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.

- Perform an 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.

- CHA₂DS₂-VASc score is the preferred tool for the assessment of stroke risk.

- Use HAS-BLED in all AF patients to assess bleeding risk. Modifiable factors that reduce risk should be addressed.

- For most patients the benefit of anticoagulation outweighs the bleeding risk. Do not withhold anticoagulants solely due to the risk of falling.

- 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, for example using the range of PDAs developed by NICE.

- 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.
Management of Atrial Fibrillation (AF)

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1. Abbreviations

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

2. Definitions

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute onset</td>
<td>Onset within the previous 48 hours</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>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</td>
</tr>
<tr>
<td>Consider</td>
<td>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</td>
</tr>
<tr>
<td>Labile INR</td>
<td>Refers to unstable/high INRs or poor time in therapeutic range (e.g. TTR &lt;60% when using the HASBLED calculator)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>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.</td>
</tr>
<tr>
<td>Offer</td>
<td>Defined as an intervention which will do more good than harm and be cost effective</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>AF which spontaneously terminates within 7 days, usually within 48 hours</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>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</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>AF which persists for more than 7 days</td>
</tr>
<tr>
<td>Pill-in-the-pocket strategy</td>
<td>Defined as the person managing paroxysmal AF themselves by taking antiarrhythmic drugs only when an episode of AF starts.</td>
</tr>
<tr>
<td>Valvular AF</td>
<td>AF in the presence of mechanical prosthetic heart valve or moderate to severe rheumatic mitral valve disease.</td>
</tr>
<tr>
<td>Non-valvular AF</td>
<td>All other AFs are non-valvular</td>
</tr>
</tbody>
</table>

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 CG180 July 2014.

5. Diagnosis and investigations

<table>
<thead>
<tr>
<th>Personalised package of care</th>
<th>Rate or rhythm control</th>
<th>Stroke prevention/ bleeding risk assessment</th>
<th>Bloods? Echo? Referral?</th>
</tr>
</thead>
</table>
| 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.  
| Rate control is the treatment of choice for the majority of patients. | Assess stroke risk using **CHA2DS2-VASc** and  
  Assess bleeding risk using **HAS-BLED** | **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) |

**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 ECG**
If paroxysmal AF suspected, undertake a 24 hour ambulatory ECG (or refer for a 7 day ECG if warranted) in those who have infrequent episodes more than 24 hours apart

**ECG confirms AF or Flutter**

- Ensure that the package of care is documented and delivered.
6. Risk assessment for anticoagulation

Stoke and bleeding risk should be assessed in all patients with AF. Use CHA$_2$DS$_2$-VASc score to assess stroke risk and the HAS-BLED to assess the risk of bleeding in patients who are starting, have started or have started an anticoagulant.

**Use CHA$_2$DS$_2$-VASc to assess stroke risk**

NICE recommend the use of CHA$_2$DS$_2$-VASc score 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)

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc items</th>
<th>CHA$_2$DS$_2$-VASc Score</th>
<th>Max. score = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure or left</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ventricular dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age ≥75</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vascular disease (prior MI, peripheral</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>artery disease, aortic plaque)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**CHA$_2$DS$_2$-VASc = 0 (Men)**
No ANTITHROMBOTICS
Reassess risks (stroke risk, bleeding risk) **annually**
Do not offer aspirin (or any other drug) for stroke prevention

Review patients not taking any anticoagulants when they reach age of 65 or if they develop any of the following at any age:
- Diabetes
- Peripheral arterial disease
- Stroke, TIA or systemic thromboembolism

**CHA$_2$DS$_2$-VASc = 1 (Men)**
Consider anticoagulation – Warfarin or a NOAC
Bearing in mind bleeding risk
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. 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

**CHA$_2$DS$_2$-VASc = 1 (Women)**
Consider anticoagulation – Warfarin or a NOAC
Bearing in mind bleeding risk
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. 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

