Lancashire & South Cumbria Medicines Management Group

NHS

Atrial Fibrillation Pathway

Pathway for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation

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Midlands and Lancashire CSU

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Version control

Version Number	Amendments made	Author	Date
1.0	N/A	SA	20/09/17
1.1	Addition of Guidelines for Antiplatelet/Anticoagulant Therapy for Primary and Secondary Prevention of Ischaemic Stroke and Transient Ischaemic Attack (TIA) as appendix 1	SA	16/07/18
1.2	Edoxaban promoted as first-line NOAC choice in-line with LMMG recommendation - December 2018. Other amendments as per NOAC steering group recommendations	SA	17/4/19
1.3	Amendments as per NOAC steering group recommendations. Updated references and addition of appendix. Title updated to give Atrial Fibrillation prominence.	SA	14/11/19

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Introduction

Non-valvular Atrial fibrillation (NVAF) is the most common cardiac arrhythmia and is a major cause of ischaemic stroke. Anticoagulation to reduce the risk of stroke is an essential part of NVAF management. NICE Guidance emphasises the importance of undertaking a stroke risk assessment for all patients with NVAF and anticoagulating, where safe and appropriate. All people with NVAF should be offered a personalised package of care which includes up-to-date, comprehensive information and practical advice on their anticoagulation in line with recommendations made in NICE CG144[1] and NICE CG180.[2]

There is a template available on EMIS to aid clinicians when prescribing oral anticoagulants in Primary Care.

Background

Estimates suggest that the prevalence of NVAF is increasing with current prevalence being estimated between 1.57% for known AF and 2.0% for the true prevalence.[3,4,5] The management of atrial fibrillation should aim to prevent complications, particularly stroke, and alleviate symptoms.

The availability of Non Vitamin K Oral Anticoagulants (NOACs), has led to a change in the management of stroke prevention in NVAF. Also there is greater understanding of how to manage warfarin, with the importance of the average time in therapeutic range (TTR) increasingly recognised.

This guidance does not override the individual responsibility of health professionals to make decisions when exercising their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. For full prescribing information please refer to the SPC for each drug.

DEFINITIONS

NOAC – Non Vitamin K Oral Anticoagulants
NVAF – AF in the absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis (usually of rheumatic origin)

Assessment of Patient: CHA_2DS_2VASc and HAS-BLED

Assess stroke risk using **$CHA_2DS_2VAS_c$** score in people with any of the following:

- symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
- atrial flutter
- a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm

Assess bleeding risk using **HAS-BLED**. Offer modification and monitoring of the following risk factors:

- uncontrolled hypertension
- poor control of international normalised ratio
- concurrent medication, for example aspirin or an NSAID
- harmful alcohol consumption

If the patient is male and $CHA_2DS_2VASc = 1$

Consider anticoagulation taking bleeding risk into account

If the patient is either male or female & $CHA_2DS_2VASc \geq 2$

Offer anticoagulation taking bleeding risk into account

- Discuss the risks & benefits of each stroke prevention strategy.
- NICE have produced a patient decision aid, available online: https://www.nice.org.uk/guidance/cg180/resources/patient-decision-aid-pdf-243734797
- Choice of anticoagulant should be based on clinical features & patient preference.

Warfarin has been used for over 60 years and has the advantages of allowing compliance to be measurable. In the case of major bleeding, anticoagulation can be reversed.

Whilst **NOACs** do not need INR monitoring, careful initiation and management is essential. There is no standard measure to assess compliance with NOACs and, as they have a relatively short half-life, **patient compliance is critical** as protection from stroke will be lost with omission of only one dose (in contrast to warfarin). Currently only dabigatran has an established antidote.

Annual stroke/VTE risk associated with CHA_2DS_2VASc	
CHA_2DS_2VASc	Annual event risk %
1	2.01
2	3.71
3	5.92
4	9.27
5	15.26
6	19.74
8	22.38
9	23.64

Annual risk of major bleed associated with HAS-BLED score		
HAS-BLED score	Annual bleed risk %	Annual bleed risk
0	1.1	Low
1	1.0	Moderate
2	1.9	High
3	3.7	High
4	8.7	High
5	12.5	High

Anticoagulant Choice

The decision to start treatment with an anticoagulant should be based on the patient's clinical features and preferences and made after an informed discussion between the clinician and the patient about the risks and benefits of warfarin compared with NOACs.

Local Recommendation:

When warfarin is not appropriate and a **NOAC** is then considered to be the most appropriate anticoagulant, **edoxaban is to be used first line for patients with NVAF unless there is a specific clinical reason not to do so**.

