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.
- 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.
- \( \text{CHA}_2\text{DS}_2\text{-VASc} \) score is the preferred tool for the assessment of stroke risk.
- Use \( \text{HAS-BLED} \) 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 cardiologist initiation only. Duration of treatment should be specified.
<table>
<thead>
<tr>
<th>Document Update</th>
<th>Date updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Page 1: the following was added to key messages – ‘and atrial flutter. Do not use this guideline for patients with significant structural heart disease’</td>
<td></td>
</tr>
<tr>
<td>Page 11: the following was added to the question 'Is the patient likely to miss doses?’ Preferred option: ‘Warfarin unless compliance aid helps’</td>
<td></td>
</tr>
<tr>
<td>P13: Pill-in the pocket strategy has the following words included – ‘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)’</td>
<td>November 2014</td>
</tr>
<tr>
<td>Page 15: the final box in the antiplatelet/anticoagulation flowchart has been reworded</td>
<td></td>
</tr>
<tr>
<td>Appendix 3: Consultant prescribing advice has been reworded to include examples – Examples where dual treatment (antiplatelet + anticoagulant) may be being considered. • Patient with stable vascular disease with newly diagnosed with atrial fibrillation. • Stroke/TIA patient with newly diagnosed atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Appendix 3: Consultant prescribing advice has been reworded: a. 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. b. 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.</td>
<td>January 2015</td>
</tr>
<tr>
<td>Page 11: the following was added to the second paragraph – ‘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’</td>
<td>April 2015</td>
</tr>
<tr>
<td>Page 21: addition of new appendix – ‘considerations for anticoagulation in NVAF for primary care’</td>
<td></td>
</tr>
<tr>
<td>Page 18: advice regarding crushing apixaban tablets included based on new revised SPC.</td>
<td>October 2015</td>
</tr>
<tr>
<td>Page 21: advice regarding use of prothrombin complex, haemodialysis and charcoal for reversibility of apixaban has been included, based on new revised SPC.</td>
<td>October 2015</td>
</tr>
<tr>
<td>Page 21: Charcoal use with rivaroxaban included as per SPC</td>
<td></td>
</tr>
<tr>
<td>Page 20: use of idarucizumab as a reversal agent included</td>
<td>March 2016</td>
</tr>
</tbody>
</table>
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>New Oral Anticoagulant (apixaban, dabigatran and rivaroxaban)</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>Term</th>
<th>Definition</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>
</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 new oral anticoagulant (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**

<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.  
| **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) |
6. Risk assessment
Stroke and bleeding risk should be assessed in all patients with AF. Use CHA₂DS₂-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)

### Assess stroke risk, assess bleeding risk

**Use CHA₂DS₂-VASc to assess stroke risk**

NICE recommend the use of CHA₂DS₂-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>CHA₂DS₂-VASc items</th>
<th>CHA₂DS₂-VASc Score</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>

Max. score = 9

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

<table>
<thead>
<tr>
<th>CHA2DS2-VASc = 0 (Men)</th>
<th>CHA2DS2-VASc =1 (Men)</th>
<th>CHA2DS2-VASc ≥ 2 (Men and women)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No ANTITHROMBOTICS</strong></td>
<td><strong>Consider anticoagulation – Warfarin or a NOAC</strong></td>
<td><strong>Offer anticoagulants - Warfarin or a NOAC</strong></td>
</tr>
<tr>
<td>Reassess risks (stroke risk, bleeding risk) annually</td>
<td>Bearing in mind bleeding risk</td>
<td>Taking bleeding risk into account</td>
</tr>
<tr>
<td>Do not offer aspirin (or any other drug) for stroke prevention</td>
<td>If anticoagulation not indicated offer no antithrombotic treatment</td>
<td>Discuss the options for anticoagulation with the patient, base the choice on their clinical features and preferences.</td>
</tr>
<tr>
<td>Review patients not taking any anticoagulants, when they reach age of 65 or if they develop any of the following at any age:</td>
<td><strong>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.</strong></td>
<td><strong>Offer is defined as an intervention which will do more good than harm and be cost effective.</strong></td>
</tr>
<tr>
<td>• Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Peripheral arterial disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Coronary heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stroke, TIA or systemic thromboembolism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

**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
8. Anticoagulation
If considering or offering anticoagulation, options include either warfarin or a NOAC (apixaban, dabigatran or rivaroxaban). 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.
✓ 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.
10. **Anticoagulation control for existing patients on Warfarin**

Exclude 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>NOAC</th>
<th>Instructions</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 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>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>
</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 table 1)
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.
- 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.
- 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.

