DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

Management of Non-valvular Atrial Fibrillation

- Guidelines for anticoagulation apply to paroxysmal, persistent and permanent AF and atrial flutter. Do not use this guideline for patients with significant structural heart disease, congenital heart disease or cardiomyopathy.
- Do not offer aspirin or clopidogrel monotherapy solely for stroke prevention to patients with AF. Anticoagulation should be the treatment of choice to reduce the risk of strokes.
- Continue treatment for existing patients who are currently stabilised and well controlled on anticoagulation for stroke prevention.
- The majority of patients with AF should be offered rate control.
- In people with atrial fibrillation presenting acutely with suspected concomitant acute decompensated heart failure, seek senior specialist input on the use of beta-blockers and do not use calcium-channel blockers.
- Perform a 12- lead ECG in all patients, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected
- Do not routinely do an echo if the decision to initiate anticoagulation has already been made unless there is another indication (e.g. murmur or LVSD suspected).
- The GRASP-AF tool can be run on GP clinical systems and used to identify patients at risk of stroke
- CHA_2DS_2-VASc score is the preferred tool for the assessment of stroke risk.
- Use ORBIT bleeding risk score in all AF patients to assess bleeding risk, if available on clinical systems. (Where ORBIT is not available, HAS-BLED may be used to assess bleeding risk). Modifiable factors that reduce risk should be addressed.
- Discuss the results of the assessments of stroke and bleeding risk with the person taking into account their specific characteristics, for example comorbidities, and their individual preferences.
- For most patients the benefit of anticoagulation outweighs the bleeding risk.
  Do not withhold anticoagulation solely because of a person's age or their risk of falls.
- For people with an increased risk of bleeding, the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important.
- In most cases there is no immediate need for anticoagulation and clinicians should allow the patient some reflective time before a decision is made.
- Where a NOAC is considered to be the most appropriate anticoagulant, edoxaban is to be used 1st line for patients with NVAF unless there is a specific clinical reason not to do so.
- Doses should be selected with care when initiating treatment with a NOAC and should be reviewed on an annual basis.
- Poor compliance with warfarin does not equate to good compliance with a NOAC. NOACs have a relatively short half-life, so poor compliance will result in uncontrolled anticoagulation.

- Available ‘real world’ data suggest variable adherence to NOAC intake from 38% to 99% depending on the setting and definition. Patient education on the need for oral anticoagulation therapy and the importance of strict adherence is important (ref EHJ)
- Refer patients promptly at any stage if treatment fails to control the symptoms of AF and more specialised management is needed. NICE define promptly as within four weeks of failed treatment.
- Amiodarone is for initiation by the consultant or specialist only. Duration of treatment should be specified. Do not offer amiodarone for long-term rate control. Amiodarone should only be used as an interim therapy and should not usually be taken for longer than 12 months.

Document Update	Date
p.18 monitoring clarified	Feb 2022
Insert advice regarding using CrCl calculator embedded in GP clinical system	April 2022
p.17 Clarify advice on edoxaban for patients with high CrCl	May 2022
Update renal advice for edoxaban, link to PCCS resource	Feb 2023
MHRA drug safety on DOAC- reminder of dose adjustments in renal impairment	June 2023
Pg 8 & 16: update advice regarding using the embedded calculator in SystmOne	Oct 2023

Contents **Page no.**

1. Abbreviations

ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body Mass Index
Cr	Creatinine
CrCl	Creatinine Clearance
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
ECG	Electrocardiogram
HF	Heart Failure
INR	International Normalised Ratio
LFT	Liver Function Test
LVSD	Left Ventricular Systolic Dysfunction
MI	Myocardial Infarction
NOAC	Non-vitamin K antagonist oral anticoagulants (apixaban, dabigatran, rivaroxaban , edoxaban)
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PDA	Patient Decision Aid
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TIA	Transient Ischaemic Attack
TTR	Time in Therapeutic Range
ULN	Upper Limit of Normal

2. Definitions

Acute onset	Onset within the previous 48 hours
Atrial flutter	Abnormal heart rhythm that occurs in the atria of the heart. This condition is initially managed by secondary care. Atrial flutter and atrial fibrillation have similar goals, including rate control, prevention of recurrent episodes and prevention of thromboembolism. But the method of restoration of sinus rhythm the pharmacological management of atrial flutter and AF are very different, as atrial flutter responds better to electrical cardioversion, and antiarrhythmic drugs are only modestly effective. Patients with atrial flutter should be given antithrombotic therapy in the same manner as those with atrial fibrillation
Consider	Defined as an intervention which will do more good than harm for most patients and be cost effective, but other options may be similarly cost effective
Labile INR	Refers to unstable/high INRs or poor time in therapeutic range (e.g. TTR <60% when using the HASBLED calculator)
Major bleed	NICE uses trials with different diagnostic criteria of major bleed e.g. haemoglobin of 2g/dL or more over 24h, transfusion of 2 units or more, bleeding that occurs in a critical site (including intracranial, intraspinal etc.) or bleeding that is fatal.
Offer	Defined as an intervention which will do more good than harm and be cost effective
Paroxysmal AF	AF which spontaneously terminates within 7 days, usually within 48 hours
Permanent AF	Persistent or long-standing persistent atrial fibrillation in which a decision has been made not to try to restore normal sinus rhythm by any means
Persistent AF	AF which persists for more than 7 days
Pill-in-the-pocket strategy	Defined as the person managing paroxysmal AF themselves by taking antiarrhythmic drugs only when an episode of AF starts.
Valvular AF	AF in the presence of mechanical prosthetic heart valve or moderate to severe rheumatic mitral valve disease.
Non-valvular AF	All other AFs are non-valvular

NICE definition

Consider	an intervention which will do more good than harm for **most** patients and be cost effective, but other options may be similarly cost effective
Offer	an intervention which will do more good than harm and be cost effective

3. Introduction

Atrial fibrillation (AF) affects about 1.2% of the population in the United Kingdom and accounts for about a sixth of all strokes. AF is the most common sustained cardiac arrhythmia and if left untreated AF is a significant risk for stroke and other morbidities. Men are more commonly affected than women and the prevalence increases steeply with age, from 0.5% of those aged 50-59 years to 10% of those over 80. The aim of treatment is to prevent complications, particularly stroke and alleviate symptoms.

4. Aim

The aim of this policy is to support prescribers in identifying and managing appropriate patients with AF for whom anticoagulation (with warfarin or a non-vitamin K antagonist oral anticoagulants (NOAC)) would be an effective and cost effective treatment for reducing stroke risk in non-valvular AF. Recommendations are based on NICE NG196[1].

5. Diagnosis and investigations

Look for AF by OPPORTUNISTIC CASE FINDING[$]

Take the pulse of those people presenting with any of the following:

- Breathlessness/dyspnoea
- Palpitations
- Syncope/dizziness
- Chest discomfort
- Stroke/transient ischaemic attack

Do not screen asymptomatic population for AF (evidence shows no benefit)
AF may also be detected as an incidental finding on clinical examination

↓

Irregular pulse detected: AF suspected: Do 12-lead ECG

Where **paroxysmal AF** suspected but undetected by 12-lead ECG, undertake a 24 hour ambulatory ECG if asymptomatic episodes are suspected or symptomatic episodes are less than 24 hours apart.
Use an ambulatory ECG monitor for a period appropriate to detect AF if symptomatic episodes are more than 24 hours apart

↓

ECG confirms AF or Flutter

Personalised package of care	Rate or rhythm control	Stroke prevention/ bleeding risk assessment	Bloods? Echo? Referral?

Patients with AF should be offered a **personalised package of care** which should include:
• Stroke awareness and measures to prevent stroke.
• Rate control.
• Assessment of symptoms for rhythm control.
• Who to contact for advice if needed
• Psychological support if needed.
• Up-to-date and comprehensive education and information on:
  ○ Cause, effects and possible complications of AF.
  ○ Management of rate and rhythm control.
  ○ Anticoagulation.
  ○ Practical advice on anticoagulation.
  ○ Support networks.
 	
Ensure that the package of care is documented and delivered.
	Rate control is the treatment of choice for the majority of patients.	Assess stroke risk using **CHA_2DS_2-VASc**
		
		and
		
		Assess bleeding risk using **ORBIT** bleeding risk score (or HAS-BLED if ORBIT unavailable)
			Bloods: NICE do not recommend any specific blood tests. Most clinicians would check FBC, renal and thyroid function as a minimum. Consider lipid profile to assess CV risk
			
			Echo: Do NOT routinely do echo. Do echo only if result will change management. Examples where echo is indicated include – left ventricular systolic dysfunction, mitral valve disease, or murmur, organise an echo if these are suspected.
			