**CHA$_2$DS$_2$-VASc ≥ 2 (Men and women)**
Offer anticoagulants - Warfarin or a NOAC
Taking bleeding risk into account
Discuss the options for anticoagulation with the patient, base the choice on their clinical features and preferences. 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

**Use HAS-BLED to assess bleeding risk**

Use the HAS-BLED score to assess the risk of bleeding in people who are 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

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

**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 (A study analysed the risk of bleeding from falls in elderly patients (≥65 years of age) who were anticoagulated for atrial fibrillation and found that a person taking warfarin must fall about 295 times in one year for warfarin not to be considered the optimal therapy). (Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999; 159:677–85)
- Do not offer aspirin (or clopidogrel) monotherapy solely for stroke prevention to people with AF.
- If considering or offering anticoagulation, options include either warfarin or a NOAC (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). The clinician should discuss the options for anticoagulation with the patient and drug choice should take into account clinical features, preferences and bleeding risk.

Discussing anticoagulant treatment options with patients to help them make an informed decision using patient decision aids (PDAs).

Following an AF diagnosis, the patient will need to make an informed decision regarding whether to commence anticoagulation or not. In most cases the decision to start immediate anticoagulation is not necessary. The patient should be given a few days to reflect and to talk over with family, friends or the healthcare professional before making their decision.

NICE have produced patient decision aids to support patients and clinicians in choosing between the recommended options for stroke prevention in AF. All the options for anticoagulation should be considered and the advantages and disadvantages of the different treatments available should be discussed with the patient before choosing a particular drug. If the patient does not wish to commence anticoagulation; the decision should be documented following discussion with the patient using the PDA’s and patient information produced By NICE.

The user guide on PDA for healthcare professionals on how to use them and communicate with patient and can be found at [patient decision aid user guide](#)

The PDAs that the clinician will use with the patient can be found at [patient decision aids](#)

See appendix 8 for an example of a PDA.

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, edoxaban is to be used 1st line for patients with NVAF unless there is a specific clinical reason not to do so. Detailed prescribing information for NOACs can be found in appendix 6

The clinical benefits of the NOACs compared to warfarin diminish with improving INR control. In existing patients where warfarin treatment is well-controlled (TTR more than 65%) the use of the NOACs may be less favourable. Clinicians will need to take the level of INR control into consideration when assessing the benefits of a potential change to a NOAC.
Key points:

**Warfarin**  (See local anticoagulation guidance for further information)

- Warfarin remains an established and cost effective option for anticoagulation in patients.
- 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.
- Warfarin - time to peak effect ranges from 3-5 days and a half-life averaging 40 hours.
- Warfarin is known to interact with certain foods e.g. cranberry, alcohol and other foods containing high amounts of vitamin K.
- 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.

**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)
- NOACs have shorter half-life and missed doses may result in more time without any anticoagulation and greater risk of thromboembolic complications.
- Adherence can be a challenge for patients managing anticoagulants
- Each NOAC has a higher acquisition cost than warfarin.
- Limited evidence on the reversal of the anticoagulant effects of the drugs.
- Renal function should be assessed and monitored using Cockcroft and Gault formula to calculate the CrCL, especially in patients with extreme BMI.
- In patients weight >120kg or BMI >40 kg/m² 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.
- 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.

**Cockcroft and Gault formula:**

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

- 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 creatinine clearance, use the calculator in the GP clinical system using an up-to-date weight and serum creatinine.