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

**Age (years), *Weight (Kg), Serum Creatinine (micromol/litre), Constant 1.23 for men; 1.04 for women.**

For web based calculation [http://nephron.com/cgi-bin/CGSI.cgi](http://nephron.com/cgi-bin/CGSI.cgi)

*When calculating creatinine clearance use ideal body weight for overweight patients if prescribing dabigatran using the Devine formula (see below). How pragmatically this may not always be practical.*

Devine Formula for calculating ideal body weight (should only be used for patients over 5feet 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)

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.
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 and apixaban 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>Preferred option:</th>
<th>Details</th>
</tr>
</thead>
</table>
| Does the patient prefer a once daily formulation? (consider concordance, reliant on carers/nursing visits) | Rivaroxaban⁵ or Warfarin | Rivaroxaban⁵ – can be given as a single dose  
Warfarin – although given as a single dose, it may be necessary to give several tablets dependant on dose  

| Does the patient require medication in a compliance aid? | Rivaroxaban or apixaban (or possibly warfarin) | Rivaroxaban⁵ – no special storage requirement, can be used in compliance aid  
Apixaban⁶ – no special storage requirement, can be used in compliance aid  
Warfarin – if risk assessment has been undertaken and a management plan is in place to manage dosage changes. |
|---|---|---|
| Does the patient have swallowing difficulties or a gastric tube? | Rivaroxaban | Swallowing difficulties  
May be crushed and mixed with water or apple puree immediately prior to use and administered orally  
Gastric tube⁴,⁵  
May be given through a nasogastric or PEG tube, after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water.  
(Rivaroxaban should not be administered through feeding tubes which do not terminate in the stomach. For example this would include NJ, PEJ AND PEGJ tubes) |
| Is the patient likely to miss doses? | Warfarin unless compliance aid helps (rivaroxaban/apixaban) | Warfarin  
Patients with poor concordance may be at a greater risk of thromboembolic complications with NOACs as the shorter half-lives of these agents compared to warfarin will potentially result in more time without any degree of anticoagulation if a dose is missed  

| Is the patient needle phobic? | No Preferred option | Warfarin – requires frequent monitoring at least 3 monthly (note near patient testing only requires capillary blood)  
NOACs-Although there is no need for regular blood tests to monitor INR, people taking NOACs require regular follow-up and monitoring. When initiating treatment baseline tests need to be performed and patients monitored on a regular basis at least annually (see appendix 4). |
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

   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.

   Considering **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

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

- **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
    - *initiated by the consultant

Dronearone in accordance with NICE TA197, however JAPC have classified this drug as ‘RED’, therefore prescribing responsibility lies with the consultant.

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.”
Appendix 1: Review of patients with AF

- 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 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 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.

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.

Prescribe warfarin and clopidogrel (follow consultant 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.

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: Detailed prescribing information for NOACs

<table>
<thead>
<tr>
<th></th>
<th>Apixaban†</th>
<th>Dabigatran</th>
<th>Rivaroxaban†</th>
</tr>
</thead>
</table>
| NICE guidance    | NICE TA275*  
http://guidance.nice.org.uk/TA275  
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  
• Symptomatic heart failure  
The risks and benefits of apixaban compared to warfarin should be discussed with the patient. | NICE TA249†  
http://guidance.nice.org.uk/TA249  
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, or systemic embolism  
• left ventricular ejection fraction < 40%  
• symptomatic heart failure  
• 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. | NICE TA256*  
http://guidance.nice.org.uk/TA256  
Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:  
• congestive heart failure  
• hypertension  
• age 75 years or older  
• diabetes mellitus  
• prior stroke or transient ischaemic attack  
The risks and benefits of rivaroxaban compared to warfarin should be discussed with the patient. |
| Licensed indication | Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF)⁶,⁷,⁸ (with at least one additional risk factor) | | |
| Doses            | 5mg twice daily  
CrCl 15-29mL/min: 2.5mg twice daily  
Patients with 2 or more of the following give 2.5mg twice daily:  
• age >80 yrs  
• body weight ≤60kg  
• serum Cr >133micromole/l⁹ | Age < 80 yrs: **150mg twice daily**  
Age ≥ 80 yrs or taking verapamil: **110mg twice daily**  
**Also consider 110 mg twice daily if:**  
- thromboembolic risk is low & bleeding risk is high  
- age 75-80 yrs  
- patients with gastroesophageal reflux, oesophagitis or gastritis  
- CrCL 30-50mL/min¹⁰ | Recommended dose: **20mg once daily**  
CrCl 15-29mL/min: **15mg once daily (use with caution)²**  
CrCl 30-49 ml/min: **15mg once daily²** |
| Mechanism of action | Direct factor Xa inhibitor | Direct thrombin inhibitor | Direct factor Xa inhibitor |

Management of Atrial Fibrillation (AF)  
Updated: September 2014  
Review date: August 2016  
Page 16 of 26
### Interactions

**Apixaban**
- 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

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

**Rivaroxaban**
- 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

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

### Contraindications (C/I)

**Apixaban**
- 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

**Dabigatran**
- 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

**Rivaroxaban**
- 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)
- Pregnancy and breast feeding
- CrCL<15mL/min

### Administration

**Apixaban**
- 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. 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

**Dabigatran**
- Swallow whole - opening capsules may increase risk of bleeding

**Rivaroxaban**
- Take with food to increase absorption. Maybe crushed and put through NG tube if required
### Monitoring