			Referral to specialist: routine referral not needed. Refer promptly if treatment fails to control symptoms.
			
			(Prompt referral is defined as no longer than 4 weeks after the final failed treatment or no longer than 4 weeks if AF recurs after cardioversion and further specialise management is needed)

$ KardiaMobile (AliveCor) Heart Monitor is a pocket-sized ECG recorder which records rhythm and can identify paroxysmal AF. It may be a useful tool to investigate irregular pulse where a full ECG is not available immediately. However, it does not replace 12 lead or continuous ECG. See NICE MTG64.

6. Risk assessment for anticoagulation

Stroke and bleeding risk should be assessed in all patients with AF. Use CHA_2DS_2-VASc score to assess stroke risk and the ORBIT bleeding risk score (if available on clinical systems) or HAS-BLED to assess the risk of bleeding in patients who are starting or have started an anticoagulant.

The decision to stop anticoagulation should be made based on a reassessment of stroke and bleeding risk using CHA2DS2-VASc and ORBIT or HAS-BLED and following a discussion of the person's preferences. Do not stop anticoagulation solely because atrial fibrillation is no longer detectable.

Use $CHA_2D_2S_2$-VASc to assess stroke risk

NICE recommend the use of CHA_2DS_2-VASc to assess the risk of stroke in people with:

- Symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
- Atrial flutter
- A continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm (cardiologist decision or CHADSVASC≥2) or catheter ablation

CHA_2DS_2-VASc items	CHA_2DS_2-VASc Score Max. score = 9
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes	1
Stroke or TIA	2
Vascular disease *(prior MI, peripheral artery disease, aortic plaque)*	1
Age 65-74	1
Sex category (female)	1

(See appendix 7 CHA2DS2-VASc score and stroke risk table)

Use ORBIT or HAS-BLED to assess bleeding risk

Use the ORBIT bleeding risk score (if available on the clinical systems) 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
- Poor control of INR ("Labile INR")
- Concurrent medication, e.g. concomitant use of aspirin or other antiplatelets or a NSAID or SSRI.
- Harmful alcohol consumption
- Reversible causes of anaemia.

ORBIT bleeding risk score	ORBIT Score of ≥ 4 suggests high risk Max. score = 7
Age ≥75	1
Reduced Haemoglobin/Reduced Haematocrit/Anaemia • Male: Hb <13 mg/dL; Hct: <40% • Female: Hb <12 mg/dL; Hct: <30% Females or • History of anaemia	2
Bleeding History	2
Insufficient renal function eGFR <60mg/dL/1.73m²	1
Treatment with Anti-platelet agents	1

ORBIT Score	Risk group	Bleeds per 100 patient-years
0-2	Low	2.4
3	Medium	4.7
4-7	High	8.1

Where ORBIT is not available, HAS-BLED may be used to assess bleeding risk

HAS-BLED **bleeding score** Max. score = 9 (**score of ≥ 3 suggests high risk**)	
Hypertension (systolic BP >160mmHg)	1
Abnormal liver function (hepatic derangement- bilirubin >2 xULN and AST/ALP or ALP > 3 xULN)	1
Abnormal renal function (serum Creatinine ≥200micromol/, Dialysis, transplant)	1
Stroke	1
Bleeding tendency (previous bleeding history and/or predisposition to bleeding, e.g. anaemia)	1
Labile INR (Unstable/high INRs, Time in Therapeutic Range < 60%)	1
Elderly (>65yrs) e.g., age > 65 years, frail condition	1
Drugs (concomitant use of drugs such as antiplatelet agents, NSAID etc.)	1
Alcohol (alcohol abuse)	1

CHA_2DS_2-VASc = 0 (Men)

CHA_2DS_2-VASc =1 (Women)

No ANTITHROMBOTICS

Reassess risks (stroke risk, bleeding risk) **annually**
Do not offer aspirin (or any other drug) for stroke prevention to people aged under 65 years with no risk factors other than their sex

Review patients not taking any anticoagulants when they reach age of 65 or if they develop any of the following at any age:

- Diabetes
- HF
- Peripheral arterial disease
- Coronary heart disease
- Stroke, TIA or systemic thromboembolism

CHA_2DS_2-VASc =1 (Men)

Consider **anticoagulation –NOAC**
Bearing in mind bleeding risk

Offer vitamin K antagonist if NOAC are contraindicated, not tolerated or not suitable
If anticoagulation not indicated offer **no** antithrombotic treatment

Discuss the options for anticoagulation with the patient, base the choice on their clinical features and preferences. Edoxaban is to be used 1st line for patients with NVAF unless there is a specific clinical reason not to do so

CHA_2DS_2-VASc ≥ 2 (Men and women)

Offer **anticoagulants - NOAC**
Taking bleeding risk into account

Offer vitamin K antagonist if NOAC are contraindicated, not tolerated or not suitable

Discuss the options for anticoagulation with the patient, base the choice on their clinical features and preferences. Edoxaban is to be used 1st line for patients with NVAF unless there is a specific clinical reason not to do so

Do not offer aspirin (or clopidogrel) monotherapy solely for stroke prevention to people with AF

Annual review for all patients (see also appendix 1)
Re-assess stroke risk and bleeding risk (If on warfarin assess time in therapeutic range; If on a NOAC assess compliance)

7. Considering or offering an anticoagulant

NICE recommend when discussing the benefits and risks of anticoagulation, explain that:

- For most patients the benefit of anticoagulation outweighs the bleeding risk
- For people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk and careful monitoring of bleeding risk is important.
- Do not withhold anticoagulation solely because the person is at risk of having a fall
- Do not offer aspirin (or clopidogrel) monotherapy solely for stroke prevention to people with AF.
- If *considering* or *offering* anticoagulation, offer a NOAC. Edoxaban is to be used 1st line for patients with NVAF unless there is a specific clinical reason not to do so. Where a NOAC is contraindicated, not tolerated or not suitable in people with atrial fibrillation, offer a vitamin K antagonist. The clinician should discuss the options for anticoagulation with the patient and drug choice should take into account clinical features, preferences and bleeding risk.

8. Choice of anticoagulant

The choice of anticoagulant in AF should be made with the patient and is dependent upon clinical features and preferences. The risks and benefits of the treatment options should be presented to the patient in an easily understandable and unbiased manner.

The NOACs edoxaban, apixaban, dabigatran and rivaroxaban have not been directly compared in the same clinical trials, so it is not possible to say which one is better. They share some of the same advantages and disadvantages compared to warfarin, but because they work slightly differently, they also have some unique characteristics that make them better suited for different types of patients.

Where a NOAC is considered to be the most appropriate anticoagulant, the following order should be considered for patients with NVAF unless there is a specific clinical reason not to do so:.

1. Edoxaban*
2. Rivaroxaban*
3. Apixaban* & Dabigatran

*subject to national procurement process

Detailed prescribing information for NOACs can be found in appendix 6

For adults with atrial fibrillation who are already taking a vitamin K antagonist and are stable, continue with their current medication and discuss the option of switching treatment at their next routine appointment, taking into account the person's time in therapeutic range.

Key points:

NOAC

- ✓ No requirement for INR monitoring.
- ✓ Provide immediate anticoagulant effect (time to peak effect ranges from 1-4 hours).
- ✓ Currently have no known food interactions.
- ✓ Reduced risk of intracerebral bleeds versus warfarin (see p17 for further details)
- X NOACs have shorter half-life and missed doses may result in more time without any anticoagulation and greater risk of thromboembolic complications.
- X Adherence can be a challenge for patients managing anticoagulants
- X Each NOAC has a higher acquisition cost than warfarin.
- X Limited evidence on the reversal of the anticoagulant effects of the drugs.
- X Renal function should be assessed and monitored using Cockcroft and Gault formula to calculate the CrCL, especially in patients with extreme BMI.
- X In patients weight >120kg or BMI >40 kg/m^2 warfarin is locally recommended ahead of NOAC because there are limited clinical data available for patients at the extreme of weight. Consult with specialist if in doubt.
- X Require baseline tests and on-going monitoring (see appendix 6)

For all patients being considered for treatment with NOACs use the Cockcroft and Gault formula to calculate the Creatinine Clearance (CrCl).

