NHS
Shropshire
Clinical Commissioning Group

ANTICOAGULANT USE IN STROKE PREVENTION IN ATRIAL FIBRILLATION

Choice of anticoagulant

There are currently three non-VKA antagonist anticoagulation agents (NOACs) licensed alongside warfarin for stroke prevention in AF. NICE states that apixaban, rivaroxaban and dabigatran etexilate are non-inferior to warfarin[1.] There are no are no head to head comparative data to show which of the NOACs might be clinically more effective or safer.

Where there is no difference in clinical effectiveness, NICE generally recommends that treatment choice should be started with the least expensive drug, taking into account administration costs, patient clinical presentation, provider delivery costs, to ensure a cost effective use of NHS resources. (in this case warfarin is the most cost effective option and NICE recommend that the risks and benefits relative to warfarin should be discussed with the patient before prescribing them.)

An alternative NICE-approved agent can be used in patients who meet the NICE criteria for anti-coagulation in AF but fail to respond to the first agent or have side effects or contra-indications to the first agent.

Changes from warfarin to non-VKA antagonists should be considered for patients who specifically request this, those whose TTR is <40 due to proven poor compliance where the use of an monitored dosage system (MDS) is considered to improve compliance for that individual patient.

Warfarin, is a well-established treatment that has been used for many years in stroke prevention. While dependent on regular monitoring of international normalised ratios (INRs), anticoagulation can also be readily reversed by administration of vitamin K, and the drug-drug and drug-food interactions of warfarin are well documented.

Dabigatran etexilate (Pradaxa®) is a pro-drug that is converted *in vitro* to the potent, orally active dabigatran, a direct inhibitor of free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.[3] Apixaban (Eliquis®) and rivaroxaban (Xarelto®) are both highly selective inhibitors of activated factor X (Xa).[4,5] All three NOACs are licensed for prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors..

All three NOACs are associated with an increased risk of haemorrhage and as such are contraindicated for use in people with a lesion or condition associated with a significant risk of major bleeding. This may include gastrointestinal ulceration, malignant neoplasm at risk of bleeding, recent brain or spinal injury, recent intracranial haemorrhage, oesophageal varices, arteriovenous malformations and vascular aneurysms.[6]

