Anticoagulation Decision Support Tool: Stroke Prevention in adults with Non-Valvular Atrial Fibrillation (NVAF) (Version 2.0)

Scope: To be used to help prescribers pick the most appropriate oral anticoagulant (after patient assessment has established that anticoagulation is appropriate)
For information on assessment for anticoagulation see the LMMG Oral Anticoagulant Consensus Statement or NICE CG180
For further prescribing information see the LMMG NOAC Prescribing Guide or the relevant SPC

Table1. NVAF Anticoagulant Decision Support Tool: Prescribers must be able to answer yes to all questions prior to initiating therapy (Refer to the SPC for Further Information about the Individual Medications)	**Yes/No**
1. The patient has Non-valvular Atrial Fibrillation[1] (AF)	
2. CHA_2DS_2-VASc is 1 or more (Men) or 2 or more (Women)[1]	
3. Bleeding risk has been assessed using HAS-BLED & correctable risk factors addressed when possible[1]	
4. Contra-Indications and cautions to anticoagulant therapy have been excluded e.g. known hypersensitivity, clinically-significant active bleeding, or concomitant use of an alternative anticoagulant.	

Drug Specific Contra-Indications [2-6,12]

Warfarin (Marevan ®)	**Dabigatran (Pradaxa ®)**	**Rivaroxaban (Xarelto®)**	**Apixaban (Eliquis ®)**	**Edoxaban (Lixiana®)**
Within 48 hours postpartum Pregnancy (1st & 3rd trimesters) Haemorrhagic stroke	CrCl less than 30mL/min Hepatic impairment or liver disease expected to have any impact on survival Contraindicated for use for prosthetic heart valves Lesion or condition considered significant risk factor for major bleeding*	Pregnancy & breast feeding Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C Lesion or condition considered significant risk factor for major bleeding*	Hepatic disease associated with coagulopathy and clinically relevant bleeding risk Lesion or condition considered significant risk factor for major bleeding*	Pregnancy & breast feeding Hepatic disease associated with coagulopathy and clinically relevant bleeding risk Uncontrolled severe hypertension Lesion or condition considered significant risk of major bleeding*

*Significant risk factors for bleeding include: current or recent GI ulceration, malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities

Use Not Recommended

	Dabigatran: SPC states not to be used in pregnancy unless clearly necessary, breast feeding to be discontinued during treatment	**Rivaroxaban**: Not recommended if CrCl less than 15mL/min	**Apixaban:** Not recommended if CrCl less than 15mL/min or if undergoing renal dialysis Not recommended in pregnancy & a risk to the child cannot be excluded in breast feeding	**Edoxaban:** Not recommended if CrCl less than 15mL/min or if undergoing renal dialysis

Cautions

Liver Function	All anticoagulants should be used with caution in mild- moderate liver impairment & avoided in severe impairment (especially if the baseline prothrombin time is prolonged).
Full Blood Count	All anticoagulants should be used with caution in patients with anaemia or low platelets. Active bleeding should be ruled out prior to initiation and more frequent monitoring may be required.

5. Potential interactions with other medications or foods have been considered. NB – For all anticoagulants, caution should be exercised with drugs that affect haemostasis, e.g. NSAIDS, aspirin & clopidogrel

Yes/No

Interactions[2-5,12] (Please note: This list is not exhaustive, please consult the relevant SPC for full details)

Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Multiple interactions requiring increased INR monitoring. Cranberry juice, alcohol, foods with high not amounts of Vitamin K e.g. leafy green veg such as cabbage, spinach, brussel sprouts and broccoli	**Contraindicated with Strong P-gp inhibitors** e.g. ketoconazole, cyclosporine, itraconazole & dronedarone. **Concomitant treatment with tacrolimus, is not recommended** **Caution with mild to moderate P-gp inhibitors** e.g. amiodarone, verapamil, quinidine, clarithromycin, rifampicin, phenytoin & carbamazepine **Caution with SSRIs & SNRIs**- increased risk of bleeding No known food interactions	**Avoid concomitant treatment with strong inhibitors of 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 (may lead to reduced rivaroxaban concentrations) **Caution with dronedarone** No known food interactions	**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 (may lead to reduced apixaban concentrations) No known food interactions	**P-gp inhibitors.** Concomitant use with ciclosporin, dronedarone, erythromycin or ketoconazole requires dose reduction to 30mg once daily. Concomitant use with P-gp inhibitors quinidine, verapamil or amiodarone does require dose adjustment. **Caution with P-gp inducers** (e.g. phenytoin, carbamazepine, phenobarbital or St. John's wort (may lead to reduced edoxaban concentrations). No known food interactions
	NOACs are contraindicated with concomitant use of other anticoagulants (except when switching therapy) **Further information relating to the use of antiplatelets with NOACs in patients with AF is available from UKMI**			

6. Baseline bloods and other relevant parameters have been checked; the dose has been adjusted if needed

Dose Adjustments[2-5,12] Nb. If CrCl is not reported it can be calculated from SrCr[9].

	Warfarin AF dose: As per INR	Dabigatran AF dose: 150mg Twice Daily	Rivaroxaban AF dose: 20mg Once Daily	Apixaban AF dose: 5mg Twice Daily	Edoxaban AF dose: 60 mg once daily,
Renal Function	Can be used with caution in renal impairment. *	**CrCl <30mL/min:** Contraindicated The SPC States 'The method used to estimate renal function (CrCL in mL/min) during clinical development was the Cockcroft-Gault method. This method is recommended when assessing patients' CrCL prior to and during treatment.'	**CrCl <15ml/min:** Not Recommended **CrCl= 15-49ml/min:** Reduce dose to 15mg once daily	**CrCl <15ml/min:** Not Recommended **CrCl=15-29ml/min:** Reduce dose to 2.5mg twice daily **SrCr ≥133micromol/litre & ≥ 80yrs or ≤ 60kg:** Reduce dose to 2.5mg twice daily	**CrCl <15 mL/min or on dialysis:** Not Recommended **CrCl = 15-50mL/min:** Reduce dose to 30 mg once daily **CrCl>50-80 mL/min**: 60 mg once daily **Nb.** There is a trend towards decreasing efficacy with increasing CrCl, therefore only use in patients with high CrCL after evaluation of the individual thromboembolic and bleeding risk. **The SPC states** Renal function should be assessed in **all** patients by calculating the CrCL prior to treatment. Renal function should also be assessed if a change is suspected (e.g. hypovolaemia, dehydration or concomitant use of certain medicines)
	*As per NICE CG 182 for patients with **CKD** and a **confirmed eGFR of 30–50 ml/min/1.73m2** and **1 or more** of the following **risk factors**: Prior stroke or transient ischaemic attack, 75 years or older, Hypertension, Diabetes mellitus or Symptomatic heart failure; apixaban may be considered in preference to warfarin.[11]				

Yes/No

Dose Adjustments Continued [2-5,12]					
	Warfarin AF dose: As per INR	**Dabigatran** AF dose: 150mg Twice Daily	**Rivaroxaban** AF dose: 20mg Once Daily	**Apixaban** AF dose: 5mg Twice Daily	**Edoxaban** AF dose: 60 mg once daily,
Age & Weight	No dose adjustment specified	**≥ 80yrs:** Reduce dose to 110mg twice daily	No dose adjustment specified	**≥ 80yrs with a body weight ≤ 60kg:** Reduce dose to 2.5mg twice daily	**Low body weight ≤60 kg** reduce to 30 mg once daily. No dose adjustment required for the elderly.
Others		**If High Risk of Bleed or Treatment with Verapamil:** Reduce to 110mg twice daily			**Concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole:** Reduce to 30 mg once daily.

7. The patient's ability to comply with medication dosing has been taken into account

Compliance Considerations [2-5,12]				
Warfarin	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Variable Dosing as Per INR Patients who forget doses may benefit from warfarin therapy because of its longer blood-thinning effect and the common use of Anticoagulation Management Services, which provide frequent reminders about medication adherence and follow-up with INR tests	Dosing is TWICE DAILY Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation **Not stable in compliance aids/ monitored dosage systems**	Dosing is ONCE DAILY with food Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation	Dosing is TWICE DAILY Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation	Dosing is ONCE DAILY Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation.