Cockcroft and Gault formula:

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

- Age (years)
- *Weight (Kg) (see p16-17 for further details of when to use IBW and ABW)
- Serum Creatinine (micromol/litre),
- Constant 1.23 for men; 1.04 for women

For practical purposes when calculating CrCl for NOAC dosing, many clinicians use the embedded calculator in the GP clinical system. If using the embedded calculator in SystmOne, ensure the creatine clearance using actual body weight is used. NB. It is very important to ensure that up-to-date weight & creatinine are used.

There are **no** published clinical trials that directly compare the NOACs against each other. See Detailed prescribing information in appendix 6.

When a decision has been made to prescribe an anticoagulant, certain patient factors may help guide treatment choice.

Those treated with NOACs should carry an anticoagulation card www.NOACforAF.eu

Warfarin (See local anticoagulation guidance for further information)

- ✓ vitamin K antagonist can be offered if NOACs are contraindicated, not tolerated or not suitable
- ✓ Reduced risk of GI bleed compared to NOAC – dabigatran, edoxaban and rivaroxaban.
- ✓ Patients with AF in the presence of mechanical prosthetic heart valve or moderate to severe rheumatic mitral valve disease should be treated **only** with warfarin **not** a NOAC.
- ✓ Clearance of warfarin is not affected by renal function.
- ✓ The benefits of NOACs over warfarin declines as the TTR on warfarin increases.
- ✓ Effective and familiar use of antidote with vitamin K should a severe bleed occur.
- ✓ INR gives clinicians a guide to patient compliance.
- ✓ Clinicians may choose to use warfarin in patients for whom the ability to readily and objectively monitor the extent of anticoagulation is paramount.
- ✓ For patients with poor adherence, the long time to onset and offset of action, maybe advantageous as the anticoagulant effect of warfarin will persist for days after the last dose.
- X Warfarin - time to peak effect ranges from 3-5 days and a half-life averaging 40 hours.
- X Warfarin is known to interact with certain foods e.g. cranberry, alcohol and other foods containing high amounts of vitamin K.
- X Patients may have difficulty around complying with or accessing INR monitoring.

Reports of calciphylaxis, a very rare but serious condition causing vascular calcification and skin necrosis have been reported to the MHRA. The mortality rate is high. Patients should consult their doctor if they develop a painful skin rash. See MHRA, July 2016.

Anticoagulation control for existing patients on Warfarin

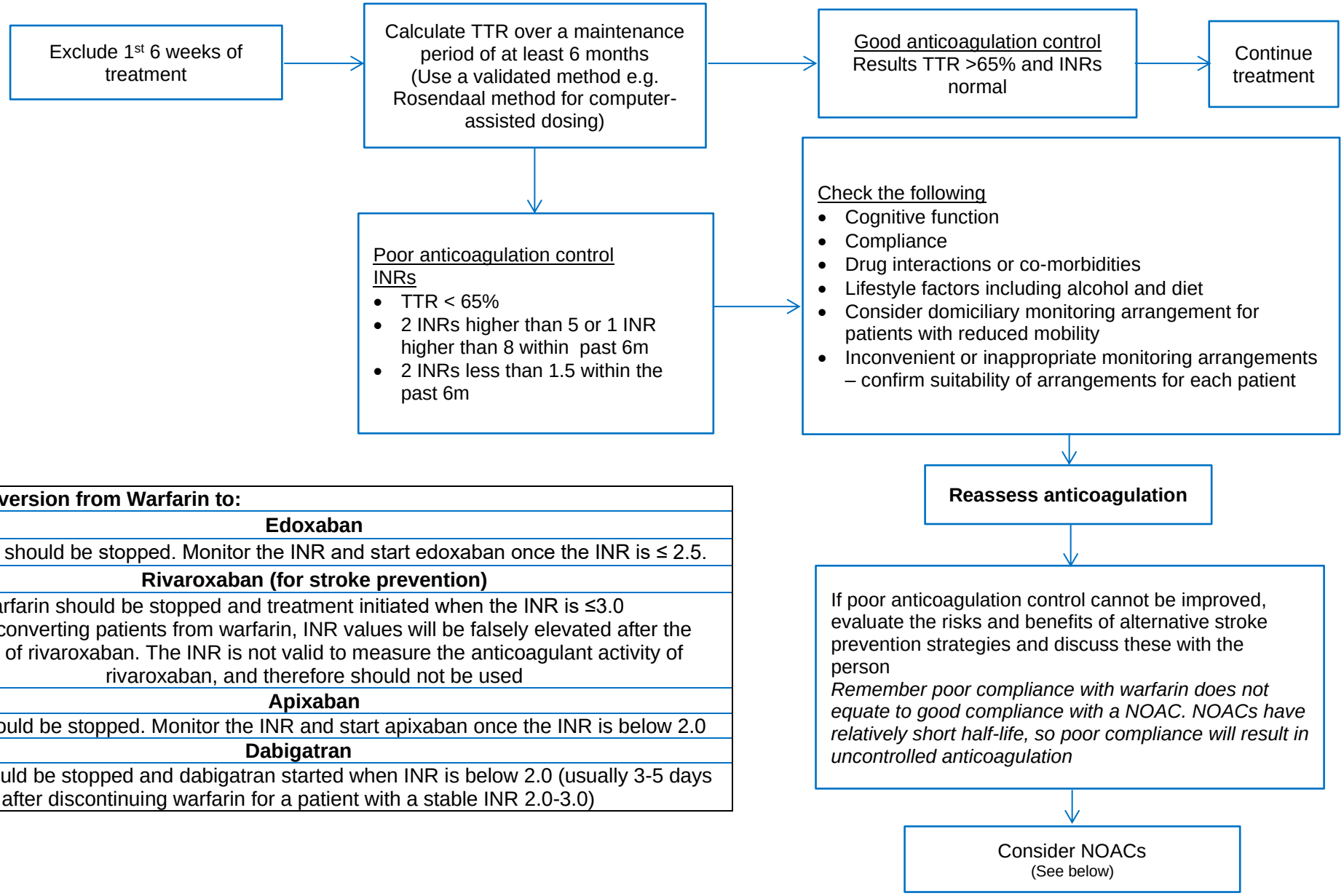


Table 1: Conversion from Warfarin to:
Edoxaban
Warfarin should be stopped. Monitor the INR and start edoxaban once the INR is ≤ 2.5.
Rivaroxaban (for stroke prevention)
Warfarin should be stopped and treatment initiated when the INR is ≤3.0 When converting patients from warfarin, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used
Apixaban
Warfarin should be stopped. Monitor the INR and start apixaban once the INR is below 2.0
Dabigatran
Warfarin should be stopped and dabigatran started when INR is below 2.0 (usually 3-5 days after discontinuing warfarin for a patient with a stable INR 2.0-3.0)