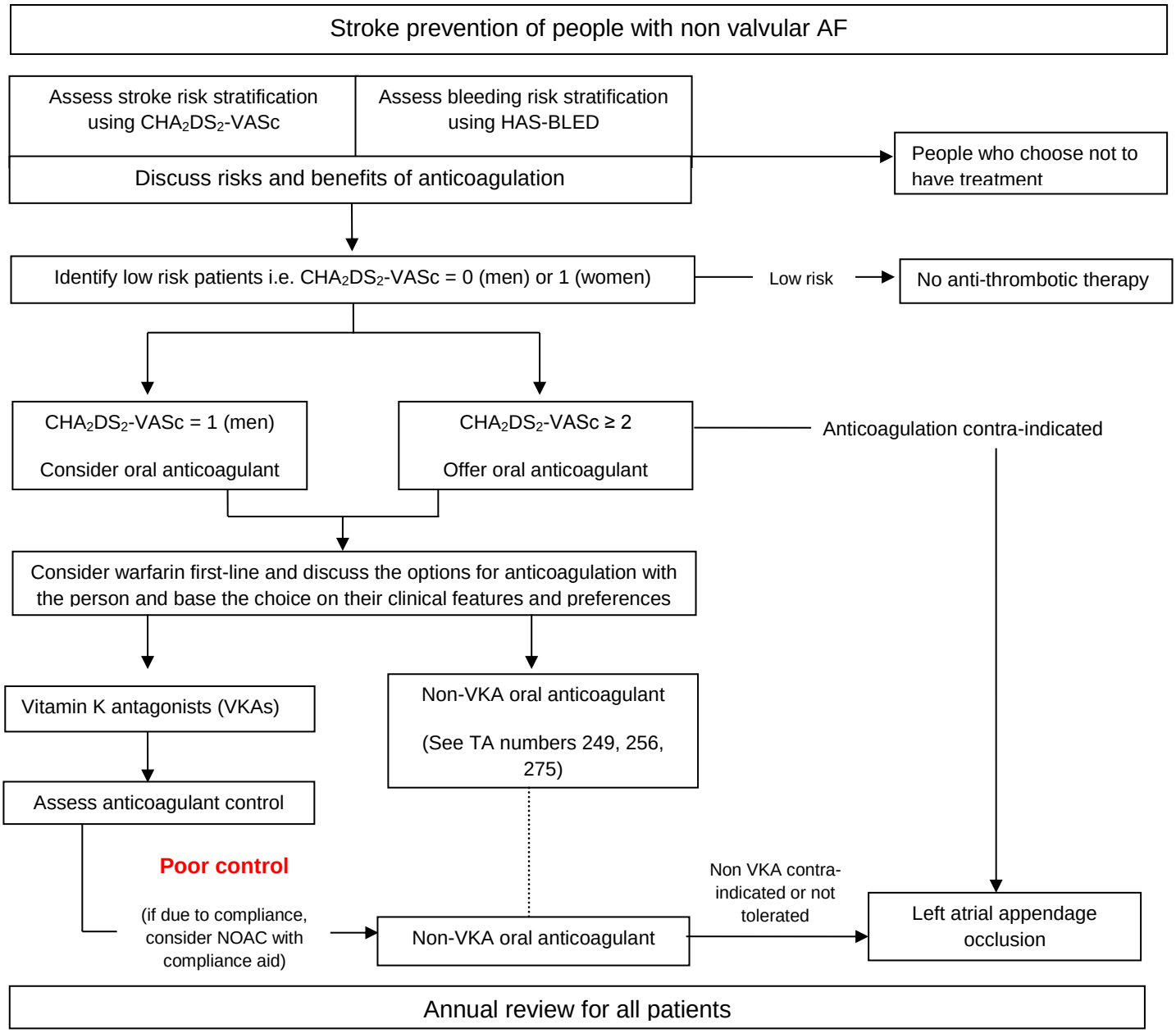
KEY INFORMATION

Prescribing of anticoagulants in AF should only be in line with the algorithm overleaf from NICE Clinical Guideline CG180 Atrial fibrillation

- It is **very important** to check the patient's renal function before prescribing any of the new oral anticoagulants as they all require drug-specific dose adjustments in renal impairment and should be used with caution, if at all, in this group. See specific drug information overleaf.
- Bleeding risk with dabigatran and rivaroxaban is increased in patients aged >75 years. Bleeding risk on dabigatran is also increased with impaired renal function or low body weight (<50 kg). The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs) which significantly increase the risk of major bleeding requires a careful benefit-risk assessment.
- There is no antidote available for dabigatran, rivaroxaban or apixaban therefore it is important to assess the bleeding risk and the patient's ability to access urgent care before starting treatment.
- Poor compliance with warfarin treatment does not mean a patient will gain good compliance when switched to a non-VKA oral anticoagulant. The reason for poor compliance should be investigated before any change in treatment is made.
- The shorter half-lives (~5-18 hours) of non-VKA oral anticoagulants compared to warfarin will potentially result in more time without any degree of anticoagulation if a dose is missed due to compliance issues.
- Warfarin and dabigatran capsules are unsuitable for compliance aids, due to the variable dosage of warfarin and moisture sensitivity of dabigatran. Dabigatran capsules **must not** be removed from their packaging before administration, and must be swallowed whole and not opened.
- Rivaroxaban and apixaban do not have any specific storage requirements so may be an option if the patient requires a compliance aid.
- Rivaroxaban can be crushed and administered via a naso-gastric tube if required (see further information overleaf).

GUIDANCE FOR ORAL ANTICOAGULANT TREATMENTS FOR AF PATIENTS
Based on NICE CG180

Algorithm 1. Anti-coagulant choice in stroke prevention in non-valvular AF[2]



Poor anticoagulant control with a vitamin K antagonist may be indicated by any of the following:

- 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months
- 2 INR values less than 1.5 within the past 6 months
- Time in therapeutic range (calculated by Rosendaal or similar method) less than 65% over 6 months

The table below summarises the estimated annual costs per patient initiated on each agent.