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
Anticoagulation control for existing patients on Warfarin

Explain 1st 6 weeks of treatment

Calculate TTR over a maintenance period of at least 6 months
(Use a validated method e.g. Rosendaal method for computer-assisted dosing)

Poor anticoagulation control
INRs
- TTR < 65%
- 2 INRs higher than 5 or 1 INR higher than 8 within past 6m
- 2 INRs less than 1.5 within the past 6m

Good anticoagulation control
Results TTR >65% and INRs normal

Continue treatment

Check the following
- Cognitive function
- Compliance
- Drug interactions or co-morbidities
- Lifestyle factors including alcohol and diet
- Consider domiciliary monitoring arrangement for patients with reduced mobility
- Inconvenient or inappropriate monitoring arrangements
  – confirm suitability of arrangements for each patient

Table 1: Conversion from Warfarin to:

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Warfarin should be stopped. Monitor the INR and start edoxaban once the INR is ≤ 2.5.</td>
</tr>
<tr>
<td><strong>Rivaroxaban (for stroke prevention)</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>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)</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Warfarin should be stopped. Monitor the INR and start apixaban once the INR is below 2.0</td>
</tr>
</tbody>
</table>

Reassess anticoagulation

If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person
Remember poor compliance with warfarin does not equate to good compliance with a NOAC. NOACs have relatively short half-life, so poor compliance will result in uncontrolled anticoagulation

Consider NOACs
(See below)
## Considerations when choosing oral anticoagulation agent

<table>
<thead>
<tr>
<th>Once daily regime preferred? (consider concordance, reliant on carers/nursing visits)</th>
<th>Preferred option:</th>
<th>Warfarin or edoxaban (rivaroxaban is also taken once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin – although given as a single dose, it may be necessary to give several tablets dependent on dose</td>
<td>Edoxaban - can be given as a single dose</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban2 – can be given as a single dose with food</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Does the patient require medication in a compliance aid?</th>
<th>Preferred option:</th>
<th>Edoxaban (rivaroxaban, apixaban or possibly warfarin are also choices)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Edoxaban - no special storage requirement. Stable outside of original packaging for 3 months at 40°C and 75% relative humidity (personal communication with company)</td>
<td>Rivaroxaban3 - no special storage requirement, can be used in compliance aid</td>
</tr>
<tr>
<td></td>
<td>Apixaban3 - no special storage requirement, can be used in compliance aid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin - if risk assessment has been undertaken and a management plan is in place to manage dosage changes. <strong>Note:</strong> Dabigatran is sensitive to moisture not suitable for compliance aid.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Does the patient have swallowing difficulties or a gastric tube?</th>
<th>Preferred option:</th>
<th>Edoxaban (rivaroxaban, apixaban are also choices)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Edoxaban Swallowing difficulties5 The tablets can be crushed and mixed with water or apple sauce for administration Enteral tubes5 The tablets can be crushed and mixed with water for administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban Swallowing difficulties May be crushed and mixed with water or apple puree immediately prior to use and administered orally Gastric tube4,6 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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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. <strong>Note:</strong> Dabigatran capsules must not be opened as it results in a substantial increase in drug bioavailability (+75%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the patient likely to miss doses?</th>
<th>Preferred option:</th>
<th>Warfarin unless compliance aid helps (Edoxaban (first choice), rivaroxaban and apixaban are suitable for compliance aids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the patient needle phobic?</th>
<th>Preferred option:</th>
<th>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. <strong>Warfarin</strong> – requires frequent monitoring at least 3 monthly (note near patient testing only requires capillary blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Warfarin – requires frequent monitoring at least 3 monthly (note near patient testing only requires capillary blood)</td>
<td></td>
</tr>
</tbody>
</table>

| Does the patient have BMI>40kg/m² or weight >120kg? | 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

Rate control strategies
(Preferred strategy for vast majority of patients)

(If rhythm control is more appropriate, refer to secondary care)
Offer rhythm control to people with AF:
- 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 an ablation strategy to restore sinus rhythm
- for whom a rhythm control strategy would be more suitable based on clinical judgement.

