Primary Care Prescriber Decision Support for the New Oral Anti-Coagulants (NOACs) for stroke prevention in Atrial Fibrillation (SPAF)

The patient has AF and using the CHA2DS2-VASc and HAS-BLED score the decision has been made to anticoagulate. Patients on any type of anticoagulant will need education. This is automatically provided through the anticoagulation clinic for patients initiated on warfarin. (http://www.patient.co.uk/health/anticoagulants). Community pharmacists can provide education under the New Medicine Service.

Patients with good INR control with warfarin may not gain additional clinical benefit by taking a NOAC.

Does the patient have **any** of the following?

- Valvular AF due to rheumatic heart disease
- CrCl <30ml/min (local advice but see over)

Yes → Refer to anticoagulation clinic for warfarin

No → Does the patient have any ONE of the following?

- Prior stroke or TIA
- >75 years
- Hypertension
- Diabetes mellitus
- Symptomatic heart failure (NYHA Class>II)

No → Refer to anticoagulation clinic for warfarin

Yes → Warfarin **OR** NOAC

Discuss relative risks and benefits of each agent **with patient** so that informed decision can be made[2]

Considerations

Warfarin	NOACs
Has been prescribed for more than 50 years	Compared to warfarin NOACs are relatively new to market
Effective antidote with prothrombin complex concentrate (PCC) and vitamin K should a severe bleed occur. Vitamin K takes hours to have an effect.	No licensed antidote (except for dabigatran). Reduced risk of intracranial haemorrhage
Time to full anticoagulation can be a week or more.	Immediate effect (peak 1-4 hours)
Patient needs regular follow up and blood sampling	Useful for patients who have difficulty getting INR measured. Minimum of U&E and LFT measured annually.
Cannot be put in a dosette box unless risk assessment has been done and a management plan is in place to manage dose adjustment	Rivaroxaban and apixaban are stable in a dosette box and so useful for patients who need external support to take medicines
For patients with ACS or stents in last 12 months follow Cardiology advice regarding use of antiplatelets. Aspirin can be stopped if chronic IHD >12 months from	For patients with IHD ACS or stents follow Cardiology advice regarding use of antiplatelets
Correct INR can be difficult to manage despite good compliance	Useful for patients with erratic INR not due to non-compliance
Warfarin and coagulation factors have long half-lives therefore missed doses result in less loss of anticoagulation compared to NOACs	**NOAC have short half-life and so missed dose have greater loss of anticoagulation than warfarin**

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Table of considerations when deciding which NOAC for Prevention of SPAF