Table 1. Annual costs of treatment for anticoagulant choices in non-valvular AF

Oral anticoagulant agent	Dosage	Cost per year[7,8,9,10]
Warfarin	Variable (average 4.5mg once daily)	£41 + £242 for INR monitoring
Apixaban	5mg twice daily or 2.5mg twice daily	£802
Rivaroxaban	20mg once daily	£767
Dabigatran etexilate	150mg twice daily or 110mg twice daily	£802

RECOMMENDED DOSING SCHEDULE FOR STROKE PREVENTION IN AF (SPAF)

The following information has been obtained from the Summary of Product Characteristics (SPCs) for each drug and is correct as of 19 May 2014 (see individual SPCs for full and most up-to-date information at www.medicines.org.uk).

The following dosage recommendations utilise estimated eGFR, though the manufacturers SPCs are based on Creatinine Clearance – if available, CrCl [mL/min] should be used instead of eGFR.

Rivaroxaban (NICE TAG 256)

Rivarobaban (Xarelto®)[5] is recommended as an option for prevention of stroke and systemic embolism in people with non-valvular AF with one or more of the following risk factors:

- Congestive heart failure
- Hypertension
- Age ≥ 75 years
- Diabetes mellitus
- Previous stroke or TIA

Additional information

Rivaroxaban tablets may be crushed and can be mixed with water or mixed with apple puree immediately prior to being administered orally. Doses taken in this way should be consumed with food shortly thereafter. Crushed tablets may also be given via gastric tubes with a small amount of water, and the tube then flushed with water. The dose should then be immediately followed by enteral feeding.

Patient specific factors	Dose
Adults with normal renal function	20mg once daily
eGFR <15 ml/min/1.73 m^2	**Do not use**
eGFR 15-29 ml/min/1.73m^2	**15mg once daily (Use with caution)**
eGFR 30-49 ml/min/1.73 m^2	15mg once daily
eGFR ≥ 50 ml/min/1.73 m^2	20mg once daily
Gastrointestinal disease without active ulceration	**Not recommended**
Vascular retinopathy, bronchiectasis, history of pulmonary bleeding	**Not recommended**
Hepatic disease associated with coagulopathy	**Do not use**

Apixaban (NICE TAG 275)

Apixaban (Eliquis®)[4] is recommended as an option for prevention of stroke and systemic embolism in people with non-valvular AF with one or more of the following risk factors:

- Previous stroke or TIA
- Age ≥ 75 years
- Hypertension
- Diabetes mellitus
- Symptomatic heart failure

Additional information

No information is available from the manufacturer regarding the crushing of tablets, so this practice cannot be recommended.

(dosing continued overleaf)

(Apixaban dosing continued)

Patient specific factors	Dose of apixaban
Adults aged <80 years with normal renal function	5mg twice daily
Adults with at least 2 of the following: wt ≤ 60kg, age>80yrs, serum creatinine ≥133micromol/L	2.5mg twice daily
eGFR ≥ 30 ml/min/1.73 m^2	5mg twice daily
eGFR 15-29 ml/min/1.73m^2	2.5mg twice daily
eGFR < 15 ml/min/1.73 m^2	**Not recommended**
Hepatic disease associated with coagulopathy	**Do not use**
Severe hepatic impairment	**Not recommended**
Mild/moderate hepatic impairment	**Use with caution**

Dabigatran (NICE TAG 249)

Dabigatran etexilate (Pradaxa®)[3] is recommended as an option for prevention of stroke and systemic embolism in people with non-valvular AF with one or more of the following risk factors:

- Previous stroke, TIA or systemic embolism
- Left ventricular ejection fraction < 40%
- Symptomatic heart failure of NYHA class 2 or above
- Age ≥ 75 years
- Age ≥ 65 with one of: diabetes mellitus, coronary artery disease or hypertension

Additional safety information

The oral bioavailability of dabigatran may be increased by up to 75% when the contents are taken without the capsule shell. Patients are advised **not** to open the capsule to sprinkle the capsule contents for use separately, as this **significantly** increases the bleeding risk.

