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.

- For existing patients on stroke prevention, who are currently stabilised on anticoagulation and well controlled, these patients should continue with the current treatment.

- 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 with AF 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.

- 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.

- Do not withhold anticoagulants solely due to the risk of falling.

- 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.

- 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.
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1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<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. 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. This condition is initially managed by secondary care.</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 metallic valve replacements or rheumatic mitral valve disease.</td>
</tr>
<tr>
<td>Non-valvular AF</td>
<td>All other AFs are non-valvular</td>
</tr>
</tbody>
</table>

Key to algorithms

- --- Secondary care responsibility
- Primary care responsibility
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 nonvalvular AF. Recommendations are based on NICE CG180 July 2014.

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 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

<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>
<tbody>
<tr>
<td>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.</td>
<td>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</td>
<td>Bloods: NICE do not recommend any specific blood tests. Most clinicians would check FBC, renal and thyroid function as a minimum. 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 specialised management is needed)</td>
<td></td>
</tr>
</tbody>
</table>
6. Risk assessment
Stroke 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, or have started an anticoagulant.

**Stroke prevention**
This includes those with:
- Persistent AF
- Permanent AF
- Paroxysmal AF
- Atrial flutter

Those in sinus rhythm after cardioversion but at high risk of going back to AF (cardiologist decision or CHADSVASC≥2)

Assess stroke risk, assess bleeding risk

---

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

NICE recommend the use of CHA$_2$DS$_2$-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

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

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

Use the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation. Offer modification and monitoring of the following risk factors:
- Uncontrolled hypertension
- 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/, 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>
7. Considering or offering anticoagulation

**Key points**

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 (at least 65 years of age) who were anticoagulated for atrial fibrillation. The study 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**

---

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

**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.

**Consider** is 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.

**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.

**Offer** is defined as an intervention which will do more good than harm and be cost effective.

---

**Annual review for all patients**

Re- assess stroke risk and bleeding risk

If on warfarin assess time in therapeutic range

If on a NOAC assess compliance

---

Management of Atrial Fibrillation (AF)
Updated: October 2016
Review date: September 2018
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8. Anticoagulation
If considering or offering anticoagulation, options include either warfarin or a NOAC (apixaban, dabigatran, rivaroxaban or edoxaban). The clinician should discuss the options for anticoagulation with the patient and base the choice on their 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 1 for an example of a PDA.

9. Key points: Warfarin
(See local anticoagulation guidance for further information)
✓ Warfarin has been prescribed for more than 50 years.
✓ 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 concomitant valve disease, including valve replacement or valvular AF should be treated only with warfarin not a NOAC.
✓ Unlike NOACs, warfarin may be considered in those patients with mechanical heart valve, valvular disease and/or hepatic impairment
✓ The benefits of NOACs over warfarin declines as the TTR on warfarin increases.
✓ INR gives clinicians a guide to patient compliance.
✓ Effective and familiar use of antidote with vitamin K should a severe bleed occur whilst being treated.
✓ All NOACs are licensed for prevention of stroke in nonvalvular atrial fibrillation plus at least one additional risk factor. Warfarin can be used with no additional risk factors.
✓ Clearance of warfarin is not affected by renal function.
✓ 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 for further details.
10. **Anticoagulation control for existing patients on Warfarin**

**Table 1: Conversion from Warfarin to:**

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Conversion Process</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Warfarin should be stopped and dabigatran should be started when the INR is ≤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>Rivaroxaban</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>Edoxaban</strong></td>
<td>Warfarin should be stopped. Monitor the INR and start edoxaban once the INR is ≤2.5.</td>
</tr>
</tbody>
</table>

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

**Good anticoagulation control**
- Results TTR >65% and INRs normal
  - Continue treatment

**Poor anticoagulation control**
- 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
  - 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
  - Exclude 1st 6 weeks of treatment
  - 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.