Considerations when choosing oral anticoagulation agent

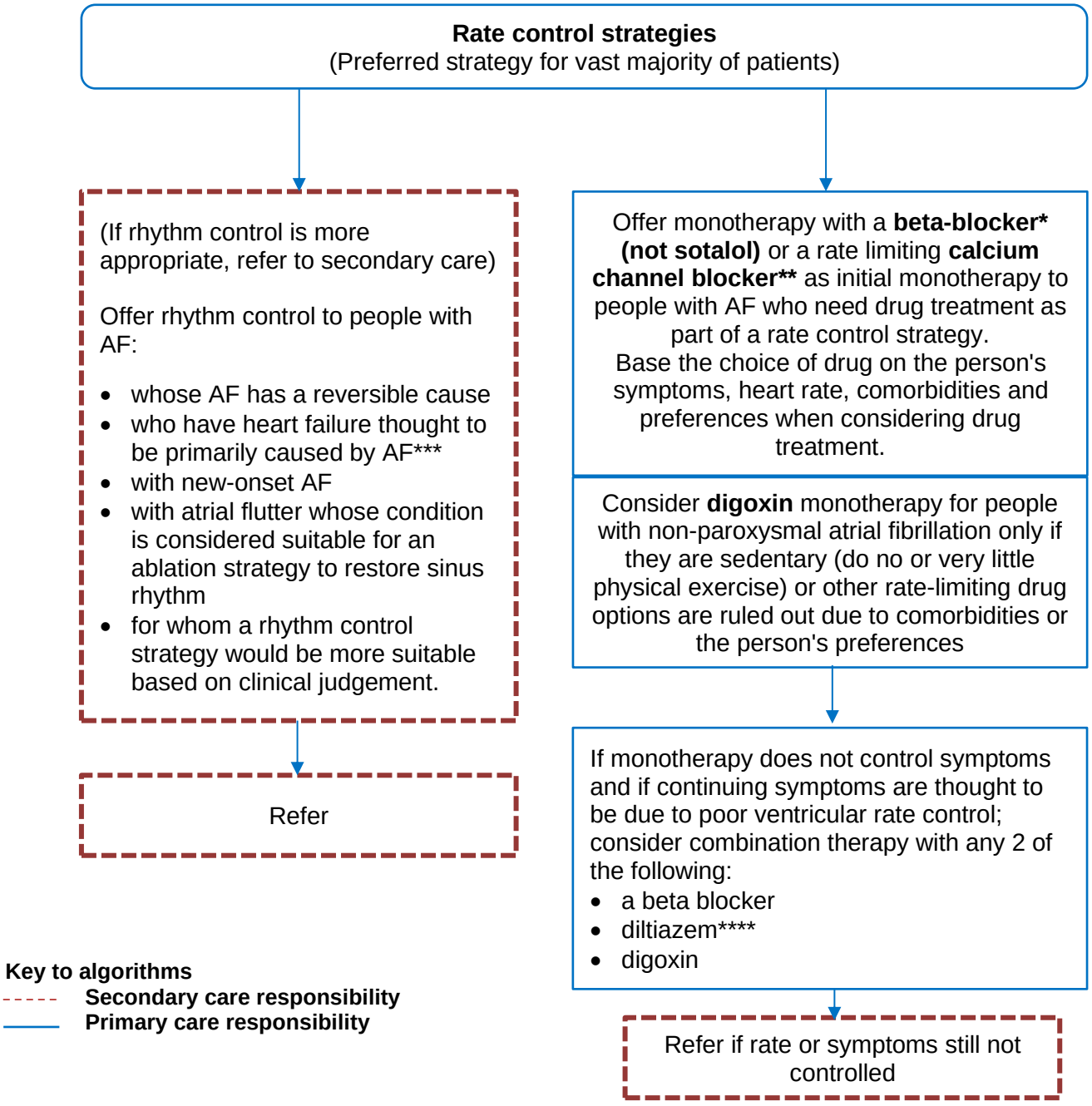
Once daily regime preferred?(consider concordance, reliant on carers/ nursing visits)	Y	**Preferred option:** edoxaban (rivaroxaban is also taken once daily) or warfarin **Edoxaban** - can be given as a single dose **Rivaroxaban[2]** – can be given as a single dose with food **Warfarin** – although given as a single dose, it may be necessary to give several tablets dependant on dose
Does the patient require medication in a compliance aid?	Y	**Preferred option:** Edoxaban (rivaroxaban, apixaban or possibly warfarin are also choices) **Edoxaban** - no special storage requirement. Stable outside of original packaging for 3 months at 40° and 75% relative humidity (personal communication with company) **Rivaroxaban[3]** - no special storage requirement, can be used in compliance aid **Apixaban[3]** - no special storage requirement, can be used in compliance aid ***Warfarin*** *- if risk assessment has been undertaken and a management plan is in place to manage dosage changes.* *Note: Dabigatran is sensitive to moisture not suitable for compliance aid.*
Does the patient have swallowing difficulties or a gastric tube?	Y	**Preferred option:** Edoxaban (rivaroxaban, apixaban are also choices) **Edoxaban** Swallowing difficulties[5] The tablets can be crushed and mixed with water or apple sauce for administration Enteral tubes[5] The tablets can be crushed and mixed with water for administration **Rivaroxaban** Swallowing difficulties May be crushed and mixed with water or apple puree immediately prior to use and administered orally Gastric tube[4,5] May be given through a nasogastric or PEG tube, after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. (Rivaroxaban should not be administered through feeding tubes which do not terminate in the stomach. For example this would include NJ, PEJ AND PEGJ tubes) **Apixaban** Swallowing difficulties Tablets can be crushed and dispersed in water, glucose 5%, apple juice, or apple puree. Take care to ensure the whole dose is administered. Enteral tubes Tablets can be crushed and dispersed in water or in glucose 5% for administration. Licensed for administration through nasogastric tubes. Take care to ensure the whole dose is administered, and flush well after each dose. *Note: Dabigatran capsules must not be opened as it results in a substantial increase in drug bioavailability (+75%)*
Is the patient likely to miss doses?	Y	**Preferred option:** Warfarin unless compliance aid helps (Edoxaban first choice, rivaroxaban and apixaban are suitable for compliance aids) **Warfarin** Patients with poor concordance may be at a greater risk of thromboembolic complications with NOACs as the shorter half-lives of these agents compared to warfarin will potentially result in more time without any degree of anticoagulation if a dose is missed
Is the patient needle phobic?	Y	**NOACs-**Although there is no need for regular blood tests to monitor INR, people taking NOACs still require regular follow-up. When initiating treatment baseline tests need to be performed and patients monitored on a regular basis at least annually (see appendix 6) however less than with warfarin. **Warfarin –** requires frequent monitoring at least 3 monthly (note near patient testing only requires capillary blood)
Does the patient have BMI>40kg/m^2 or weight >120kg?	Y	**Preferred option-** Warfarin (local recommendation) Consult with specialist if in doubt

9. Treatment of arrhythmia

a. Rate control strategies

Offer rate control as the first-line strategy to people with AF, except in people:

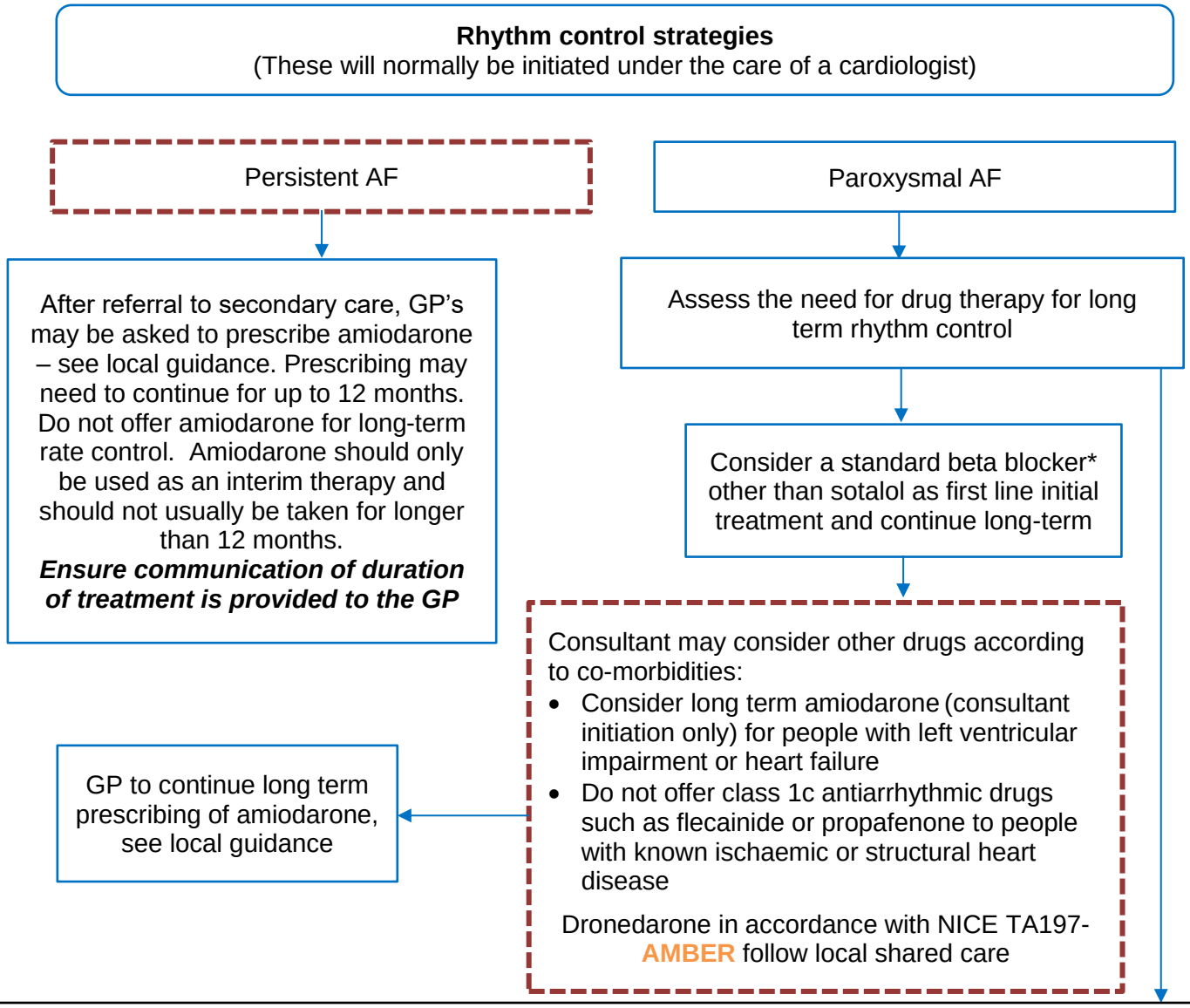
- whose AF has a reversible cause
- who have heart failure thought to be primarily caused by AF
- with new-onset AF
- with atrial flutter whose condition is considered suitable for ablation strategy to restore sinus rhythm
- for whom a rhythm control strategy would be more suitable based on clinical judgement



