South West Cardiovascular Strategic Clinical Network

Non-vitamin K oral anticoagulants ('NOAC's)
for the prevention of stroke and systemic embolism in Atrial Fibrillation

This Network guidance is to inform prescribers and other healthcare professionals about the appropriate use of the newer non-vitamin K oral anticoagulants (NOACs: dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Lixiana®)) as ***options*** for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (AF). This is a new area of prescribing and this guidance sets out the main considerations and patient groups where these alternatives to warfarin may be useful.

NICE Technology Appraisals for the four licenced NOACs were issued in 2012-2015, and Guidelines for their use are contained within **NICE CG180 Atrial Fibrillation**, issued in 2014. The text for each NOAC is very similar. Note that the age limits mentioned in the guidance are risk factors rather than thresholds for treatment.

Dabigatran

(NICE Guidance TA249 issued March 2012)

Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:

- **previous stroke, transient ischaemic attack or systemic embolism**
- **left ventricular ejection fraction below 40%**
- **symptomatic heart failure (NYHA Class 2 or more)**
- **age 75 or older**
- **age 65 or older with one of the following: diabetes mellitus, coronary artery disease or hypertension**

Rivaroxaban

(NICE Guidance TA256 issued May 2012)

Rivaroxaban is recommended as an option for preventing stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more risk factors such as:

- **congestive heart failure**
- **hypertension**
- **age 75 or older**
- **diabetes mellitus**
- **prior stroke or transient ischaemic attack**

Apixaban

(NICE Guidance TA275 issued February 2013)

Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with 1 or more risk factors such as:

- **prior stroke or transient ischaemic attack**
- **age 75 or older**
- **hypertension**
- **diabetes mellitus**
- **symptomatic heart failure**

Edoxaban

(NICE Guidance TA355 issued September 2015)

Edoxaban is recommended, within its marketing authorisation, as an option for preventing stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors, including:

- **congestive heart failure**
- **hypertension**
- **diabetes**
- **prior stroke or transient ischaemic attack**
- **age 75 years or older**

The decision about whether to start treatment with a NOAC should be made after an informed discussion between the clinician and the person about the risks and benefits of the various anticoagulant options. For people who are taking warfarin, the potential risks and benefits of switching to a NOAC should be considered in light of their level of INR control *(see 'poor anticoagulant control' below).*

As always, each drug should be used according to the SPC for Dabigatran, Rivaroxaban, Apixaban, Edoxaban and warfarin.

Key things to consider when choosing between the available oral anticoagulant options are:

1. **Renal Function.**
   Dabigatran is contraindicated for people with creatinine clearance [CrCl, or the surrogate eGFR] <30 ml/min/ 1.73m^2, and the lower dose (110 mg BD) should be used in moderate renal impairment (CrCl 30-50) and for people aged over 80.
   Rivaroxaban is contraindicated for people with CrCl <15, and the dose should be reduced to 15 mg OD for people with CrCl 15-49.
   Apixaban is contraindicated for people with CrCl <15, and the dose should be reduced to 2.5 mg BD for people with CrCl 15-29, and for people aged ≥80 with serum creatinine >133 µmol/L or weight <60 kg. Apixaban is the preferred anticoagulant for patients with CrCl 30-50 in the NICE Chronic Kidney Disease guideline CG182.
   Edoxaban is contraindicated for people with CrCl <15, and the dose should be reduced to 30mg OD for people with CrCl between 15-50 or weight <60 kg.

With all the NOACs drug accumulation can occur with impaired renal function. Renal function should be checked prior to initiation and monitored when necessary, such as when other drugs with renal effects are introduced or altered, or with dehydration/vomiting/diarrhoea. Renal function should be monitored at least annually in patients over 75 years and in those with renal impairment. Liver function should be checked prior to initiating apixaban and edoxaban. As clinical experience accumulates, these requirements may be eased.

2. The efficacy and safety of the NOACs in people unable or unwilling (for whatever reason) to take warfarin, or in whom warfarin is relatively or absolutely contraindicated, have not been conclusively established. All patients in the principal published studies (n >70,000) were eligible to be randomized to warfarin. There are still only small amounts of data on the safety and efficacy of NAOCs in patients who have had previous serious bleeding or other adverse events with warfarin.
3. There is limited experience in the use of NOACs in patients for whom warfarin is considered too risky. The use of a stroke risk score such as CHA_2DS_2-VASc and the bleeding risk score HAS-BLED is recommended when making individualised assessments of the risks and benefits of anticoagulation, before then considering which anticoagulant to use.
4. Idarucizumab (Praxbind®) has recently been approved in the US and Europe for the emergency reversal of bleeding in association with dabigatran therapy. At present, there is no specific antidote for patients taking a factor Xa inhibitor who present with haemorrhage requiring emergency treatment. Advice on the management of haemorrhage or suspected overdose is included on Page 4.
5. As relatively new drugs, all the NOACs other than dabigatran carry a 'black triangle'. There are no long term effectiveness data for these drugs beyond the approximate 2 year average in the published trials, and post-marketing safety studies are in progress. Warfarin has over 50 years of accumulated clinical experience.
6. Dabigatran and apixaban are taken twice daily. Rivaroxaban, edoxaban and warfarin are taken once daily.
7. Dabigatran is not suitable for use with a compliance aid (e.g. blister pack) as the capsules are moisture sensitive and should not be stored outside their packaging.