**Calculate TTR**
- Over a maintenance period of at least 6 months
- Using a validated method (e.g., Rosendaal method for computer-assisted dosing)

**Good anticoagulation control**
- Results TTR >65% and INRs normal
  - Continue treatment

**Poor anticoagulation control**
- 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
  - 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
  - Exclude 1st 6 weeks of treatment
  - 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.
11. **Key points: NOACs**
- No requirement for INR monitoring.
- NOACs provide immediate anticoagulant effect (time to peak effect ranges from 1-4 hours).
- NOACs currently have no known food interactions.
- Reduced risk of intracerebral bleeds versus warfarin (see p20 for further details)
- The sole responsibility of anticoagulation remains with the prescriber without the support of anticoagulation clinic services.
- 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.
- No published systematic clinical studies 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 [J Thromb Haemost 2016; 14: 1308–13] Consult with specialist if in doubt.
- Does require baseline tests and on-going monitoring (see appendix 4) For all patients being considered for treatment with NOACs use the Cockcroft and Gault formula to calculate the Creatinine Clearance.

**Cockcroft and Gault formula:**

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

- Age (years)
- *Weight* (Kg) (see p19 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.

It is essential to remember there are no published clinical trials that directly compare the NOACs against each other. Detailed prescribing information for NOACs can be found on p15-20.

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

12. **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 dabigatran, rivaroxaban, apixaban and edoxaban 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. However, a decision algorithm (appendix 6) can be used as a guide to address both practical issues of logistics for the patient and clinical considerations after all treatment options have been discussed with the patient.

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.
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No</th>
<th>Preferred Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the patient prefer a once daily formulation?</td>
<td>Y</td>
<td>Preferred option: Rivaroxaban or edoxaban or Warfarin</td>
</tr>
<tr>
<td>(consider concordance, reliant on carers/nursing visits)</td>
<td></td>
<td><strong>Rivaroxaban</strong>(^2) – can be given as a single dose with food</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Edoxaban</strong> – can be given as a single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Warfarin</strong> – although given as a single dose, it may be necessary to give</td>
</tr>
<tr>
<td></td>
<td></td>
<td>several tablets dependant on dose</td>
</tr>
<tr>
<td>Does the patient require medication in a compliance aid?</td>
<td>Y</td>
<td>Preferred option: Rivaroxaban or apixaban or edoxaban (or possibly warfarin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Rivaroxaban</strong>(^3) – no special storage requirement, can be used in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>compliance aid</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Apixaban</strong>(^3) – no special storage requirement, can be used in compliance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aid</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Edoxaban</strong> -no special storage requirement. Stable outside of original</td>
</tr>
<tr>
<td></td>
<td></td>
<td>packaging for 3 months at 40(^°) and 75% relative humidity (personal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>communication with company)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Warfarin</strong> – if risk assessment has been undertaken and a management plan is in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>place to manage dosage changes.</td>
</tr>
<tr>
<td>Does the patient have swallowing difficulties or a gastric tube?</td>
<td>Y</td>
<td>Preferred option: Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Rivaroxaban</strong>(^4) – no special storage requirement, can be used in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>compliance aid</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Swallowing difficulties</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be crushed and mixed with water or apple puree immediately prior to use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and administered orally</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Gastric tube</strong>(^4,5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be given through a nasogastric or PEG tube, after confirmation of the</td>
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<tr>
<td></td>
<td></td>
<td>correct gastric placement of the tube. The crushed tablet should be</td>
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<td></td>
<td></td>
<td>administered in a small amount of water via a gastric tube after which it</td>
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<tr>
<td></td>
<td></td>
<td>should be flushed with water.</td>
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<tr>
<td></td>
<td></td>
<td>(Rivaroxaban should not be administered through feeding tubes which do not</td>
</tr>
<tr>
<td></td>
<td></td>
<td>terminate in the stomach. For example this would include NJ, PEJ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AND PEGJ tubes)</td>
</tr>
<tr>
<td>Is the patient likely to miss doses?</td>
<td>Y</td>
<td>Preferred option: Warfarin unless compliance aid helps (rivaroxaban/apixaban/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>edoxaban)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Warfarin</strong> Patients with poor concordance may be at a greater risk of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>thromboembolic complications with NOACs as the shorter half-lives of these agents</td>
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<tr>
<td></td>
<td></td>
<td>compared to warfarin will potentially result in more time without any degree of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anticoagulation if a dose is missed</td>
</tr>
<tr>
<td>Is the patient needle phobic?</td>
<td>Y</td>
<td>No Preferred option</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Warfarin</strong> – requires frequent monitoring at least 3 monthly (note near patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>testing only requires capillary blood)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NOACs</strong>-Although there is no need for regular blood tests to monitor INR,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>people taking NOACs still require regular follow-up. When initiating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment baseline tests need to be performed and patients monitored on</td>
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<td></td>
<td></td>
<td>a regular basis at least annually (see appendix 5).</td>
</tr>
<tr>
<td>Does the patient have BMI&gt;40kg/m(^2) or weight &gt;120kg?</td>
<td>Y</td>
<td>Preferred option- Warfarin (local recommendation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consult with specialist if in doubt</td>
</tr>
</tbody>
</table>
13. 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)