*Beta-blockers licensed to treat AF: atenolol, acebutolol, metoprolol, nadolol, oxprenolol, propranolol. Locally bisoprolol is also routinely used for AF patients.
**Calcium channel blocker: diltiazem (unlicensed indication and need to obtain and document informed consent) or verapamil
***For people with atrial fibrillation and concomitant heart failure, follow the recommendations in NICE's guideline on chronic heart failure.
****Unlicensed indication

b. Rhythm control strategies

Consider pharmacological and/or electrical rhythm control for people whose symptoms continue after heart rate has been controlled or if a rate control strategy was not successful.



Pill in the pocket strategy will be decided after cardiologist's assessment and communicated to primary care clinicians who may provide on-going supplies. (E.g. flecainide dose 200- 300mg one stat dose)
'Pill-in-the-pocket' should be considered and discussed with the patient when:

- they have infrequent paroxysms and few symptoms
- symptoms are induced by known precipitants (such as alcohol, caffeine)

In patients with paroxysmal atrial fibrillation, a 'pill-in-the-pocket' strategy should be considered for those who:

- have no history of left ventricular dysfunction (confirmed through echo) or valvular or ischaemic heart disease *and*
- have a history of infrequent symptomatic episodes of paroxysmal atrial fibrillation *and*
- have a systolic blood pressure greater than 100 mmHg and a resting heart rate above 70 bpm *and*
- are able to understand how to, and when to take the medication

There is no definition of the frequency of paroxysmal AF. NICE do state:
"*Therapy for paroxysmal AF should be tailored to the patient. For example, episodes of AF for 1 to 2 minutes once a year or for 10 hours twice a day are both paroxysmal AF, but their impact on the patient's quality of life, if symptomatic, would be quite different. In patients with infrequent and brief paroxysms, the regular use of antiarrhythmic therapy may not be necessary (and is commonly not prescribed in current clinical practice). Such patients may be suitable for the pill-in-the-pocket approach. However, for infrequent but protracted and symptomatic paroxysmal AF, rapid cardioversion of each event and/or antiarrhythmic drug prophylaxis may be considered*."

From this they concluded "where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket 'strategy should be considered and discussed with the person."

10. References

1. Atrial fibrillation: diagnosis and management, NICE Guideline NG196, updated 10/06/21, accessed 28/06/21, https://www.nice.org.uk/guidance/ng196
2. SPC Xarelto, accessed August 2014 http://www.medicines.org.uk/emc/medicine/21265
3. Derbyshire Medicines Management Prescribing and Guidelines. The prevention of stroke and systemic embolism in atrial fibrillation (AF) with warfarin and Non-vitamin K Antagonist Oral Anticoagulants (NOACs) http://www.derbyshiremedicinesmanagement.nhs.uk/home
4. Prescriber decision support of new oral anticoagulant, December 2013. Greater Manchester Commissioning Support Unit, Medicines Optimization Team.
5. Newt Guidelines for administration of medication to patients with enteral feeding tubes or swallowing difficulties. Accessed September 2014. http://www.newtguidelines.com/
6. NICE TA 275. Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. February 2013.
7. NICE TA 249. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. March 2012.
8. NICE TA 256. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. May 2012
9. SPC Eliquis, accessed August 2014 http://www.medicines.org.uk/emc/medicine/24988
10. SPC Pradexa, accessed August 2014 http://www.medicines.org.uk/emc/medicine/20760
11. http://cks.nice.org.uk/, accessed September 2014
12. Granger CB et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2011; 365: 981-92. (ARISTOTLE trial)
13. Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-115. (RE-LY trial)
14. Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in Non-valvular Atrial Fibrillation. N Engl J Med 2011;365:883-91. (ROCKET-AF trial)
15. NICE TA355. Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. September 2015
16. Giugliano RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med; 369:2093-104 (ENGAGE AF-TIMI 48 trial)
17. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016; 14: 1308–13.
18. European Heart Journal (https://academic.oup.com/eurheartj/article/39/16/1330/4942493) accessed August 2018
19. PCCS, PCPA, UKCPA Anticoagulation for non-valvular atrial fibrillation following NHSE DOAC commissioning recommendations July 2022 [accessed February 2023] https://pcpa.org.uk/454kgekwj545c87as234lg/FINAL_Guidance_on_prescribing_anticoagulation_in_NVAF_July_22_v2(2).pdf

11. Authors

Medicines Management, Clinical Effectiveness Team
In consultation with:

- Dr. Julia Baron, Dr. A McCance consultant cardiologist Royal Derby Hospital
- Dr. Justin Cooke, consultant cardiologist Chesterfield Royal hospital

Appendix 1: Review of patients with AF

Patients with AF are at an increased risk of stroke and should be encouraged to take anticoagulants. Discuss the risks Vs benefits at every opportunity with the patient, but not less than annually.

- For patients who are taking an anticoagulant, review the need for anticoagulation at least annually or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk.
- For patients who are not taking an anticoagulant, review stroke risk when they reach age of 65 or if they develop any of the following at any age – diabetes, HF, peripheral arterial disease, coronary heart disease, stroke, TIA or systemic thromboembolism.
- For patients who are not taking an anticoagulant because of bleeding risk or other factors, review stroke and bleeding risks at least annually and ensure all review and decisions are documented.

Appendix 2: Existing patients on treatment considered outside of current NICE guidelines

1. Existing patients on aspirin

Aspirin monotherapy is **not** recommended solely for stroke prevention in people with AF. NICE concluded there was no clinical benefit of aspirin in reducing mortality and systemic emboli.
There may be existing patients in primary care on aspirin monotherapy. At the next routine visit reassess the patient's stroke and bleeding risk using the CHA_2DS_2-VASc and ORBIT bleeding risk scores or HAS-BLED and treat according to the guidance, to reduce the risk of stroke.

2. Existing patients on 'no treatment'

There will be existing patients (at low or high risk) who have chosen not to have any treatment or patients who are at low risk and so require no anti-thrombotic treatment. At the next annual review reassess these patients' stroke and bleeding risk using the CHA_2DS_2-VASc and ORBIT bleeding risk scores or HAS-BLED and offer treatment again. Explore the patient's views regarding anticoagulation and offer all therapeutic options.

3. Existing patients on dual antiplatelet therapy, solely for AF.

NICE do not make a specific recommendation regarding dual antiplatelet solely to treat AF because they felt the potential number of patients was low. However dual therapy (with aspirin and clopidogrel) may be considered by a cardiologist in patients whom all anticoagulation is contra-indicated or not tolerated. Existing patient on dual antiplatelet solely for AF will need to be reviewed in light of the new guidance and offered anticoagulation if not done so previously.

Appendix 3: Consultant prescribing advice

1a. Patient with stable vascular disease with newly diagnosed atrial fibrillation

Conclusive evidence of benefit for dual treatment for long term use is limited and is associated with an increased bleeding risk. The following advice is from local consultants:
Patients with established CVD taking long term aspirin who develop AF requiring anticoagulation should usually have their aspirin stopped when INR reaches therapeutic levels.
Do not prescribe the newer antiplatelets (ticagrelor and prasugrel) with warfarin or a NOAC in stable vascular disease.