The reasons for using a particular anticoagulant should be documented

Warfarin is the least expensive and is the preferred option for those people with NVAF:

- Who have never taken an anticoagulant (after discussing risks and benefits with the patient)
- Who are at risk of drug interactions with a non-vitamin K oral anticoagulant
- Who have Grade 4 or higher (eGFR <30 ml/min/1.73m^2) chronic kidney disease[a]
- Who have no additional risk factors

Edoxaban is currently the least expensive, preferred first-line choice NOAC,[6] after informed consideration, for the following groups of NVAF patients at high risk of stroke

- Not able or prepared to take warfarin after informed consideration (document in notes).
- Poor INR control with warfarin despite good compliance.
- Suffered a stroke or systemic embolism whilst on warfarin despite good compliance.
- On multiple drug therapy with high risk of warfarin drug interactions.
- Taking regular blood samples presents a practical problem.
- Initiation by specialists for NVAF patients requiring rapid INR control.

NICE CG182 (2014) recommends **apixaban** in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more of the following risk factors:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure[7,8,9]

However, more recent evidence (2016-18) has shown that Edoxaban has a similar clinical profile to Apixaban in patients with eGFR of 30-50ml/min/1.73m^2 [10,11]

NVAF patients that can be well controlled on warfarin (i.e. Time in INR Treatment Range / TTR more than or equal to 65%) **are not locally recommended as priority candidates for the use of NOACs**. If a patient is found not to be in range then it is important to review the possible reasons e.g. poor compliance.

In these patients, the potential advantages of the NOACs vs warfarin are debateable. Therefore, the local recommendation is to adopt a cautious approach to the prescribing of this newer class of oral anticoagulants, whilst also supporting informed patient decision making.

[a] Patients with AF and CKD have an increased morbidity and mortality due to their excessive risk for both thromboembolic and severe bleeding events

Good medication compliance is as important with the NOACs as it is with warfarin, as missing a dose, or overdoses, will also have significant efficacy or safety implications.

A recent clinical trial has shown an increased risk of recurrent thrombotic events associated with rivaroxaban compared with warfarin, in patients with antiphospholipid syndrome and a history of thrombosis. Other direct-acting oral anticoagulants (NOACs) may be associated with a similarly increased risk. As a result the MHRA have issued the following advice:

- direct-acting oral anticoagulants (NOACs) are not recommended in patients with antiphospholipid syndrome, particularly high-risk patients (those who test positive for all 3 antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies)
- review whether continued treatment with a NOAC is appropriate for patients diagnosed with antiphospholipid syndrome, particularly high-risk patients, and consider switching to a vitamin K antagonist such as warfarin.[12]

Anticoagulant Initiation

It is IMPORTANT to:

- Record patient's age at initiation
- Record patient's weight at initiation and at least annually
- The following blood tests are required: FBC / U&Es/ LFTs/ Hb/ Platelets/ INR/PTT
- Renal function must be calculated prior to initiation and monitored when necessary e.g. when other drugs with renal effects are introduced or with dehydration/vomiting/ diarrhoea.

DOSE may need adjusting dependent on recorded age, weight and renal function

Which body weight to use when dosing NOACs

- For patients under 40kg and patients over 120kg NOACs should **not** be prescribed.
- For patients 40-120kg ACTUAL bodyweight should normally be used in the calculation unless:

The patient's actual bodyweight is within this range but is >120% of their ideal bodyweight. For such patients, individual risk factors should be considered when determining appropriate dosage. EMIS gives an estimated CrCl, using both the patient's actual and ideal bodyweight, allowing the clinician to use their clinical judgement in this situation.

Estimation of renal function

EMIS states that the Cockcroft -Gault equation may underestimate the creatinine clearance in overweight patients and caution should be used when NOAC dose adjustment is being considered (as there is a risk of under-coagulation). The Cockcroft-Gault equation may produce an estimation that is different to that calculated for eGFR.

EMIS have updated their system (April 2019) to align with manufacturer's letters of clarification, and evidence base from their clinical trials. Patients with an active prescription for Apixaban, Edoxaban and Rivaroxaban or an issue of the above within the last 3 months will have estimated creatinine clearance calculated using **actual** body weight. The manufacturer of Dabigatran advises use of ideal or adjusted body weight in overweight or obese patients. EMIS Web uses **ideal** body weight for patient's on Dabigatran

Use the Cockcroft-Gault formula to calculate eligibility for and dosing of the NOACs in patients with AF as follows:

$$\text{Estimated Creatinine Clearance in ml / minute} = \frac{(140-\text{age}) \times \text{Weight} \times \text{Constant}}{\text{Serum Creatinine}}$$

Weight = actual body weight (as detailed above)
Constant = 1.23 for men; 1.04 for women
Serum creatinine in micromole / litre

Routine monitoring

Patients require monitoring tests including haemoglobin, renal and liver function at one month after initiation and then at regular intervals usually annually or more often if a higher risk patient or they become unwell.