- 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

**Calcium channel blocker: diltiazem (unlicensed indication. Obtain and document informed consent)

- 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

- Refer if rate or symptoms still not controlled
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# 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, however JAPC have classified this drug as 'RED', therefore prescribing responsibility lies with the consultant.

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

---

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. flecanide 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 an 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.”
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: Prescribing advice for 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 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 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 cases 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.

AF Patient with MI  ➔  Consider risk Vs. benefits

Offer clopidogrel with warfarin to people with a sensitivity to aspirin

Prescribe Aspirin+ warfarin

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.

Prescribe warfarin and clopidogrel (follow consultant plan)

Review 12 months after an MI and refer to original management plan.

Continue anticoagulation and consider the need for on-going antiplatelet therapy taking into account the following:
- Indication for anticoagulation
- thromboembolic risk
- bleeding risk
- cardiovascular risk
- the person’s wishes

There is no evidence for NOACs with antiplatelet agents therefore warfarin should be used where possible.

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 after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation

This is a guide only and GPs should follow the advice of cardiologist.

In the event where cardiologist considers 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.

Kirchhof, P et al, Eur Heart J 2016 Accessed 17/17/2017
Appendix 6: Detailed prescribing information for NOACs

<table>
<thead>
<tr>
<th>NICE guidance</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE TA275° <a href="http://guidance.nice.org.uk/TA275">http://guidance.nice.org.uk/TA275</a></td>
<td>Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with 1 or more risk factors such as: prior stroke or transient ischaemic attack, age 75 years or older, hypertension, diabetes mellitus, and symptomatic heart failure. The risks and benefits of apixaban compared to warfarin should be discussed with the patient.</td>
<td>NICE TA249' <a href="http://guidance.nice.org.uk/TA249">http://guidance.nice.org.uk/TA249</a></td>
<td>Dabigatran etexilate is an option for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and with one or more of the following risk factors: previous stroke, transient ischaemic attack, age ≥ 75 years, age ≥ 65 years in patients with diabetes mellitus, coronary artery disease, or hypertension. The risks and benefits of dabigatran compared to warfarin should be discussed with the patient.</td>
<td>NICE TA355° <a href="https://www.nice.org.uk/guidance/ta355">https://www.nice.org.uk/guidance/ta355</a></td>
</tr>
</tbody>
</table>

**Licensed indication**

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) [6,7,8,15](http://guidance.nice.org.uk/TA275) (with at least one additional risk factor)