There are 4 categories of people in which the NOACs may be a useful option:

1. People with AF not taking warfarin because of allergy or intolerance, or in circumstances where routine INR monitoring may be impractical (provided that monitoring of renal and/or liver function is still practicable).

2. People with AF currently taking warfarin who, despite evidence of good compliance with medication and monitoring, have poor anticoagulant control

This group represents a significant proportion of people with AF, most of whom are at a high risk of stroke without anticoagulation. Patients should be reviewed on an individual basis taking into consideration their time in the therapeutic range (TTR) on warfarin, to decide whether a NOAC would be an appropriate treatment option. Measures known to improve TTR (such as self-testing or self-management, using a NICE-recommended point-of-care device such as Coaguchek® or INRatio2 PT/INR®)may be the preferred option for some people rather than a switch to another agent.

Poor anticoagulant control is defined in the NICE AF Clinical Guideline CG180 as: two INRs above 5 or one INR above 8 in the last 6 months; or two INRs below 1.5 in the last 6 months; or a TTR <65% (calculated electronically or as a simple percentage of tests within the therapeutic range). NICE recommends that anticoagulant quality is reviewed at least annually.

3. People with AF at risk of drug interactions

A NOAC may be useful in some patients where concomitant medication increases the risk of interaction with warfarin. The main interactions of the NOACs are with P-gp inhibitors (e.g.: cyclosporine, dronedarone, the –romycins, the –conazoles) and P-gp inducers (e.g.: phenytoin, carbamazepine, phenobarbital, St John's Wort), when they should either be avoided or in some instances, have the dose reduced (always refer to the BNF). Where there is caution or uncertainty about the potential effect of an interaction, the ability to monitor and adjust the warfarin dose based on the INR may make it the preferable anticoagulant.

4. People with AF who have never taken warfarin

NICE guidance states that it is not reasonable to expect ***all*** patients to be tried on warfarin before a NOAC is considered. Patients are not obliged to have a trial of warfarin but prescribers may feel in consultation with their patient that a well established drug with which they have substantial experience may be a more appropriate choice.

Some people with AF have previously been recommended to take aspirin instead of warfarin based either on their risk assessment for stroke (using $CHADS_2$ or similar) or their risk of bleeding. For the former category, recent expert guidelines recommend that anticoagulation is considered for all people with AF over the age of 65, or those under the age of 65 with a CHA_2DS_2-VASc score of 1 or more*. For the latter category, there may be modifiable risk factors for bleeding identified using the HAS-BLED score that can be addressed such that anticoagulation can then be safely introduced.

The NICE AF clinical guideline no longer recommends the use of aspirin to prevent thromboembolic events in people with AF, and people taking aspirin solely for this indication should be reviewed as a matter of priority.

unless the score of 1 arises purely from female sex.

Decision-making Guide for Anticoagulation in Non-valvular Atrial Fibrillation

Person with AF
(paroxysmal, persistent or permanent)

Moderate-high risk of stroke:
Aged over 65
OR
Aged under 65 with CHA_2DS_2-VASc score ≥1

No → **'Truly low risk':**
No antithrombotic treatment
Review this decision annually and at age 65

Yes

Assess risk of bleeding → **Absolute contraindication to anticoagulation:**
No antithrombotic treatment
For some patients who could safely take aspirin long-term, referral for a Left Atrial Appendage Occlusion device is appropriate

Assess relative contraindications and cautions with anticoagulation using HAS-BLED score (0-9)

HAS-BLED <3
Still address any modifiable factors for bleeding e.g alcohol and/or BP reduction, concomitant medications etc.

HAS-BLED ≥3
Reduce bleeding risk by addressing any modifiable factors e.g alcohol and/or BP reduction, concomitant medications etc.

Recommend anticoagulation
(with warfarin, dabigatran, rivaroxaban, apixaban or edoxaban)

Note that at almost any level of HAS-BLED score, the benefits of anti-coagulation still outweigh the risks → **Unmodifiable high bleeding risk:**
No antithrombotic treatment
For some patients who could safely take aspirin long-term, referral for a Left Atrial Appendage Occlusion device is appropriate

CHA_2DS_2-VASc stroke risk score

C	Congestive Heart Failure/ LV dysfunction	1
H	Hypertension	1
A	Age ≥75 years	2
D	Diabetes mellitus	1
S	Stroke/TIA/previous embolism	2
V	Vascular disease (MI, PVD)	1
A	Age 65-74 years	1
Sc	Sex category: female	1

Maximum 9 points

HAS-BLED bleeding risk score

H	Hypertension (SBP>160)	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Previous Stroke	1
B	Bleeding history	1
L	Labile INRs (TTR <65%)	1
E	Elderly (aged >65)	1
D	Drugs (aspirin, NSAIDs) or alcohol abuse (1 point each)	1 or 2