1b. Stroke/TIA patient with newly diagnosed atrial fibrillation

For patients taking a long term antiplatelet (usually clopidogrel) for stroke/TIA who then develop AF and require an oral anticoagulant, in most case the antiplatelet should be stopped. Stroke physicians may occasionally prescribe this combination for patients who have a further stroke despite therapeutic anticoagulation after carefully considering individual risks and benefits and that will be clearly communicated to primary care.

2. Triple therapy (dual antiplatelet and anticoagulant)

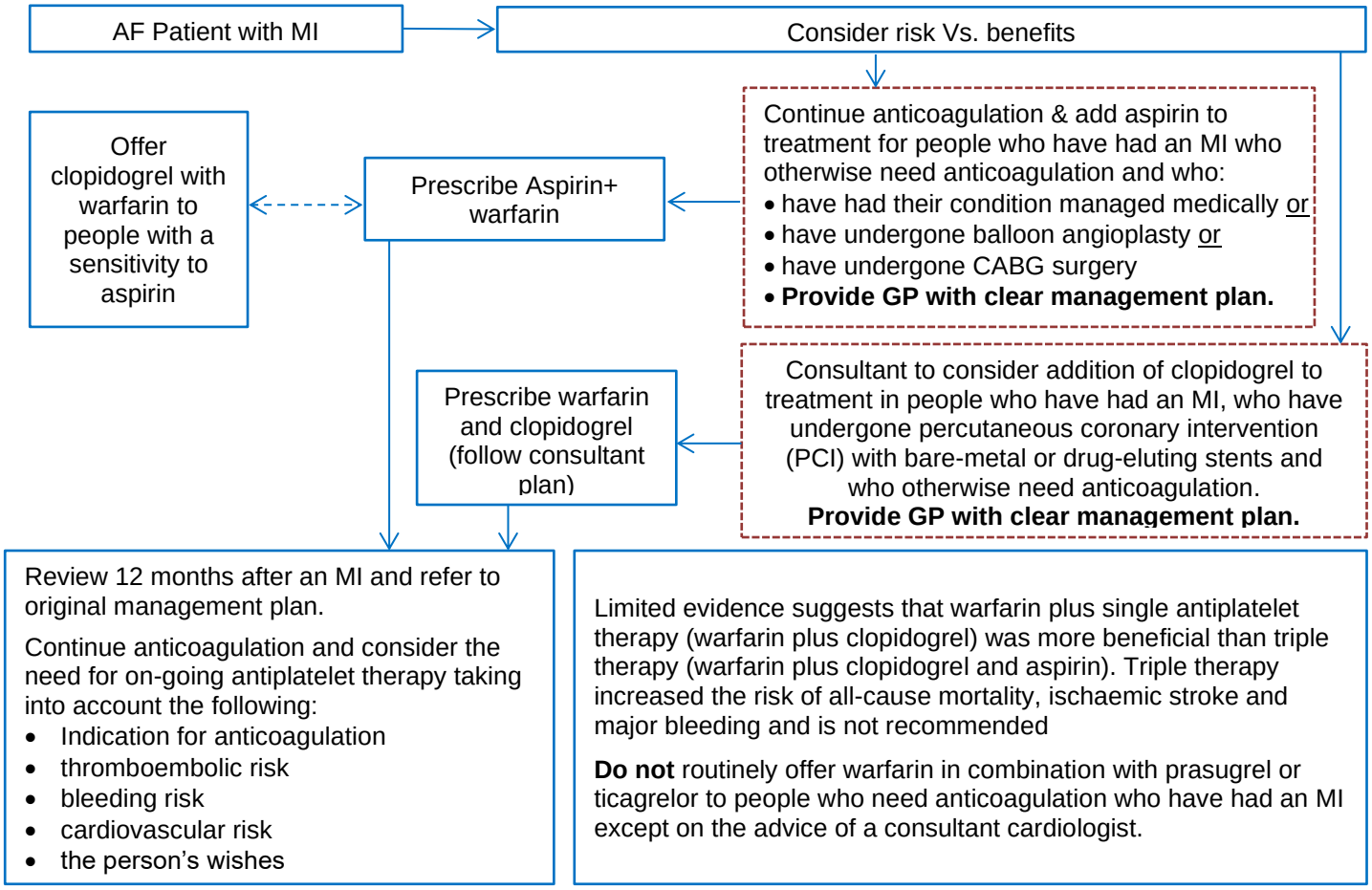
Triple therapy combination will only be initiated under the advice of a cardiologist through a shared management plan. Example where triple therapy is indicated includes patient with AF undergoing coronary stent. GPs should not discontinue an antiplatelet without the agreement of a cardiologist.

3. Left atrial appendage devices

In selected patients with a high stroke risk due to AF, unsuitable for anticoagulation left atrial appendage closure may be appropriate. Refer to cardiology.

Appendix 4: Antiplatelets and Anticoagulation

Antiplatelets maybe indicated in combination with anticoagulants, for other conditions associated with AF, such as myocardial infarction.



Appendix 5: Antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI (This is a guide only and GPs should follow the advice of cardiologist)

In the event where a cardiologist considers a patient to require dual antiplatelet treatment with oral anticoagulation (OAC), this diagram represents the likely duration of treatment for triple therapy, dual therapy and OAC monotherapy. (European Heart Journal, (2021) 23, 1612–1676)

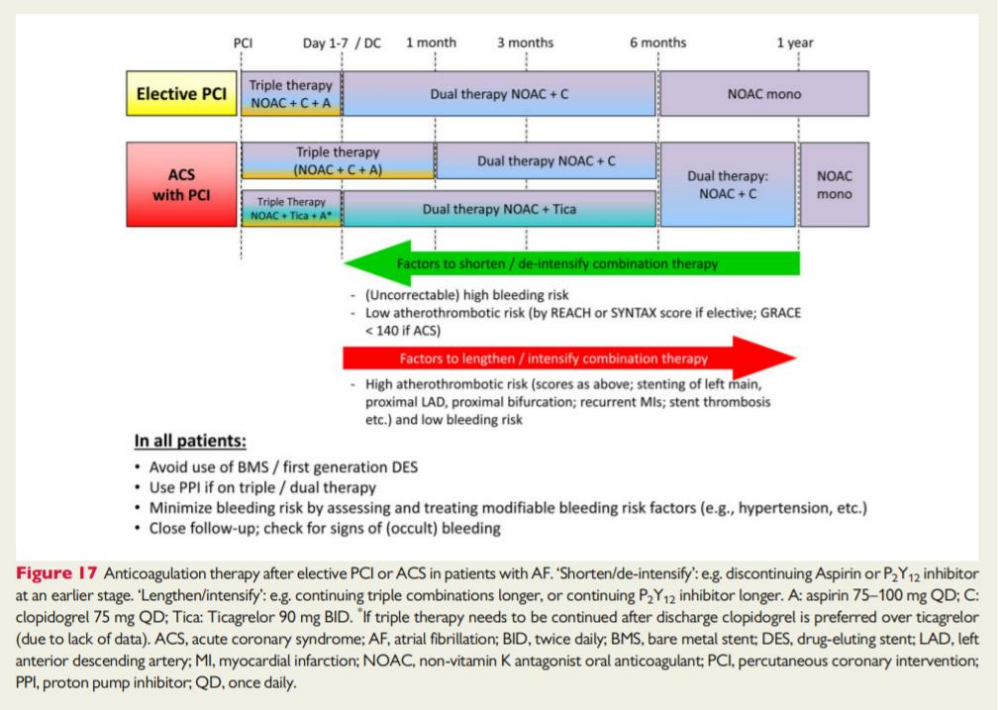


Figure 17 Anticoagulation therapy after elective PCI or ACS in patients with AF. 'Shorten/de-intensify': e.g. discontinuing Aspirin or P_2Y_{12} inhibitor at an earlier stage. 'Lengthen/intensify': e.g. continuing triple combinations longer, or continuing P_2Y_{12} inhibitor longer. A: aspirin 75–100 mg QD; C: clopidogrel 75 mg QD; Tica: Ticagrelor 90 mg BID. *If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data). ACS, acute coronary syndrome; AF, atrial fibrillation; BID, twice daily; BMS, bare metal stent; DES, drug-eluting stent; LAD, left anterior descending artery; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; QD, once daily.