**Doses**

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5mg twice daily</strong></td>
<td><strong>Age &lt; 80 yrs: 150mg twice daily</strong></td>
<td><strong>Age ≥ 80 yrs or taking verapamil: 110mg twice daily</strong></td>
<td><strong>Recommended dose: 20mg once daily</strong></td>
</tr>
<tr>
<td>CrCl 15-29mL/min: 2.5mg twice daily</td>
<td>Age ≥ 80 yrs: 110mg twice daily</td>
<td><strong>Also consider 110mg twice daily</strong></td>
<td><strong>CrCl 15-29mL/min: 15mg once daily (use with caution)</strong></td>
</tr>
<tr>
<td>Patients with 2 or more of the following give 2.5mg twice daily: age &gt;80 yrs, body weight ≤60kg, serum Cr ≥133micromole/l</td>
<td><strong>If:</strong> thromboembolic risk is low &amp; bleeding risk is high</td>
<td><strong>CrCl 15-50mL/min</strong></td>
<td><strong>CrCl 30-49 ml/min: 15mg once daily</strong></td>
</tr>
<tr>
<td>60mg once daily. (For CrCl 50-80mL/min)</td>
<td><strong>Also consider 30mg once daily</strong></td>
<td>Body weight ≤60kg</td>
<td><strong>Concomitant P-glycoprotein inhibitors – ciclosporin, dronedarone, erythromycin, ketoconazole</strong></td>
</tr>
</tbody>
</table>

Management of Atrial Fibrillation (AF)
Updated: October 2016
Review date: September 2018
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<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor Xa inhibitor</td>
<td>Potential for P-gp interactions e.g. amiodarone, verapamil, quinidine, ketoconazole, clarithromycin, rifampicin, phenytoin and carbamazepine</td>
<td>Concomitant use with P-gp inhibitor (e.g. cirlosporin, dronedarone, erythromycin, or ketoconazole) requires dose reduction to 30mg once daily.</td>
<td>Avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors</td>
<td>Avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors</td>
</tr>
</tbody>
</table>

**Interactions (list not exhaustive – refer to current SPC)**

- 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
- 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
- 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

**Contraindications (C/I) (list not exhaustive – refer to current SPC)**

- Hypersensitivity
- A lesion or condition, if considered a significant risk factor for major bleeding
- Active bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Anticoagulant in use (except during switching -see below)
- CrCL<15mL/min
- Hypersensitivity
- A lesion or condition, if considered a significant risk factor for major bleeding
- Active bleeding
- Hepatic disease or impairment expected to impact survival
- Anticoagulant in use (except during switching -see below)
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone
- CrCL<30mL/min
- Prosthetic heart valves
- Hypersensitivity
- Clinically significant active bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition, if considered to be a significant risk for major bleeding.
- Uncontrolled severe hypertension
- Anticoagulant in use (except during switching -see below)
- Pregnancy and breast-feeding
- CrCL<15mL/min

**Administration**

- Take with or without food
- Apixaban tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally.
- Swallow whole - opening capsules may increase risk of bleeding
- Take with or without food
- Take with food to increase absorption. Maybe crushed and put through NG tube if required
- Take with or without food
<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban</strong></td>
<td>Alternatively, apixaban tablets may be crushed and suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube. Crushed apixaban tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.</td>
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<tr>
<td><strong>Monitoring</strong></td>
<td><strong>Every 3 months assess:</strong></td>
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<td></td>
<td>• Compliance and reinforce advice regarding the importance of a regular dosing schedule. (see 6 month non-persistence section below)</td>
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<tr>
<td></td>
<td>• Adverse effects (e.g. bleeding)</td>
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</tr>
<tr>
<td></td>
<td>• Thromboembolic events (e.g. symptoms of stroke or breathlessness)</td>
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<tr>
<td></td>
<td><strong>Baseline monitoring includes:</strong></td>
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<tr>
<td></td>
<td>• Clotting screening</td>
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</tr>
<tr>
<td></td>
<td>• Renal and liver function tests</td>
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<tr>
<td></td>
<td>• FBC</td>
<td></td>
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<tr>
<td></td>
<td>(Monitoring requirements for edoxaban follow the CKS recommendation for the other NOACs)</td>
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</tr>
<tr>
<td><strong>Monitoring continued</strong></td>
<td>Repeat renal and liver function tests and FBC at least annually&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Repeat renal and liver function tests and FBC at least annually&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Assess renal function in all patients by calculating the CrCL prior to initiation of treatment.&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Repeat renal and liver function tests and FBC at least annually&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>If renal function has declined review treatment, as apixaban may need to be stopped or a lower dose may be required</td>
<td>If renal function has declined review treatment, as dabigatran may need to be stopped or a lower dose may be required</td>
<td>Renal function should also be assessed when a change in renal function is suspected during treatment. (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products)</td>
<td>If renal function has declined review treatment, as rivaroxaban may need to be stopped or a lower dose may be required</td>
</tr>
<tr>
<td></td>
<td>Repeat renal function tests:&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Repeat renal function tests:&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Preform liver function test prior to initiating edoxaban.</td>
<td>Repeat renal function tests:&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• If CrCl 30-60ml/min - every 6 months</td>
<td>• If CrCl 30-60ml/min - every 6 months</td>
<td>Periodic hepatic monitoring is recommended for patients continuing treatment beyond 1 year</td>
<td>• If CrCl 30-60ml/min - every 6 months</td>
</tr>
<tr>
<td></td>
<td>• If CrCl 15-30ml/min - every 3 months</td>
<td>• &gt;75 years old and</td>
<td></td>
<td>• If CrCl 15-30ml/min - every 3 months</td>
</tr>
<tr>
<td></td>
<td>Renal and liver function tests should be performed more often if there is intercurrent illness that may impact on renal and hepatic function.&lt;sup&gt;11&lt;/sup&gt;</td>
<td>• Is fragile</td>
<td>Renal and liver function tests should be performed more often if there is intercurrent illness that may impact on renal and hepatic function.&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Renal and liver function tests should be performed more often if there is intercurrent illness that may impact on renal and hepatic function.&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
### Management of Atrial Fibrillation (AF)

