

	calculating CHA_2DS_2-VASc (excludes DVT/PE) but this may highlight different dose requirement
"Have you ever had an operation on your heart?"	This is to check if the patient may have had a mechanical heart valve replacement or valve repair that has not been recorded on the PMR which may contraindicate treatment of any DOAC
IF APPROPRIATE: Check if the patient is pregnant or breastfeeding	DOACs are normally contraindicated during pregnancy and women of child- bearing potential should avoid becoming pregnant during treatment. Advise to use reliable contraception and discuss with the GP if planning pregnancy. DOACs also normally contraindicated during breastfeeding, it should be decided whether to cease therapy or to discontinue breastfeeding. Seek specialist advice from haematology if pregnant or breastfeeding
Explain decision to change patient to another DOAC or change the dose of existing therapy if relevant	Advise patient of necessary changes and why. If DOAC agent changing to alternative e.g. to edoxaban, explain rationale – works as well, clinically appropriate for the patient and will facilitate cost savings to the NHS
If further advice is needed from a specialist outside of the GP practice	Patients already discussed with the GP but who need further information, advice may be sought from a secondary care specialist pharmacist who may discuss with a Cardiologist if necessary

Cover these key questions and counselling points with the patient and/or carer **AFTER** decision of DOAC change

Counselling points	
If DOAC treatment to be changed	If a DOAC is going to be changed to another DOAC, assure the patient that the new DOAC will have the same beneficial effect as their current anticoagulant and their risk of stroke due to AF will be controlled in the same way as before. Explain that their full history and medication has been reviewed and the new DOAC is appropriate and the most cost-effective. This change is in accordance with regional guidance as agreed by local experts in AF and anticoagulation
Changing from one DOAC to another	When changing from one DOAC to another advise the patient to use up the remainder of their existing DOAC first. It is important that the new DOAC is started when the NEXT dose was due of the ORIGINAL DOAC. The dose should then be continued as labelled (see below for how change in DOAC directions should be explained to each patient) **Twice daily DOAC changing to a once daily DOAC (Edoxaban where possible):** Finish the last dose of the existing twice daily DOAC and start the new DOAC 12 hours later (when the existing DOAC would have been due). Then continue on the new DOAC every 24 hours, once a day **Once daily DOAC to twice daily DOAC (where Edoxaban is not suitable):** Finish the last dose of the existing once daily DOAC and start the new DOAC 24 hours later then continue taking the new DOAC every 12 hours twice a day

Dosage and Directions	Clearly explain the dosage and directions of the DOAC Edoxaban and rivaroxaban have **ONCE daily administration** Apixaban and dabigatran are taken **TWICE daily** Edoxaban, apixaban and dabigatran can be taken **with or without food** and should be swallowed whole and do not chew (do not open dabigatran capsules) Rivaroxaban should be taken with food Explain importance of good adherence to medication
Missed Dose	Explain the importance of good compliance. Explain that to ensure optimal protection from blood clots, never skip a dose and NOT to stop taking unless advised by a clinician If the patient misses a dose of edoxaban or rivaroxaban they should take it immediately and then continue the following day with the once-daily intake as recommended. The patient should **not** take double the prescribed dose on the same day to make up for a missed dose If a dose of apixaban is missed, the patient should take apixaban immediately and then continue with twice daily intake as before A missed dose of dabigatran may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted
General additional advice for DOACs	It is important that patients inform other health professionals treating them, including their dentist and pharmacist that they are taking this medicine Inform a healthcare specialist if they need to have surgery or an invasive procedure Patients should seek urgent medical attention if they fall or injure themselves during treatment, especially if they hit their head, due to the increased risk of bleeding Lifestyle advice regarding contact sports or extreme sports should be included in the counselling where appropriate as an injury whilst taking a DOAC could cause serious bruising or bleeding
Reversal Agents	There are reversal agents available which can be used in severe bleeding or if emergency surgery/procedure is required in an emergency under specific circumstances. Refer to other document for information on
Alert Card	Advise the patient/carer to always carry their alert card (supplied with medication) and always inform health professionals that they are taking an anticoagulant prior to any procedure
Weight change	Advise that the patient should inform the clinician about any significant weight change. Refer to other document for information on extremes of weight
Monitored Dosage System	Check if patient uses a monitored dosage system and inform the community pharmacy if any change to treatment is required. There are no known issues with using edoxaban in a compliance device