Offer monotherapy with a beta-blocker* (not sotalol) or a rate limiting calcium channel blocker** as initial monotherapy to people with AF who need drug treatment as part of a rate control strategy.
Base the choice of drug on the person's symptoms, heart rate, comorbidities and preferences when considering drug treatment.
Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no or very little physical exercise)

If monotherapy does not control symptoms and if continuing symptoms are thought to be due to poor ventricular rate control; consider combination therapy with any 2 of the following:
- a beta blocker
- diltiazem
- digoxin

*Beta-blockers licensed to treat AF: atenolol, acebutolol, metoprolol, nadolol, oxprenolol, propranolol
**Calcium channel blocker: diltiazem (unlicensed indication. Obtain and document informed consent)

Key to algorithms
--- Secondary care responsibility
----- Primary care responsibility
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.

**Rhythm control strategies**
(These will normally be initiated under the care of a cardiologist)

**Persistent AF**

After referral to secondary care, GP’s may be asked to prescribe amiodarone – see local guidance. Prescribing may need to continue for up to 12 months.

*Ensure communication of duration of treatment is provided to the GP*

**Paroxysmal AF**

Assess the need for drug therapy for long term rhythm control

Consider a standard beta blocker* other than sotalol as first line initial treatment and continue long-term

Consultant may consider other drugs according to co-morbidities:
- Consider long term amiodarone (consultant initiation only) for people with left ventricular impairment or heart failure
- Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischaemic or structural heart disease

Dronedarone in accordance with NICE TA197-AMBER follow local shared care

GP to continue long term prescribing of amiodarone, see local guidance

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
8. NICE TA 256. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. May 2012

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 CHA2DS2-VASc and HAS-BLED scores and treat accordingly, 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 CHA2DS2-VASc and HAS-BLED scores 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.

Consider risk Vs. benefits

Continue anticoagulation & add aspirin to treatment for people who have had an MI who otherwise need anticoagulation and who:
- have had their condition managed medically or
- have undergone balloon angioplasty or
- have undergone CABG surgery

Provide GP with clear management plan.

Consultant to consider addition of clopidogrel to treatment in people who have had an MI, who have undergone percutaneous coronary intervention (PCI) with bare-metal or drug-eluting stents and who otherwise need anticoagulation.

Provide GP with clear management plan.

Limited evidence suggests that warfarin plus single antiplatelet therapy (warfarin plus clopidogrel) was more beneficial than triple therapy (warfarin plus clopidogrel and aspirin). Triple therapy increased the risk of all-cause mortality, ischaemic stroke and major bleeding and is not recommended.

Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI except on the advice of a consultant cardiologist.

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.

### Appendix 6: Detailed prescribing information for NOACs

<table>
<thead>
<tr>
<th>SPC</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Licensed indication</strong></td>
<td>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)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct inhibitor of factor Xa,</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct thrombin inhibitor</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Standard Doses</strong></td>
<td>60mg once daily</td>
<td>20mg once daily</td>
<td>150mg twice daily (Age &lt; 80 yrs)</td>
<td>5mg twice daily</td>
</tr>
<tr>
<td><strong>Dose reduction</strong></td>
<td>30mg once daily in</td>
<td>15mg once daily in</td>
<td>110mg twice daily in</td>
<td>2.5mg twice daily in</td>
</tr>
</tbody>
</table>

- CrCl 15-50ml/min
- Body weight ≤60kg
- Concomitant P-glycoprotein inhibitors – ciclosporin, dronedarone, erythromycin, ketoconazole

- CrCl 30-49 ml/min
- CrCl 15-29ml/min (use with caution)\(^2\)

- 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 < 15ml/min (CrCl<30ml/min for dabigatran)**
- Anticoagulant in use (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.

### Contraindications (CI)
- Hypersensitivity
- Active bleeding
- Mechanical prosthetic heart valves
- Moderate to severe rheumatic mitral stenosis
- Pregnancy and breast feeding

**CrCL< 15ml/min (CrCl<30ml/min for dabigatran)**
- Anticoagulant in use (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

### Administration
- Take with or without food
- Take with food to increase absorption. Maybe crushed and put through NG tube if required (see p.9)
- Swallow whole - opening capsules may increase risk of bleeding (substantial increase in drug bioavailability (+75%))
- Take with or without food may be crushed and put through NG tube if required (see p.9)