Testing frequency should be modified as follows:

- repeat all tests every 6 months if ≥75 years (especially if on dabigatran) or frail
- repeat renal function tests
  - annually if CrCl>60ml/min
  - 6 monthly if CrCl 30-60-ml/min
  - 1-3 monthly if CrCl 15-30 ml/min or has shown a decline since initiation.

Additional Information

- Reinforcing the bleeding risks associated with NOACs to patients will be important, to avoid patients becoming complacent with their anticoagulant dosing in the absence of the need for regular monitoring blood tests.
- The efficacy and safety of the NOACs in people in whom warfarin is relatively or absolutely contraindicated, has not been conclusively established.
- Rivaroxaban, edoxaban and apixaban (but NOT dabigatran) can be dispensed in standard monitored dosage system (MDS) compliance aids such as dosset boxes. (Special MDS containers are required for dabigatran capsules as they are moisture sensitive).
- Rivaroxaban doses of ≥15mg must be taken with food
- The NICE AF guidance (June 2014) no longer recommends the use of aspirin to prevent thromboembolic events in people with AF. People taking aspirin solely for this indication should be reviewed as a matter of priority.
- Patients should be advised to carry an appropriate anticoagulant alert card.

Dose reductions required / contraindications: NOACs – renal impairment, age, weight

Normal Adult Dose	Reduced Dose	Contraindication
Edoxaban 60mg od	30mg daily if CrCl 15-50 ml/min **or** weight < 60kg	Contraindicated if CrCl <15 ml/min **or** on dialysis
Apixaban 5mg bd	2.5mg bd if CrCl 15-29 ml/min **or** if at least two of the following : age ≥ 80 years; body weight, ≤ 60 kg; or serum creatinine ≥ 133 micromole/L.	Contraindicated if CrCl <15ml/min
Dabigatran 150mg bd	110mg bd if CrCl 30-50 ml/min and at high risk of bleeding **or** if >80 years	Contraindicated if CrCl <30 ml/min
Rivaroxaban 20mg od	15mg daily if CrCl 15-49 ml/min	Contraindicated if CrCl <15 ml/min

Management of Patients with non-valvular AF and Cardiovascular Disease

AF and stable vascular disease (i.e. no acute events or revascularization for >12 months, whether coronary or peripheral artery disease):

- The European Society of Cardiology ESC guidelines for the management of AF recommend that patients with stable vascular disease can be managed with oral anticoagulant (OAC) alone. In such stable patients, there is no need for concomitant aspirin, which could increase the risk of serious haemorrhage, including intracranial haemorrhage.[13]

AF and unstable cardiovascular disease (Acute Coronary Syndrome and/or PCI/stent procedure in the preceding year):

- It is expected that a cardiologist will advise on the most appropriate treatment strategy for this patient group.

- Data on triple therapy with OACs (when given at stroke prevention doses in AF patients) are limited. ESC Guidelines based on expert consensus opinion recommend a period of triple therapy is needed (OAC plus aspirin plus clopidogrel), followed by the combination: OAC plus single antiplatelet drug. After one year, management can be with OAC alone in stable patients. Combination therapy with any OAC and antiplatelets significantly increases the risk of bleeding.[13]

Other Stroke Prevention Strategies

In addition to the use of antiplatelets/anticoagulation for the primary and secondary prevention of stroke/TIA, other risk management strategies should also be considered e.g. Blood Pressure management, lipid modification, control of diabetes and lifestyle interventions:

- NICE CG181[14] (July 2014 / updated September 2016) Cardiovascular disease: risk assessment and reduction, including lipid modification covers lifestyle modifications as well as lipid modifications for the primary and secondary prevention of CVD

- Lifestyle advice and further drug treatments (including statins and BP management) for secondary prevention of stroke/TIA is available from NICE CKS[15]

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CONSIDERATIONS FOR PATIENTS STARTING NOACs

Write patient details or affix identification label

NHS number: **Date of Birth:**
Name:
Address:

Information		**Tick**
Reason for anticoagulation		
Mode of action of NOAC		
Monitoring	No need for routine monitoring Renal checks Reversal	
Tablets	Strengths Dosage regime	
NOAC administration		
Pharmacology	Half life Missed doses	
Compliance	Aids to help / drug storage	
Food and alcohol		
Blood tests	Initial Ongoing	
Drug interactions / Side effects		
Follow up/ monitoring arrangements		
Warnings	Over anticoagulation bleeding / bruising Re falls / injury Signs of stroke Signs of blood clot	
General Advice (if applicable)	Weight loss/gain Avoid contact sports Pregnancy	
Surgical / Dental Procedures		
Yellow treatment book, patient literature and medic alert card		

APPENDIX 1: USEFUL INFORMATION

Administration

Apixaban - (Eliquis) take with or without food.[16,17]
Dabigatran - (Pradaxa) with or without food. Swallow whole with a full glass of water.[18,19]
Edoxaban - (Lixiana) - Take with or without food.[20,21,22]
Rivaroxaban - (Xarelto) 15mg and 20mg **must** be taken with food.[23,24]

Missed Doses[25]

DOACs have a shorter half-life usually between 5-14 hours so although they act quickly their efficacy also reduces quickly and missed doses may result in more time without any anticoagulation and greater risk of thromboembolic complications. Compliance with these medications is vital as there is no monitoring of the patients' anticoagulation status.
Missed doses need to be addressed as follows:

- **Apixaban** - (Eliquis) Missed dose - may still be taken up to 6 hours prior to next scheduled dose. If within 6 hours, the dose should be omitted and then take the next scheduled dose. If the patient has taken a double dose – advise that the next scheduled dose should be omitted and treatment resumed in 24 hours as normal. If the patient is uncertain whether they have taken their dose, advise them not to take it and to resume with next scheduled dose (that is after 12 hours).
- **Dabigatran** - (Pradaxa) Missed dose - may still be taken up to 6 hours prior to next scheduled dose. If within 6 hours, the dose should be omitted and then take the next scheduled dose. If the patient has taken a double dose– advise that the next scheduled dose should be omitted and treatment resumed in 24 hours as normal. If the patient is uncertain whether they have taken their dose advise them not to take it and to resume with next scheduled dose (that is after 12 hours).
- **Edoxaban** - (Lixiana) Missed dose should be taken up to 12 hours prior to when next dose is due. If that is not possible, that dose should be omitted and next scheduled dose taken as normal. If the patient has taken a double dose – advise them that the next scheduled dose should be taken as normal the next day. If the person is uncertain whether they have taken their dose, advise them: When bleeding risk is low or thrombotic risk is high, to take another pill and then take the next scheduled dose taken as normal. When bleeding risk is high or thrombotic risk is low, to wait until the next scheduled dose.
- **Rivaroxaban** - (Xarelto) Missed dose should be taken up to 12 hours prior to when next dose is due. If that is not possible, that dose should be omitted and next scheduled dose taken as normal. If the patient has taken a double dose – advise them that the next scheduled dose should be taken as normal the next day. If the person is uncertain whether they have taken their dose, advise them: When bleeding risk is low or thrombotic risk is high, to take another pill and then take the next scheduled dose taken as normal. When bleeding risk is high or thrombotic risk is low, to wait until the next scheduled dose.

Summary of Recommendations for Switching To and From Edoxaban (Lixiana)[20,21,22]

Switching TO Edoxaban			Switching FROM Edoxaban		
From	**To**	**Recommendation**	**From**	**To**	**Recommendation**
Vitamin K Antagonist	**Edoxaban**	Discontinue the vitamin K antagonist and start edoxaban when the international normalised ratio (INR) is ≤ 2.5.	**Edoxaban**	**Vitamin K Antagonist**	There is a potential for inadequate anticoagulation during the transition from edoxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. **Oral option:** For patients currently on a 60 mg dose, administer an edoxaban dose of 30 mg once daily together with an appropriate VKA dose. For patients currently on a 30 mg dose (for one or more of the following clinical factors: moderate to severe renal impairment (CrCL 15 – 50 mL/min), low body weight, or use with certain P-gp inhibitors), administer an edoxaban dose of 15 mg once daily together with an appropriate VKA dose. Patients should not take a loading dose of VKA in order to promptly achieve a stable INR between 2 and 3. It is recommended to take into account the maintenance dose of VKA and if the patient was previously taking a VKA or to use valid INR driven VKA treatment algorithm, in accordance with local practice. Once an INR ≥ 2.0 is achieved, edoxaban should be discontinued. Most patients (85%) should be able to achieve an INR ≥ 2.0 within 14 days of concomitant administration of edoxaban and VKA. After 14 days it is recommended that edoxaban is discontinued and the VKA continued to be titrated to achieve an INR between 2 and 3. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least three times just before taking the daily dose of edoxaban to minimise the influence of edoxaban on INR measurements. Concomitant edoxaban and VKA can increase the INR post edoxaban dose by up to 46%.