8. Safety information and comparative bleeding risks have been considered

Relevant Bleeding Risk				
Warfarin	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban** [12, 13]
See respective agent for comparison N.B. Falls are not a contraindication to the use of warfarin. Analytical models estimate that elderly patients would need to fall 295 times a year for their risk of developing subdural haematomas to outweigh the benefit of being anticoagulated with warfarin[7] **Long term safety data based on over 50yrs use & anticoagulant effects can be rapidly reversed in the event of major bleeding**	**Major bleeding:** No difference between dabigatran 150 mg BD and warfarin. Less common with dabigatran 110 mg BD than warfarin **GI bleeding:** More common with dabigatran 150mg BD than warfarin (p=0.0008). No difference between dabigatran 110mg BD and warfarin. **Intracranial bleeding:** Less common with both doses of dabigatran than with warfarin (p<0.001) **Bleeding risk** high in frail/ elderly particularly with renal impairment and low weight	**Major bleeding:** No difference between rivaroxaban and warfarin. **GI bleeding:** More common with rivaroxaban than warfarin (p<0.001) Approximately 88% of major bleeding episodes associated with rivaroxaban originate in the GI tract[10] **Intracranial bleeding:** less common with rivaroxaban than warfarin (p=0.02)	**Major bleeding:** Less common with apixaban than warfarin (p<0.001) **GI bleeding:** No difference between apixaban and warfarin **Intracranial bleeding:** Less common with apixaban than warfarin (p<0.001)	**Major bleeding:** significantly reduced rate of major bleeding and of several secondary bleeding endpoints for 60mg/30mg edoxaban compared to warfarin (p≤0.01) **Major GI bleeding:** Occurred slightly more frequently in edoxaban 60mg/30mg than in warfarin p=0.03. In clinical studies mucosal bleedings and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment, therefore in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.
	No information available on long-term safety. Dabigatran is the only NOAC with an established antidote i.e. Idarucizumab (licensed December 2015).			

Table 2. Oral Anticoagulation Patient Counselling Checklist	Yes /No
1. An Anticoagulant Alert Card has been given to the patient	
2. A medication specific patient information leaflet has been given to the patient Links to Patient Information: warfarin, apixaban, rivaroxaban, dabigatran and edoxaban	
3. The purpose of anticoagulation in AF has been explained AF Patient Information Anticoagulation in AF Patient Information	
4. The rationale for use of the chosen anticoagulant has been discussed and explained	
5. The potential side effects have been explained. (Bleeding is common side effect for all anticoagulants). If taking a NOAC explain that there is no known antidote to the anticoagulant effects of apixaban, rivaroxaban or edoxaban unlike warfarin and dabigatran.	
6. The patient understands that they should inform healthcare professionals, including doctors, pharmacists and dentists that they are taking an oral anticoagulant and to show their Patient Alert card. (Local organisations should have arrangements for sourcing and disseminating alert cards. Online cards are also available for printing from the AF association anticoagulant alert cards).	
7. The need for an annual review/blood test to monitor renal function has been explained	
8. The patient knows how to take the medication including: The frequency of administration To take with water, with or without food To take regularly What to do if a dose is missed If an extra dose is taken accidentally, advise patient to seek medical advice Remind patient not to stop taking the medication unless advised to do so by a healthcare provider	
9. If initiating Warfarin; the patient has been informed if a LMWH is co-prescribed and arrangements have been made for the supply and administration of the LMWH (LMWH should be continued until the INR is in range for 2 consecutive days)	

Version Control: Please access documents via the LMMG website to ensure the correct version is in use.

Version Number	Amendments Made	Author	Date
Version 1.0	First Version Approved	SMcKernan	
Version 2.0	Edoxaban incorporated	SMcKernan	March 2016

References

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