**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**

### Interactions

**Uncontrolled severe hypertension**

- 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 unless the patient is closely observed for signs and symptoms of thrombosis. Caution with dronedarone

**Potential for P-gp interactions e.g. amiodarone, verapamil, quinidine, ketoconazole, clarithromycin, rifampicin, phenytoin & carbamazepine**

**SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups**

**Concomitant treatment with systemic ketoconazole, ciclosporine, itraconazole, tacrolimus and dronedarone is contraindicated**

**Avoid concomitant use with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors**

**Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort as they may lead to reduced apixaban concentrations**

**Caution in patients treated concomitantly with NSAIDs (including acetylsalicylic acid) and anti-platelets as these typically increase the risk of bleeding**
### Monitoring

**Baseline monitoring:** clotting screening; renal and liver function tests; FBC

**Every 3 months assess:**
- Compliance and reinforce advice regarding the importance of a regular dosing schedule. (see 6 month non-persistence section below)
- Adverse effects (e.g. bleeding)
- Thromboembolic events (e.g. symptoms of stroke or breathlessness)

**Repeat renal and liver function tests and FBC at least annually,** and more frequently if the patient has:
- Renal impairment. Check renal function:
  - every 6 month if CrCl 30-60ml/min
  - every 3 month 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.
  Patients need to be alerted that in such situations they should seek contact with their healthcare provider.
- Dabigatran/ Edoxaban: 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 below.

### 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 above. 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:**

\[
\text{CrCL} = \left(\frac{140 - \text{Age}}{\text{Weight}} \times \text{Constant}\right)
\]

**Serum creatinine**

\[
\text{[Age (in years), Weight (in kilograms), Constant = 1.23 (Men); 1.04 (Women), Serum creatinine (in micromole/litre)]}
\]


Further information is available on the SPS website [see link](http://www.medicinescomplete.com/mc/bnf/current/PHP18586-creatinine-clearance.htm).

During clinical development of edoxaban, the Cockcroft-Gault formula was used to calculate CrCl.

Note A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Manufacturer advises: Edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.

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 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)

The manufacturer’s advice to use actual bodyweight for all patients (Actual body weight was used in the clinical trials)

<table>
<thead>
<tr>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not recommended in CrCl &lt;15ml/min</strong></td>
<td>Use with caution if CrCL15-29mL/min</td>
<td>Contraindicated in CrCL&lt;15mL/min</td>
<td>Not recommended in CrCL&lt;15mL/min</td>
</tr>
</tbody>
</table>

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Management of Atrial Fibrillation (AF)