#### 6 month non-persistence

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence</td>
<td>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 3 monthly compliance check for NOACs.</td>
<td>No evidence</td>
<td>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 3 monthly compliance check for NOACs.</td>
</tr>
</tbody>
</table>

#### Efficacy for stroke prevention

- **Superior to warfarin (ARISTOTLE)\(^{12}\)**
- **Slightly superior to warfarin with 150mg twice daily dose**
- **Non-inferior to warfarin (ENGAGE AF-TIMI 48)\(^{18}\)**
- **Non-inferior to warfarin (ROCKET-AF)\(^{14}\)**

#### Mean time in therapeutic range

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>62%(^{12})</td>
<td>64%(^{13})</td>
<td>64.9%(^{16})</td>
<td>55%(^{14})</td>
</tr>
</tbody>
</table>

#### Poor adherence

- **NOACs have shorter half-life therefore missed doses may result in more time without any anticoagulation and greater risk of thromboembolic complications.**
- **Warfarin – longer half-life and once a day dosing**

- **Twice a day dosing**
- **Once daily dosing**

| 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 | 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. |

#### Requirement for compliance aid

- **Shelf-life of 3 years and no special storage requirement – can be used in compliance aids**
- **Not suitable for compliance aids**
- **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)**
- **Shelf-life of 3 years and no special storage requirement – can be used in compliance aids**

#### Mechanical heart valve

- **Not studied – not recommended**
- **Contraindicated**
- **Not studied – not recommended**
- **Not studied – not recommended**
<table>
<thead>
<tr>
<th>Valvular disease</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not studied – not recommended</td>
<td>Not studied – not recommended</td>
<td>Not studied - not recommended</td>
<td>Not studied – not recommended</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extremes of BMI</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin is locally recommended in patients with BMI ≥ 40 kg/m² or weight ≥ 120 kg 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.</td>
<td>Not studied – not recommended</td>
<td>Not studied – not recommended</td>
<td>Not studied – not recommended</td>
<td></td>
</tr>
</tbody>
</table>

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.

Cockcroft and Gault formula: 
\[
\text{CrCL} = (140 - \text{Age}) \times \text{Weight} \times \text{Constant}
\]

Serum creatinine
\[
\text{Constant} = 1.23 \text{ (Men); 1.04 (Women). Serum creatinine (in micromole/litre)}
\]

(see BNF: Prescribing in renal impairment and electronic calculator link http://www.medicinescomplete.com/mc/bnf/current/PHP18586-creatinine-clearance.htm)

Patients must have a baseline renal function test before initiating NOAC. Renal function can decline while on treatment hence monitor annually or more often in high risk patients. Note: 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.