Maximum 9 points

Warfarin may be the preferred option for those people with AF:

- Who are currently well controlled on warfarin
- Who have never taken an anticoagulant (after discussing risks and benefits with the patient)
- Who are at risk of drug interactions with a novel oral anticoagulant
- Who have a CrCl (eGFR) <30 ml/min/1.73m^2

Dabigatran, rivaroxaban, apixaban or edoxaban may be the preferred option for those people with AF:

- Who are not taking warfarin because of allergy or intolerance, or in circumstances where routine INR monitoring may be impractical (provided that monitoring of renal and liver function is still practicable)
- Who are currently taking warfarin but, despite evidence of good compliance with medication and monitoring, have poor anticoagulant control
- Who are at risk of drug interactions with warfarin
- Who have never taken an anticoagulant (after discussing risks and benefits with the patient)

What about people with AF who are currently well controlled on warfarin?

People with stable, good INR control (defined by NICE as an annual TTR of >65%) are much less likely to gain any clinical benefit by switching from warfarin to a NOAC. NICE guidance states that even people with very good control should not be refused a NOAC as a potential treatment option, but local expert opinion would be that this category would not be a priority for active switching.

Initiating treatment with a non-vitamin K oral anticoagulant (NOAC)

- The recommended daily dose of **dabigatran** is one 150 mg capsule twice daily. People aged 80 years or above should be treated with one 110 mg capsule twice daily due to the increased prevalence of renal impairment in this population. People who reach the age of 80 on dabigatran treatment should drop to the lower dose
- The recommended daily dose of **rivaroxaban** is one 20 mg tablet once daily. For people with CrCl of 15-49, 15 mg once daily should be given
- The recommended daily dose of **apixaban** is one 5 mg tablet twice daily. For people with CrCl of 15-29, or those aged ≥ 80 with serum creatinine >133 μmol/L or weight <60 kg, 2.5 mg twice daily should be given
- The recommended daily dose of **edoxaban** is one 60 mg tablet once daily. For people with CrCl of 15-50, or with weight <60 kg, or taking ciclosporin, dronedarone, erythromycin or ketoconazole, 30 mg once daily should be given
- When switching from warfarin, the drug should be stopped and the new anticoagulant initiated at the appropriate dose when the INR drops below 2.0 for dabigatran and apixaban, 2.5 for edoxaban or 3.0 for rivaroxaban

Patient education – prevention and management of bleeding

- Patients need to understand the benefits and risks of anticoagulation and the NOACs through fully informed decision making – a copy of this guidance may be appropriate for some patients
- **Patients should be advised to carry an appropriate anticoagulant alert card**. The current yellow NPSA Oral Anticoagulant Therapy card may be useful (a patient card is available for each NOAC), and patients and carers should have a copy of the relevant patient information leaflet
- Patients with AF and their carers should be taught to recognise the signs of a stroke (the FAST test, see http://www.nhs.uk/actfast/Pages/stroke.aspx) and the action to be taken if they spot them
- Patients should be advised that in the event of any haemorrhage or significant acute illness to OMIT their anticoagulant medication and seek urgent medical advice
- A forgotten 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, the missed dose should be omitted. No double doses should be taken
- A forgotten dose of rivaroxaban or edoxaban should be taken immediately and continued as normal the following day. No double doses should be taken
- A forgotten dose of apixaban should be taken immediately and then continued as normal with the next scheduled dose. No double doses should be taken
- Overdose: oral activated charcoal if within 2 hours of ingestion. Dabigatran can be dialysed

Assessment and hospital management of major bleeding (cerebral or GI)

- Determining the time since last dose of therapy is vital as interruption of treatment may be sufficient. The estimated time for restoration of haemostasis after cessation of therapeutic doses with adequate renal function is usually within 12 hours for dabigatran and apixaban, and 24 hours for rivaroxaban and edoxaban
- Initiate resuscitation with compression, IV fluids, blood transfusion and other supportive measures as necessary
- Check FBC, U&E's and a coagulation screen (PT, Thrombin Time and APTT). A normal Thrombin Time can be used to exclude any clinical relevant level of dabigatran. However, a normal PT or APTT cannot be used to rule out a therapeutic concentration of the factor Xa inhibitors rivaroxaban, apixaban or edoxaban
- **Antidotes**. An agent to rapidly reverse the anticoagulant effect of dabigatran (idarucizumab [Praxbind®] as a single 5g bolus injection) has recently been licenced and made available in the US and Europe. 4-factor prothrombin complex concentrate (PCC) reverses the effect of the factor Xa inhibitors in normal volunteers and should be considered (at a dose of 50 IU/kg), but there is very limited clinical experience with its use in patients taking new oral anticoagulants and this recommendation is based on limited data

Prior to emergency surgery	If possible, wait 12 hours (dabigatran) or 24 hours (rivaroxaban, apixaban and edoxaban) after the last dose
In the event of thrombosis	Wait 12 hours (dabigatran, apixaban) or 24 hours (rivaroxaban, edoxaban) after the last dose before switching to a parenteral anticoagulant

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