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<table>
<thead>
<tr>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic impairment</strong>&lt;br&gt;Not recommended in severe hepatic impairment. Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.</td>
<td>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 &amp; C</td>
<td>Not recommended in patients with elevated liver enzymes &gt;2 upper limit of normal. Contraindicated in patients with hepatic impairment or liver disease expected to impact on survival</td>
<td>Not recommended in severe hepatic impairment as requires hepatic metabolism. Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk</td>
</tr>
<tr>
<td><strong>Age (≥80 yrs)</strong>&lt;br&gt;No dose reduction is required</td>
<td>No dose reduction unless age related renal impairment</td>
<td>Use reduced dose -110mg twice daily</td>
<td>Consider dose reduction in ≥80yrs – 2.5mg twice daily only when patient also has either: body weight ≤60kg or serum Cr &gt;133micromole/l</td>
</tr>
<tr>
<td><strong>Pregnancy &amp; breastfeeding</strong>&lt;br&gt;Contraindicated</td>
<td>Contraindicated</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Mechanical prosthetic heart valve</strong>&lt;br&gt;Not studied – not recommended</td>
<td>Not studied – not recommended</td>
<td>Contraindicated</td>
<td>Not studied – not recommended</td>
</tr>
<tr>
<td><strong>Moderate to severe rheumatic mitral valve disease</strong>&lt;br&gt;Not studied – not recommended</td>
<td>Not studied – not recommended</td>
<td>Not studied – not recommended</td>
<td>Not studied – not recommended</td>
</tr>
<tr>
<td><strong>Extremes of BMI</strong></td>
<td>Warfarin is locally recommended in patients with BMI ≥ 40 kg/m² 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 (&lt;50 kg or &gt;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.</td>
<td>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 &amp; rivaroxaban) may support concordance. Warfarin – longer half-life and once a day dosing</td>
<td></td>
</tr>
<tr>
<td><strong>Poor adherence</strong>&lt;br&gt;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.</td>
<td>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</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td><strong>Requirement for compliance aid</strong>&lt;br&gt;Shelf-life of 3 years and no special storage requirement. Edoxaban stable outside of original packaging for 3 months at 40○ and 75% relative humidity (personal communication with company)</td>
<td>Shelf-life of 3 years and no special storage requirement – can be used in compliance aids</td>
<td>Not suitable for compliance aids</td>
<td>Shelf-life of 3 years and no special storage requirement – can be used in compliance aids</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Edoxaban*</td>
<td>Rivaroxaban*</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Haemodialysis does not significantly contribute to edoxaban clearance. (SPC: 4 hour haemodialysis session reduced total edoxaban exposures by &gt; 9%)</td>
<td>Haemodialysis will not clear rivaroxaban 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</td>
<td>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.</td>
</tr>
<tr>
<td>Conversion from warfarin to NOAC</td>
<td>Discontinue warfarin and start edoxaban when the INR is ≤ 2.5</td>
<td>Discontinue warfarin and start rivaroxaban when INR ≤ 3.0 (prevention of stroke and systemic embolism)</td>
<td>Discontinue warfarin and start dabigatran when the INR&lt;2.0</td>
</tr>
<tr>
<td>Conversion from NOAC to warfarin/alternative NOAC</td>
<td>NOACs have shorter half-life and converting a NOAC to an alternative NOAC should be theoretically uncomplicated. (see SPC for specific advice)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor/Nuisance Bleeding 18</td>
<td>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 urinary tract infection, etc.).</td>
<td>If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.</td>
<td>Depending on renal function stop dabigatran 1 - 4 day’s prior elective surgery or invasive procedure. If acute, surgery/invasive procedure should be delayed if possible until at least 12 hours after the last dose</td>
</tr>
<tr>
<td>Before surgery</td>
<td>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.</td>
<td>If possible, based on the clinical judgement of the physician, discontinue 24 hours before surgery or invasive procedure.</td>
<td>Discontinue at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding.</td>
</tr>
</tbody>
</table>

Management of Atrial Fibrillation (AF)

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<table>
<thead>
<tr>
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<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy for stroke prevention</strong></td>
<td>Non-inferior to warfarin (ENGAGE AF-TIMI 48)(^{16})</td>
<td>Non-inferior to warfarin (ROCKET-AF)(^{14})</td>
<td>Slightly superior to warfarin with 150mg twice daily dose&lt;br&gt;Non-inferior to warfarin with 110mg twice daily dose (RE-LY)(^{13})</td>
</tr>
</tbody>
</table>