Appendix 6: Detailed prescribing information for NOACs

See also PCCS/PCPA/UKCPA guidance on prescribing anticoagulation in NVAF

	Edoxaban▼	Rivaroxaban▼	Apixaban▼	Dabigatran
Licensed indication	Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF)[6,7,8,15] (with at least one additional risk factor)			
Mechanism of action	Direct & reversible inhibitor of factor Xa	Direct factor Xa inhibitor	Direct inhibitor of factor Xa	Direct thrombin inhibitor
Standard Doses	**60mg once daily**	**20mg once daily**	**5mg twice daily**	**150mg twice daily**
Dose reduction	30mg once daily in • CrCl 15-50ml/min • Body weight ≤60kg • Concomitant P-glycoprotein inhibitors – ciclosporin, dronedarone, erythromycin, ketoconazole	15mg once daily in • CrCl 30-49 ml/min • CrCl 15-29mL/min (use with caution)[2]	2.5mg twice daily in • CrCl 15-29mL/min • 2 or more of the following: ○ age >80 yrs ○ body weight ≤60kg or ○ serum Cr >133micromol/l	110mg twice daily in • Age ≥ 80 years or • taking verapamil Consider if: • thromboembolic risk is low & bleeding risk is high • age 75-80 years • patients with gastroesophageal reflux, oesophagitis or gastritis • CrCL 30-50mL/min[10]
Administration	Take with or without food	Take with food to increase absorption. Maybe crushed and put through NG tube if required (see p.10)	Take with or without food may be crushed and put through NG tube if required (see p.10)	Take with or without food Swallow whole - opening capsules may increase risk of bleeding (substantial increase in drug bioavailability (+75%))
Renal impairment *(see additional advice above in Doses)*	Patients must have a baseline renal function test before initiating NOAC. Renal function can decline while on treatment hence monitor as suggested in the monitoring section below. In practice eGFR and CrCL are not interchangeable; however for most drugs and for most patients (over 18 years) of average build and height, eGFR could provide some guidance. The SPC of each NOAC recommends that 'Cockcroft and Gault' formula is used for dosing and monitoring **Cockcroft and Gault formula: CrCL = (140-Age) X Weight X Constant / Serum creatinine** ***[Age (in years). Weight (in kilograms). Constant = 1.23 (Men); 1.04 (Women). Serum creatinine (in micromole/litre)]*** (see BNF: Prescribing in renal impairment[14] and electronic calculator link http://www.medicinescomplete.com/mc/bnf/current/PHP18586-creatinine-clearance.htm) For practical purposes when calculating CrCl for NOAC dosing, many clinicians use the embedded calculator in the GP clinical system. If using the embedded calculator in SystmOne, ensure the creatine clearance using actual body weight is used. NB. It is very important to ensure that up-to-date weight & creatinine are used. MHRA May 2023 Ensure all patients with renal impairment receive an appropriate DOAC dose and monitor renal function during treatment to ensure dose remains appropriate.			

		Edoxaban ▼	Rivaroxaban ▼	Apixaban ▼	Dabigatran
Renal impairment *(see additional advice above in Doses)*	Contraindicated / Not recommended	CrCl<15ml/min	CrCl <15ml/min	CrCl<15ml/min	CrCl<30ml/min
	Cautions See also individual SPCSs	CrCl>95ml/min :- **Consider alternative NOAC** in line with SmPC* (e.g. rivaroxaban 20mg once daily), See UKCPA/PCCS/PCPA advice *Edoxaban should be used in patients with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk.	CrCl<30ml/min	-	-
	notes	During clinical development the Cockcroft-Gault formula was used to calculate CrCl.	The manufacturer's advice to use actual bodyweight for all patients when calculating CrCl. (Actual body weight was used in the clinical trials)	The manufacturer's advice to use actual bodyweight for all patients (Actual body weight was used in the clinical trials)	The manufacturer's advice to use ideal bodyweight (IBW) in patients who are overweight and actual body weight should be used in underweight patients. The Devine formula can be used to calculate IBW (should only be used for patients over 5 feet in height): • For Male = 50kg + (2.3kg x height in inches over 5 feet) For Female = 45.5kg + (2.3kg x height in inches over 5 feet)
Hepatic impairment		Not recommended in severe hepatic impairment. Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.	Use with caution as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C	Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Not recommended in patients with elevated liver enzymes >2 upper limit of normal. Contraindicated in patients with hepatic impairment or liver disease expected to impact on survival
Contraindications (C/I) *(list not exhaustive – refer to current SPC)*		• Hypersensitivity • Active bleeding • Mechanical prosthetic heart valves • Moderate to severe rheumatic mitral stenosis • Pregnancy and breast feeding • Uncontrolled severe hypertension (for edoxaban) • Moderate to severe rheumatic mitral stenosis (for edoxaban) • CrCL< 15ml/min (CrCl<30ml/min for dabigatran)		• Concomitant treatment with any other anticoagulant (except during switching -see below) • A lesion or condition, if considered a significant risk factor for major bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • See also interactions section below.	
		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) see MHRA June 2019			

	Edoxaban ▼	Rivaroxaban ▼	Apixaban ▼	Dabigatran
Interactions *(list not exhaustive – refer to current SPC)*	• Concomitant use with P-gp inhibitor (e.g., ciclosporin, dronedarone, erythromycin, or ketoconazole) **requires dose reduction to 30mg once daily.** • Use with caution when co-administered with P-gp inducers (e.g., phenytoin, carbamazepine, St. John's Wort or phenobarbital)	• Avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp e.g., ketoconazole, itraconazole, voriconazole or HIV protease inhibitors • Concomitant administration of a strong CYP3A4 inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) should be avoided. • Concomitant use of rivaroxaban and dronedarone is not recommended	• Avoid concomitant use with strong inhibitors of both CYP3A4 and P-gp e.g., ketoconazole, itraconazole, voriconazole or HIV protease inhibitors • Concomitant use with strong CYP3A4 inducers e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort should be avoided	• Concomitant use with P-gp inducers (e.g., rifampicin, St. Jon's wort, carbamazepine, or phenytoin) should be avoided. • SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups • Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone is contraindicated
	Caution in patients treated concomitantly with NSAIDs (including acetylsalicylic acid) and anti-platelets as these typically increase the risk of bleeding (See SPC for further details)			
Monitoring[18]	Baseline monitoring: clotting screening • serum creatinine (for creatinine clearance) (Cockcroft and Gault is recommended for calculating creatinine clearance for DOACs) • FBC • liver function tests • Body weight (SPS – monitoring) SPS suggests NOAC review appointment is carried out every 3 months (best practice) to assess: • Compliance and reinforce advice regarding the importance of a regular dosing schedule. (see 6-month non-persistence section below) • Adverse effects or signs of bleeding or anaemia; Thromboembolic events (e.g. symptoms of stroke or breathlessness) • Drug interactions & modifiable risk factors for bleeding e.g. uncontrolled hypertension; and check NOAC dosing Repeat renal and liver function tests and FBC at least annually, and more frequently if the patient has the following: • Renal impairment. Check renal function: ○ every 6 months if CrCl 30-60ml/min ○ every 3 months if CrCl 15-30ml/min (Dabigatran C/I in CrCl<30ml/min) • Intercurrent acute illness that may impact on renal/hepatic function e.g. infections, acute heart failure. Repeat renal &liver functions tests as needed *Patients need to be alerted that in such situations they should seek contact with their healthcare provider*. • check renal function every 6 months if patient has additional risk factors e.g., frail, multiple co-morbidities or age ≥75 years			
	If renal function has declined review treatment, as NOAC may need to be stopped or a lower dose may be required- see renal section above			