The following formula (Devine formula) can be used to calculate ideal body weight (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)

Not recommended if CrCL<15mL/min

Contraindicated in CrCL<30mL/min

Not recommended if CrCl<15ml/min

Use with caution if CrCL 15-29mL/min

Contraindicated in CrCL<15mL/min

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<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic impairment</strong></td>
<td>Not recommended in severe hepatic impairment as requires hepatic metabolism. Check baseline LFTs prior to initiation</td>
<td>Not recommended in patients with elevated liver enzymes &gt;2 upper limit of normal. Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk</td>
<td>Not recommended in severe hepatic impairment. Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.</td>
</tr>
<tr>
<td><strong>Age (≥80 yrs)</strong></td>
<td>Consider dose reduction in ≥80yrs – 2.5mg twice daily</td>
<td>Use reduced dose -110mg twice daily</td>
<td>No dose reduction is required</td>
</tr>
<tr>
<td><strong>Pregnancy &amp; breastfeeding</strong></td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Contraindicated in pregnancy and breastfeeding</td>
</tr>
<tr>
<td><strong>Major bleed risk compared to warfarin</strong></td>
<td>Reduced risk (ARISTOTLE)</td>
<td>Similar risk with 150mg twice daily Reduced risk with 110mg twice daily (RE-LY)</td>
<td>Reduced risk (ENGAGE AF-TIMI 48)</td>
</tr>
<tr>
<td><strong>Intracranial bleed risk compared to warfarin</strong></td>
<td>Reduced risk (ARISTOTLE)</td>
<td>Reduced risk (RE-LY)</td>
<td>Reduced risk (ENGAGE AF-TIMI 48)</td>
</tr>
<tr>
<td><strong>Major GI bleed risk compared to warfarin</strong></td>
<td>Similar risk (ARISTOTLE)</td>
<td>Significantly increased risk with 150mg twice daily Similar risk with 110mg twice daily (RE-Y)</td>
<td>Increased risk with high dose edoxaban (60mg od)</td>
</tr>
<tr>
<td><strong>Risk of dyspepsia/upper GI side effects compared to warfarin</strong></td>
<td>Non-reported (ARISTOTLE)</td>
<td>Dyspepsia was significantly more common with both doses of dabigatran (RE-LY)</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Risk of MI compared to warfarin</strong></td>
<td>Reduced risk (ARISTOTLE)</td>
<td>Increased risk but trend did not reach statistical significance (RE-LY)</td>
<td>Reduced risk but not statistically significant</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>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</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. The SPC states haemodialysis will also clear dabigatran.</td>
<td>Haemodialysis does not significantly contribute to edoxaban clearance. (SPC states: a 4 hour haemodialysis session reduced total edoxaban exposures by less than 9%) Currently there is no antidote.</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>Dabigatran</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Administration of activated charcoal reduces apixaban exposure</td>
<td>Therefore the use of idarucizumab or haemodialysis can be used in the case of uncontrolled bleeding associated with dabigatran therapy</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Conversion from warfarin to NOAC (consult locally agreed pathways if available)</strong></td>
<td>Discontinue warfarin and start apixaban when the INR&lt;2.06</td>
<td>Discontinue warfarin and start dabigatran when the INR&lt;2.0 Caution: INR values will be falsely elevated when taking dabigatran</td>
<td>Discontinue warfarin and start edoxaban when the INR is ≤ 2.5.</td>
</tr>
<tr>
<td><strong>Conversion from NOAC to warfarin/alternative NOAC (consult locally agreed pathways if available)</strong></td>
<td>Continue with apixaban for at least 2 days after starting warfarin therapy. Check INR after 2 days of co-administration. Obtain INR before next schedule dose of apixaban. Continue co-administration until the INR is &gt;2.0 then discontinue apixaban.</td>
<td>CrCL ≥50mL/min – Start warfarin 3 days before discontinuing dabigatran. CrCL ≥30- &lt;50mL/min – Start warfarin 2 days before discontinuing dabigatran. Caution: INR values will be falsely elevated. INR testing should not be performed until dabigatran has been stopped for at least 2 days.</td>
<td></td>
</tr>
<tr>
<td><strong>CrCL ≥50mL/min</strong></td>
<td>Start warfarin 3 days before discontinuing dabigatran.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td></td>
<td>Concomitant edoxaban and warfarin can increase the INR post edoxaban dose by up to 46%.</td>
<td></td>
</tr>
</tbody>
</table>