					Parenteral option: Discontinue edoxaban and administer a parenteral anticoagulant and VKA at the time of the next scheduled edoxaban dose. Once a stable INR of ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued, and the VKA continued.
Dabigatran[a] Apixaban[b] Rivaroxaban[c]	**Edoxaban**	Discontinue dabigatran, rivaroxaban or apixaban and start edoxaban at the time of the next dose of the oral anticoagulant.	**Edoxaban**	**Dabigatran[a] Apixaban[b] Rivaroxaban[c]**	Discontinue edoxaban and start the non-VKA anticoagulant at the time of the next scheduled dose of edoxaban.
Parenteral anticoagulants	**Edoxaban**	These medicinal products should not be administered simultaneously. **Subcutaneous anticoagulant (i.e., LMWH, fondaparinux):** Discontinue subcutaneous anticoagulant and start edoxaban at the time of the next scheduled subcutaneous anticoagulant dose. **Intravenous unfractionated heparin (UFH):** Discontinue the infusion and start edoxaban 4 hours later.	**Edoxaban**	**Parenteral anticoagulants**	These agents should not be administered simultaneously. Discontinue edoxaban and start the parenteral anticoagulant at the time of the next scheduled dose of edoxaban.

Please note:

a. The SPC for Dabigatran only lists recommendations for switching to and from parenteral anticoagulants.
b. The SPC for Apixaban only lists recommendations for switching to and from parenteral anticoagulants and Vitamin K Antagonist therapy.
c. The SPC for Rivaroxaban only lists recommendations for switching to and from parenteral anticoagulants and Vitamin K Antagonist therapy.

Summary of Recommendations for Switching To and From Apixaban, Dabigatran and Rivaroxaban

Switching TO Apixaban, Dabigatran or Rivaroxaban			Switching FROM Apixaban, Dabigatran or Rivaroxaban		
From	**To**	**Recommendation**	**From**	**To**	**Recommendation**
Vitamin K Antagonist	**Apixaban, Dabigatran or Rivaroxaban**	Discontinue the Vitamin K Antagonist and measure the international normalised ratio (INR). •If the INR is less than 2, start treatment with chosen NOAC. •If the INR is between 2 and 2.5, start treatment with chosen NOAC the next day. •If the INR is greater than 2.5, wait until the person's INR has dropped to less than 2 before starting treatment with the chosen NOAC.	**Apixaban, Dabigatran or Rivaroxaban**	**Vitamin K Antagonist**	Start treatment with warfarin. Do not stop NOAC treatment. Prescribe warfarin and NOAC concomitantly until the person's INR is in the target range. The INR should be measured just before the person takes their next NOAC dose. Once the INR is in the target range, stop treatment with the NOAC. After treatment with the NOAC has stopped: •Measure the INR after 24 hours to ensure adequate anticoagulation. •Monitor the person's INR closely (e.g. once a week) in the first month of warfarin treatment until the person has three consecutive stable INR values (e.g. between 2–3).
Apixaban, Dabigatran or Rivaroxaban	**Apixaban, Dabigatran or Rivaroxaban**	Stop treatment with current NOAC and start treatment with alternative NOAC when the next dose of current NOAC is due	**Apixaban, Dabigatran or Rivaroxaban**	**Apixaban, Dabigatran or Rivaroxaban**	Stop treatment with current NOAC and start treatment with alternative NOAC when the next dose of current NOAC is due

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[15] National Institute for Health and Care Excellence Clinical Knowledge Summary Stroke and TIA http://cks.nice.org.uk/stroke-and-tia#!topicsummary accessed 1/3/18

[16] Eliquis 2.5 mg film-coated tablets SPC https://www.medicines.org.uk/emc/product/4756/smpc

[17] Eliquis 5 mg film-coated tablets SPC https://www.medicines.org.uk/emc/product/2878/smpc

[18] Pradaxa 110 mg hard capsules SPC https://www.medicines.org.uk/emc/product/6229/smpc

[19] Pradaxa 150 mg hard capsules SPC https://www.medicines.org.uk/emc/product/4703/smpc

[20] Lixiana 15mg Film-Coated Tablets SPC https://www.medicines.org.uk/emc/product/6907/smpc

[21] Lixiana 30mg Film-Coated Tablets SPC https://www.medicines.org.uk/emc/product/6906/smpc

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