	Apixaban	Rivaroxaban	Dabigatran
Dose	5 mg BD	20 mg OD	150 mg BD
Dose in renal impairment (See SPC eg if >80 yr)	2.5 mg BD (if CrCl 15-29 ml/min)	15 mg OD with food (if CrCl 15-49 ml/min)	110 mg BD (if high risk of bleeding. Dabigatran is contraindicated if CrCl <30ml/min)
Hepatic impairment	Not recommended in severe hepatic impairment as requires hepatic metabolism (25% hepatic, 25% renal, rest faecal elimination). Check baseline LFTs prior to initiation.	Use with caution as required hepatic metabolism (67% hepatic, 33% renal excretion)	Not recommended in patients with elevated liver enzymes >2 upper limit of normal (15% hepatic and 85% renal excretion)
Contraindications	HIV protease inhibitors, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St Johns Wort, erythromycin, clarithromycin	HIV protease inhibitors, ketoconazole, itraconazole, voriconazole, posaconazole and dronedarone. Caution with rifampicin, carbamazepine, phenytoin, phenobarbital, St Johns Wort, erythromycin, clarithromycin	HIV protease inhibitors, rifampicin, carbamazepine, phenytoin, phenobarbital, St Johns Wort, dronedarone, ciclosporin, tacrolimus, ketoconazole, itraconazole, voriconazole and posaconazole. Caution with amiodarone, verapamil, erythromycin, clarithromycin
	Care should be taken with drugs directly affecting bleeding risk eg NSAIDs, anticoagulants, antiplatelets SSRIs and SNRIs. Recent MHRA guidance can be found here		
Extremes of BMI	If <50 kg or >100-120 kg then exposure of NOAC is variable by 20-30%. It is recommended that at these body weights the Cockcroft and Gault formula is used to calculate CrCl rather than use eGFR.		
Efficacy for Stroke or Systemic Embolism Prevention	Event rate of 1.27% in apixaban group vs 1.6% in warfarin group (hazard ratio 0.79; 95% CI, 0.66 to 0.95; P<0.01 for noninferiority and P = 0.01 for superiority (ARISTOTLE[3])	Event rate of 1.7% per year in the rivaroxaban group vs 2.2% in warfarin group (hazards ratio in the rivaroxaban group,0.79; 95% CI, 0.66 to 0.96; P<0.001 for noninferiority (ROCKET-AF[4])	For 150 mg BD dose event rate of 1.11% vs 1.69% for warfarin group (relative risk 0.66; 95% CI, 0.53-0.82 P<0.001 for superiority. For dabigatran dose 110mg BD 1.53% vs 1.69% for warfarin. Relative risk, 0.91; 95% CI 0.74 to 1.11; P<0.001 for noninferiority. (RE-LY[5])
Major bleed risk compared to warfarin	Event rate of 2.13% in the apixaban group vs 3.09% in warfarin group (hazard ratio 0.69; 95%CI, 0.6 to 0.8;P=<0.001)[3]	Event rate of 3.6% in rivaroxaban group and 3.4% in warfarin group (hazard ratio, 1.04; 95% CI, 0.90 to 1.20; P=0.58[4]	Event rate of 3.11% in the dabigatran 150 mg BD group (relative risk 0.93; 95% CI (0.81 to 1.07) P=0.31 and 2.72% in the dabigatran 110mg BD group (relative risk 0.80 95% C.I. 0.69-0.93 P=0.003 vs 3.36% in the warfarin group[5]
Intracranial bleed risk compared to warfarin	Event rate of 0.33% in the apixaban group and 0.80% in the warfarin group (hazard ratio, 0.42; 95% CI, 0.30 to 0.58; P<0.001[3]	Event rate of 0.5% rivaroxaban group vs 0.7% in warfarin group Hazard ratio 0.67; 95% CI, 0.47 to 0.93, P=0.02[4]	Event rate of 0.30% (relative risk, 0.40; 95% CI, 0.27 to 0.60; P<0.001) in the dabigatran 150 mg BD group and 0.23% in the 110 mg BD dabigatran group (0.31; 95% CI, 0.20 to 0.47; P<0.001) vs 0.74% in the warfarin group[5]
Major GI bleed risk compared to warfarin	Event rate of 0.76% in apixaban group vs 0.86% in the warfarin group. Hazard ratio 0.89 95% CI 0.70-1.15 P=0.37[3]	Event rate of 3.2% rivaroxaban group vs 2.2% warfarin group P=<0.001[4]	For dabigatran 150mg BD event rate of 1.51% Relative risk 1.50; 95% CI 1.19-1.89 P<0.001 For dabigatran 110 mg BD 1.12% Relative risk 1.10; 95% CI (0.86-1.41) P=0.43 vs warfarin event rate of 1.02%[5]

Requirements for GP for monitoring NOACs

Prior to initiation and at least annually, U&Es, LFT and FBC

Provide yellow anticoagulation card (these can be ordered by e mailing nhsforms@mmm.doc with delivery and invoice address. Cost is £0.82 per 50).

Please refer to APC 005: NOAC use in atrial fibrillation (version 2) for full information.

References

1) Singh P, Arrevad PS, Peterson GM, Bereznicki LR. Evaluation of antithrombotic usage for atrial fibrillation in aged care facilities. J Clin Pharm and Therapeutics Apr 2011; 36(2): 166-171

2) NICE clinical guideline 180 Atrial Fibrillation: the management of atrial fibrillation. June 2014

3) Granger CB et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation N Engl J Med 2011; 365:981-92

4) Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in non-valvular Atrial Fibrillation N Engl J Med 2011; 365:883-91

5) Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N. Engl J Med 2009; 361:1139

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