NOACs have shorter half-life and converting a NOAC to an alternative NOAC should be theoretically uncomplicated. To date there is little evidence of such practice and it would be advisable to seek advice from specialist anticoagulant team or GPwSI when necessary. (see edoxaban SPC for specific advice)

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

<table>
<thead>
<tr>
<th>Before surgery (see SPC for details)</th>
<th>Discontinue at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding.</th>
<th>Discontinue at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding.</th>
<th>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.</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If possible, based on the clinical judgement of the physician, discontinue 24 hours before surgery or invasive procedure.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from and thanks to Greater Manchester Commissioning Support Unit Medicines Optimisation Team
Appendix 7: Considerations for anticoagulation in NVAF for primary care

Please note that the following algorithm is intended as a guide to support clinicians and should not replace individual clinical decisions. All anticoagulants in this algorithm are recommended as options by NICE and commissioners may only recommend an individual drug after a patient and prescriber have discussed all treatment options and only if they have no preference about which medicine they want to use.

Is the patient:
1. Poorly controlled by warfarin (TTR < 65%, or in the past 6 months: 2 INRs > 5, one INR > 8, or 2 INRs < 1.5) despite good compliance?
2. Predicted to have a lot of interacting medicines (e.g. COPD patient requiring frequent courses of antibiotics)?
3. Known to have a high alcohol intake (especially if there are major changes in alcohol consumption (e.g. Binge drinking))? 
4. Unable or unwilling to take warfarin for other reasons (e.g. Difficulty with monitoring requirements, unable to cope with variable dosing)

NOACs are not recommended if there are concerns about adherence. Warfarin is preferred as INR is monitored regularly to check adherence, unless patient is considered for a compliance aid - see NOAC flow chart

Is patient’s creatinine clearance < 30ml/min?

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For full prescribing details please refer to SPC or BNF

Apixaban, rivaroxaban and edoxaban are black triangle drugs and all adverse reactions and side effects should be reported using the yellow card scheme. Serious side effects that may be due to warfarin or dabigatran should also be reported.
Appendix 8: 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>CHA2DS2-VASc Score</th>
<th>n</th>
<th>Events per 100 patients/year</th>
<th>Ischaemic stroke</th>
<th>Stroke/TIA/</th>
<th>peripheral emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5343</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6770</td>
<td>0.6</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11,240</td>
<td>2.5</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17,689</td>
<td>3.7</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>19,091</td>
<td>5.5</td>
<td>7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14,488</td>
<td>8.4</td>
<td>11.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9577</td>
<td>11.4</td>
<td>15.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4465</td>
<td>13.1</td>
<td>18.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1559</td>
<td>12.6</td>
<td>17.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>268</td>
<td>14.4</td>
<td>20.3</td>
<td></td>
<td></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>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>5</td>
<td>5.7</td>
</tr>
<tr>
<td>6</td>
<td>15.5</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>


Appendix 9: Resources for patients

- NICE, information for the public: [http://www.nice.org.uk/guidance/CG180/IFP/chapter/About-this-information](http://www.nice.org.uk/guidance/CG180/IFP/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)
14. References
8. NICE TA 256. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. May 2012

15. Authors
Medicines Management, Clinical Effectiveness Team
In collaboration with:
- Cardiologists at Royal Derby Hospital
- Cardiologists at Chesterfield Royal Hospital
- Medicines Management Teams for
  - Southern Derbyshire CCG,
  - Erewash CCG,
  - North Derbyshire CCG and
  - Hardwick CCG.