Patient specific factors	Dose
Adults aged <75 years	150 mg twice daily
Adults aged 75–80 years	150 mg twice daily (consider 110mg twice daily if thromboembolic risk low and bleeding risk high)
Adults aged >80 years	110 mg twice daily
eGFR <30 ml/min/1.73 m^2	**Do not use**
eGFR 30–50 ml/min/1.73 m^2	150 mg twice daily (consider 110mg twice daily after assessment of thromboembolic and bleeding risks)
+ Verapamil	110 mg twice daily
Gastritis, oesophagitis or GORD	110mg twice daily (patients at risk of major GI bleeding)
+ Aspirin/ clopidogrel/ NSAID	Consider 110mg twice daily
Other patients with increased bleeding risk	Consider 110mg twice daily
Hepatic impairment (liver enzymes > 2x ULN)	**Not recommended**

References

1. *Apixaban and rivaroxaban for stroke prevention in AF. DTB* 2014;**52**:6-9 doi:10.1136/dtb.2014.1.0228
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5. Rivaroxaban (Xarelto®) SPC. Available at http://www.medicines.org.uk/emc/medicine/25586
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Conversion to and from warfarin with NOACs in AF

Approximately 80% of active dabigatran, 25% of apixaban and ~33% of rivaroxaban dose are excreted unchanged in the kidney, therefore a sufficient renal function and adequate monitoring is essential prior to, and periodically during, therapy with these agents.[7] **Please consult the relevant SPC for the most up-to-date prescribing data.**

Table 2. Initial doses of, and conversions to and from, NOACs

	Initiation doses in AF	Switching **from** warfarin in **AF**	Switching **to** warfarin **in AF**
Dabigatran etexilate[3]	**150mg twice daily** or **110mg twice daily** (if patient > 80 years, high risk of bleeding or on verapamil) **Contra-indicated** if CrCl < 30 ml/min	Stop warfarin and start dabigatran etexilate when INR < 2.0.	If CrCl ≥ 50 ml/min, start warfarin 3 days prior to dabigatran withdrawl. If CrCl ≥ 30 to < 50 ml/min, start warfarin 2 days prior to dabigatran withdrawl. Dabigatran etexilate can affect INR, do not measure until 48 hours after withdrawl
Apixaban[4]	**5mg twice daily** or **2.5mg twice daily** if CrCl 15-29 ml/min, or at least two of age ≥ 80 years, weight ≤ 60kg or, serum creatinine ≥ 1.5mg/dL **Not recommended** if CrCl < 15 ml/min	Stop warfarin and start apixaban when INR < 2.0	Co-administer apixaban and warfarin for two days, then measure INR. Warfarin can be continued as monotherapy when INR ≥ 2.0. Apixaban can affect INR, measure at least 24 hours after previous dose but prior to next dose
Rivaroxaban[5]	**20mg daily**, or **15mg daily** if CrCl 30-49 ml/min, CrCl 15-29 ml/min (use with caution) **Not recommended** if CrCl < 15 ml/min	Stop warfarin and start rivaroxaban when INR ≤ 3.0	Co-administer rivaroxaban and warfarin until INR ≥ 2.0. Rivaroxaban can affect the INR, measure at least 24 hours after the previous dose but prior to the next dose.