	Edoxaban▼	Rivaroxaban▼	Apixaban▼	Dabigatran
Age (≥80 yrs)	No dose reduction is required	No dose reduction unless age related renal impairment	Consider dose reduction in ≥80yrs- 2.5mg twice daily only when patient also has either: body weight ≤60kg or serum Cr >133micromole/l	Use reduced dose -110mg twice daily
Pregnancy & breastfeeding	Contraindicated	Contraindicated	Not recommended	Not recommended
Mechanical prosthetic heart valve	Not studied – not recommended	Not studied – not recommended	Not studied – not recommended	Contraindicated
Moderate to severe rheumatic mitral valve disease	Not studied – not recommended	Not studied – not recommended	Not studied – not recommended	Not studied – not recommended
Extremes of BMI	Warfarin is locally recommended in patients with BMI ≥ 40 kg/m^2 or weight ≥120kg because there are limited clinical data available for NOAC for patients at extreme weight, and available pharmacokinetics/pharmacodynamics evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increased weight (concerns about underdosing). Consult with specialist if in doubt. Exposure of NOACs may vary by 20-30% at extremes of bodyweight (<50 kg or >100-120 kg). This may be problematic given the difficulties in monitoring the therapeutic effects. It is recommended that Cockcroft and Gault formula is used to calculate CrCL to adjust NOAC dosage.			
Poor adherence	NOACs have shorter half-life therefore missed doses may result in more time without any anticoagulation and greater risk of thromboembolic complications. Once daily dosing (edoxaban & rivaroxaban) may support concordance Warfarin – longer half-life and once a day dosing			
Missed dose	Missed dose should be taken immediately and then continued the following day with the once-daily intake as before. Do not double dose within the same day to make up for missed dose.	Missed dose should be taken immediately and then continued on the following day with once-a-day dosing. Do not double dose within the same day to make up for missed dose	Missed dose should be taken immediately and then continued with twice a day as before Do not double dose within the same day to make up for missed dose	Missed dose may still be taken up to 6 hours prior to next scheduled dose If within 6 hours of next dose, the missed dose should be omitted
Requirement for compliance aid	Warfarin not suitable for compliance aids unless risk assessment has been undertaken and a management plan is in place to manage dosage changes			
	Shelf-life of 5 years and no special storage requirement. Stable outside of original packaging for 3 months at 40◦ and 75% relative humidity (personal communication with company)	Shelf-life of 3 years and no special storage requirement – can be used in compliance aids	Shelf-life of 3 years and no special storage requirement – can be used in compliance aids	Not suitable for compliance aids

	Edoxaban ▼	Rivaroxaban ▼	Apixaban ▼	Dabigatran
Reversibility	Haemodialysis does not significantly contribute to edoxaban clearance. (SPC: 4-hour haemodialysis session reduced total edoxaban exposures by less than 9%) Currently there is no antidote. For life-threatening bleeding, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion.	A specific reversal agent (andexanet alfa), which antagonises the pharmaco-dynamics effect of rivaroxaban is available. However currently there is very limited clinical experience. Data suggest reversibility with prothrombin complex concentrate (PCC) has been successful; however currently there is very limited clinical experience. The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered	Haemodialysis is unlikely to clear apixaban and currently there is no antidote. Data suggest reversibility with prothrombin complex concentrate (PCC) has been successful; however currently there is very limited clinical experience Administration of activated charcoal reduces apixaban exposure	For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent – idarucizumab (Praxbind)) is available. The SPC states haemodialysis will also clear dabigatran. Therefore, the use of idarucizumab or haemodialysis can be used in the case of uncontrolled bleeding associated with dabigatran therapy
Conversion from warfarin to NOAC *(consult locally agreed pathways if available)*	Discontinue warfarin and start edoxaban when the INR is ≤ 2.5	Discontinue warfarin and start rivaroxaban when INR ≤3.0 (prevention of stroke and systemic embolism). Caution: INR values will be falsely elevated after the intake of rivaroxaban	Discontinue warfarin and start apixaban when the INR<2.0	Discontinue warfarin and start dabigatran when the INR<2.0 Caution: INR values will be falsely elevated when taking dabigatran
Conversion from NOAC to warfarin/ alternative NOAC *(consult locally agreed pathways if available)*	NOACs have shorter half-life and converting a NOAC to an alternative NOAC should be theoretically uncomplicated. (see SPC for specific advice) Because of the slow onset of action of warfarin, it may take 5–10 days before the INR is in the therapeutic range, with large individual variations. Therefore, the NOAC and warfarin should be administered concomitantly until the INR is in a range. As NOACs may have an impact on INR measurements, it is important that the INR is measured • just before the next intake of the NOAC during concomitant administration and • is re-measured early after stopping the NOAC to assure adequate anticoagulation. It is also recommended to closely monitor INRs within the first month until stable values have been attained (i.e., three consecutive measurements within therapeutic range).			
Minor/ Nuisance Bleeding[18]	Nuisance bleeds can usually be managed by delaying intake or withholding the NOAC for a maximum of one dose. Minor bleedings may require more aggressive therapy with a focus aimed at treating the cause of the bleeding (e.g., PPI for gastric ulcers, antibiotics for UTI, etc.).			
Before surgery *(see SPC for details)*	If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.			
	Edoxaban should be stopped as soon as possible and preferably at least 24 hours before the procedure. In deciding whether a procedure should be delayed until 24 hours after the last dose of edoxaban, the increased risk of bleeding should be weighed against the urgency of the intervention.			

		Edoxaban▼	Rivaroxaban▼	Apixaban▼	Dabigatran
Efficacy for stroke prevention		Non-inferior to warfarin (ENGAGE AF-TIMI 48)[16]	Non-inferior to warfarin (ROCKET-AF)[14]	Superior to warfarin (ARISTOTLE) [12]	Slightly superior to warfarin with 150mg twice daily dose. Non-inferior to warfarin with 110mg twice daily dose (RE-LY)[13]
Risk compared to warfarin	**Major bleed**	Reduced risk (ENGAGE AF-TIMI 48)[16]	Similar risk (ROCKET-AF)[14]	Reduced risk (ARISTOTLE)[12]	Reduced risk with 110mg twice daily Similar risk with 150mg twice daily (RE-LY)[13]
	Intracranial bleed	Reduced risk (ENGAGE AF-TIMI 48)[16]	Reduced risk (ROCKET-AF)[14]	Reduced risk (ARISTOTLE)[12]	Reduced risk (RE-LY)[13]
	Major GI bleed	Increased risk with high dose edoxaban (60mg od)	Increased risk (ROCKET-AF)[14]	Similar risk (ARISTOTLE)[12]	Similar risk with 110mg twice daily Significantly increased risk with 150mg twice daily (RE-Y)[13]
	dyspepsia/ upper GI side effects	Not reported	Similar risk of dyspepsia (ROCKET-AF)[14]	Non-reported (ARISTOTLE)[12]	Dyspepsia was significantly more common with both doses of dabigatran (RE-LY)[13]
	MI	Reduced risk but not statistically significant	Reduced risk but trend did not reach statistical significance (ROCKET-AF)[14]	Reduced risk (ARISTOTLE)[12]	Increased risk but trend did not reach statistical significance (RE-LY)[13]
Mean time in therapeutic range		64.9%[16]	55%[14]	62%[12]	64%[13]
6-month non-persistence		No evidence Evidence reinforces 3monthly compliance check for NOACs	Study [17](n=25,976) found at 6 months, **31.9%** of patients were **non-persistent rivaroxaban**. Stroke/TIA/death was higher with non-persistence vs. persistence Evidence reinforces 3monthly compliance check for NOACs.	No evidence Evidence reinforces 3monthly compliance check for NOACs	A study[17] (n=25,976) found at 6 months, **36.4%** of patients were **non-persistent to dabigatran.** Stroke/TIA/death was higher with non-persistence vs. persistence. Evidence reinforces 3monthly compliance check for NOACs

Table adapted from and thanks to Greater Manchester Commissioning Support Unit Medicines Optimisation Team

Appendix 7: CHA2DS2-VASc score and stroke risk table

CHA_2DS_2-VASc Score	n	Events per 100 patients/year	
		Ischaemic stroke	Stroke/TIA/ peripheral emboli
0	5343	0.2	0.3
1	6770	0.6	1.0
2	11,240	2.5	3.3
3	17,689	3.7	5.3
4	19,091	5.5	7.8
5	14,488	8.4	11.7
6	9577	11.4	15.9
7	4465	13.1	18.4
8	1559	12.6	17.9
9	268	14.4	20.3

Adapted from Friberg L, Rosenqvist M, and Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. European Heart Journal (2012) 33 (12): 1500–1510

Appendix 8: Resources for patients

- Atrial fibrillation: diagnosis and management, NICE Guideline NG196, updated 10/06/21, accessed 28/06/21, https://www.nice.org.uk/guidance/ng196
- British Heart Foundation: https://www.bhf.org.uk/informationsupport/conditions/atrial-fibrillation
- The UK Atrial fibrillation Association: http://www.atrialfibrillation.org.uk/
- Atrial fibrillation oral anticoagulation card http://www.escardio.org/communities/EHRA/publications/novel-oral-anticoagulants-for-atrial-fibrillation/Pages/welcome.aspx