| **Major bleed** | Reduced risk (ENGAGE AF-TIMI 48)\(^{16}\) | Similar risk (ROCKET-AF)\(^{14}\) | Reduced risk with 110mg twice daily<br>Similar risk with 150mg twice daily (RE-LY)\(^{13}\) | Reduced risk (ARISTOTLE)\(^{12}\) |
| **Intracranial bleed** | Reduced risk (ENGAGE AF-TIMI 48)\(^{16}\) | Reduced risk (ROCKET-AF)\(^{14}\) | Reduced risk (RE-LY)\(^{13}\) | Reduced risk (ARISTOTLE)\(^{12}\) |
| **Major GI bleed** | Increased risk with high dose edoxaban (60mg od) | Increased risk (ROCKET-AF)\(^{14}\) | Similar risk with 110mg twice daily<br>Significantly increased risk with 150mg twice daily (RE-Y)\(^{13}\) | Similar risk (ARISTOTLE)\(^{12}\) |
| **Risk compared to warfarin** | Not reported | Similar risk of dyspepsia (ROCKET-AF)\(^{14}\) | Dyspepsia was significantly more common with both doses of dabigatran (RE-LY)\(^{13}\) | Non-reported (ARISTOTLE)\(^{12}\) |
| **dyspepsia/upper GI side effects** | | | | |
| **MI** | Reduced risk but not statistically significant | Reduced risk but trend did not reach statistical significance (ROCKET-AF)\(^{14}\) | Increased risk but trend did not reach statistical significance (RE-LY)\(^{13}\) | Reduced risk (ARISTOTLE)\(^{12}\) |
| **Mean time in therapeutic range** | 64.9%\(^{16}\) | 55%\(^{14}\) | 64%\(^{13}\) | 62%\(^{12}\) |
| **6 month non-persistence** | No evidence | 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.<br> 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.<br> Evidence reinforces 3monthly compliance check for NOACs | No evidence |

Table adapted from and thanks to Greater Manchester Commissioning Support Unit Medicines Optimisation Team
Appendix 7: Patient decision aids
Examples of PDA’s are available here

Example of Patient decision aid with a CHA2DS2-VASc score 2

No treatment: CHA2DS2-VASc score 2

If 1000 people with AF and a CHA2DS2-VASc score of 2 take no anticoagulant, over 1 year on average:

- 975 people will not have an AF-related stroke (the green faces)
- 25 people will have an AF-related stroke (the red faces)

Anticoagulant: CHA2DS2-VASc score 2

If all 1000 people take an anticoagulant, over 1 year on average:

- 975 people will not have an AF-related stroke (the green faces), but would not have done anyway
- 17 people will be saved from having an AF-related stroke (the yellow faces)
- 8 people will still have an AF-related stroke (the red faces)

Example of Patient decision aid with a HAS-BLED score 2

No treatment: HAS-BLED score 2

If 1000 people with AF and a HAS-BLED score of 2 take no anticoagulant, over 1 year on average:

- 993 people will not have a major bleed (the green faces)
- 7 people will have a major bleed (the red faces)

Anticoagulant: HAS-BLED score 2

If all 1000 people take an anticoagulant, over 1 year on average:

- 981 people will not have a major bleed (the green faces)
- 7 people will have a major bleed (the red faces), just as they would have done anyway
- An extra 12 people will have a major bleed (the green faces with the red cross)
Other tools which include stroke risk and bleeding risk can be found below

### CHA2DS2-VASc score and stroke risk

<table>
<thead>
<tr>
<th>CHA(_2)DS(_2)-VASc Score</th>
<th>n</th>
<th>Events per 100 patients/year</th>
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<tr>
<td></td>
<td></td>
<td>Ischaemic stroke</td>
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<tr>
<td>------------------------------</td>
<td>-----</td>
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<tr>
<td>8</td>
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<td>12.6</td>
</tr>
<tr>
<td>9</td>
<td>268</td>
<td>14.4</td>
</tr>
</tbody>
</table>


### HAS-BLED score and risk of major bleeding

<table>
<thead>
<tr>
<th>HAS-BLED score</th>
<th>Major bleeding events per 100 patients/year in anticoagulant users n=48,599</th>
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</tbody>
</table>


### Appendix 8: Resources for patients

- NICE, information for the public: [http://www.nice.org.uk/guidance/C180/IPF/chapter/About-this-information](http://www.nice.org.uk/guidance/C180/IPF/chapter/About-this-information)
- UKMI have produced a useful Q&A summary regarding how to [assess and manage bleeding risks in patients requiring oral anticoagulation for AF](http://www.escardio.org/communities/EHRA/publications/novel-oral-anticoagulants-for-atrial-fibrillation/Pages/welcome.aspx)