Drug-drug interaction with NOACs

Dabigatran does not undergo extensive hepatic metabolism, though is extensively excreted by the kidney and so is affected to a greater extent by other drugs that affect renal function. Conversely, the greater hepatic metabolism of apixaban and rivaroxaban via the CYP3A4/3A5 system means that inhibitors or inducers of this pathway will affect plasma levels of these agents. All three NOACs are substrates of the P-glycoprotein (P-gp) efflux system and concomitant administration of other drugs affecting P-gp will affect plasma levels accordingly.[11]

Table 3. Current known drug-drug interactions with NOACs[3,4,5]

Drugs directly affecting bleeding risk	**Drugs affecting the kidney**	**Inducers of hepatic metabolism**	**Inhibitors of hepatic metabolism**	**Inducers of P-glycoprotein**	**Inhibitors of P-glycoprotein**
Other anticoagulants[A] NSAIDs Antiplatelets Thrombolytic agents Selective serotonin re-uptake inhibitors Serotonin-noradrenline re-uptake inhibitors	Diuretics NSAIDs ACE inhibitors Angiotensin-II receptor antagonists	Rifampicin St John's Wort Carbamazepine Phenytoin Phenobarbital	Azole antifungals[B,E,F] Verapamil[C] Amiodarone[D] Ciclosporin[B] Tacrolimus[B] HIV protease inhibitors[E,F]	Rifampicin St John's Wort Carbamazepine Phenytoin Phenobarbital	Dronedarone[B, F] Quinidine[D] Azole antifungals [B,E,F] Amiodarone[D] Diltiazem Verapamil[C] Clarithromycin Ticagrelor HIV protease inhibitors[E,F]

A. Contra-indicated except when switching between agents[6]
B. Contra-indicated with dabigatran etexilate
C. Dose adjustment of dabigatran etexilate required (reduce to 110mg twice a day). Use with caution
D. Dose adjustment of dabigatran etexilate required in orthopaedic use
E. Not recommended with apixaban
F. Not recommended with rivaroxaban

ASSESSMENT OF STROKE AND BLEEDING RISKS

Stroke Risk

Use CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following:

- Symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation[2]
- Atrial flutter[2]
- A continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm[2]

CHA_2DS_2-VASc tool

Congestive heart failure history		+1	The presence of signs and symptoms of either right or left ventricular failure or both, confirmed by non-invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction, such as LVEF < 40%
Hypertension history		+1	A resting blood pressure > 140 mmHg systolic and/or > 90 mmHg diastolic on at least 2 occasions or current antihypertensive drug treatment
Age in Years	<65	0	
	65-74	+1	
	≥ 75	+2	
Diabetes mellitus		+1	Fasting plasma glucose ≥ 7.0 mmol/L or treatment with oral hypoglycaemic agent/insulin
Stroke/TIA/thromboembolism history		+2	Prior MI, angina pectoris, percutaneous coronary intervention or coronary artery bypass surgery. The presence of any of the following: intermittent claudication, previous surgery or percutaneous intervention on the abdominal aorta or lower extremity vessels, abdominal or thoracic surgery, arterial or venous thrombosis
Vascular disease history		+1	
Sex	Male	0	
	Female	+1	

Bleeding risk

Use the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation. Offer modification and monitoring of the following risk factors:

- Uncontrolled hypertension[2]
- Poor control of international normalised ratio (INR) ('labile INRs')[2]
- Concurrent medication, for example concomitant use of aspirin or a non-steroidal anti-inflammatory drug (NSAID)[2]
- Harmful alcohol consumption[2]

HAS-BLED tool

Hypertension history	+1	Uncontrolled, >160 mmHg systolic
Abnormal renal function	+1	Dialysis, transplant, Cr >2.6mg/dL or 200 µmol/L
Abnormal liver function	+1	Cirrhosis, bilirubin >2x normal, AST/ALT/AP >3x normal
Stroke history	+1	Previous history, particularly lacunar
Bleeding risk	+1	Bleeding history or predisposition (anaemia)
Labile INR	+1	Unstable/high INRs, time in therapeutic range < 60%
Elderly	+1	Age > 65 years
Drugs predisposing	+1	Antiplatelets, NSAIDs
Alcohol usage history	+1	≥ 8 units per week

A HAS-BLED score of 3 or more indicates increased one year bleed risk on anticoagulation, sufficient to justify caution or more regular review (risk is for intracranial bleed, bleed requiring hospitalisation or haemoglobin drop >2g/dL or that needs transfusion.)