#### Apixaban

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

**Baseline monitoring includes:**
- Clotting screening
- Renal and liver function tests
- FBC

**Monitoring continued**

Repeat renal and liver function tests and FBC at least annually\(^{11}\)

If renal function has declined review treatment, as apixaban may need to be stopped or a lower dose may be required

Repeat renal function tests:\(^{11}\)
- If CrCl 30-60ml/min - every 6 months
- If CrCl 15-30ml/min - every 3 months

Renal and liver function tests should be performed more often if there is intercurrent illness that may impact on renal and hepatic function.\(^{11}\)

#### Dabigatran

Repeat renal and liver function tests and FBC at least annually\(^ {11}\)

If renal function has declined review treatment, as dabigatran may need to be stopped or a lower dose may be required

Repeat renal function tests every 6 months if the person:\(^ {11}\)
- CrCl 30-60ml/min
- >75 years old
- Is fragile

Dabigatran is contraindicated if CrCl <30ml/min

Renal and liver function tests should be performed more often if there is intercurrent illness that may impact on renal and hepatic function.\(^ {11}\)

#### Rivaroxaban

Repeat renal and liver function tests and FBC at least annually\(^ {11}\)

If renal function has declined review treatment, as rivaroxaban may need to be stopped or a lower dose may be required

Repeat renal function tests:\(^ {11}\)
- If CrCl 30-60ml/min - every 6 months
- If CrCl 15-30ml/min - every 3 months

Renal and liver function tests should be performed more often if there is intercurrent illness that may impact on renal and hepatic function.\(^ {11}\)

### Efficacy for stroke prevention

- **Superior to warfarin (ARISTOTLE)\(^ {12}\)**
- Slightly superior to warfarin with 150mg twice daily dose
- Non-inferior to warfarin with 110mg twice daily dose (RE-LY)\(^ {13}\)
- Non-inferior to warfarin (ROCKET-AF)\(^ {14}\)

### Mean time in therapeutic range

- Apixaban: 62\(^ {12}\)%
- Dabigatran: 64\(^ {13}\)%
- Rivaroxaban: 55\(^ {14}\)%

### 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
<table>
<thead>
<tr>
<th>Missed dose</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice a day dosing</td>
<td>Twice a day dosing</td>
<td>Once daily dosing may support concordance - once a day dosing</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Requirement for compliance aid</th>
<th>Warfarin – not suitable for compliance aids unless risk assessment has been undertaken and a management plan is in place to manage dosage changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Twiceday dosing</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Missed dose may still be taken up to 6 hours prior to next scheduled dose, if within 6 hours of next dose, missed dose should be omitted</td>
</tr>
<tr>
<td>Rivaroxaban</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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanical heart valve</th>
<th>Not studied – not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular disease</td>
<td>Not studied – not recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extremes of BMI</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Twiceday dosing</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Missed dose may still be taken up to 6 hours prior to next scheduled dose, if within 6 hours of next dose, missed dose should be omitted</td>
</tr>
<tr>
<td>Rivaroxaban</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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal impairment (see additional advice above in Doses)</th>
<th>Cockcroft and Gault formula: CrCL = (140-Age) X Weight X Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Serum creatinine [Age (in years), Weight (in kilograms), Constant = 1.23 (Men); 1.04 (Women), Serum creatinine (in micromole/litre)]</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic impairment</th>
<th>Not recommended in severe hepatic impairment as requires hepatic metabolism. Check baseline LFTs prior to initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Contraindicated in patients with hepatic impairment or liver disease expected to impact on survival</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Use caution if CrCL 15-29mL/min Contraindicated in CrCL&lt;15mL/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (≥80 yrs)</th>
<th>Consider dose reduction in ≥80yrs – 2.5mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Use reduced dose -110mg twice daily</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Use caution if CrCL 15-29mL/min Contraindicated in CrCL&lt;15mL/min</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Use caution if CrCL 15-29mL/min Contraindicated in CrCL&lt;15mL/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy &amp; breastfeeding</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>No dose reduction unless age related renal impairment</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Contraindicated in pregnancy and breastfeeding</td>
</tr>
</tbody>
</table>

---

Management of Atrial Fibrillation (AF)  
Updated: September 2014  
Review date: August 2016  
Page 19 of 26
<table>
<thead>
<tr>
<th>Major bleed risk compared to warfarin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced risk (ARISTOTLE)(^\text{12})</td>
<td>Similar risk with 150mg twice daily</td>
<td>Reduced risk with 110mg twice daily (RE-LY)(^\text{13})</td>
<td>Similar risk (ROCKET-AF)(^\text{14})</td>
</tr>
</tbody>
</table>

| Intracranial bleed risk compared to warfarin | Reduced risk (ARISTOTLE)\(^\text{12}\) | Reduced risk (RE-LY)\(^\text{13}\) | Reduced risk (ROCKET-AF)\(^\text{14}\) |

| Major GI bleed risk compared to warfarin | Similar risk (ARISTOTLE)\(^\text{12}\) | Significantly increased risk with 150mg twice daily | Increased risk (ROCKET-AF)\(^\text{14}\) |

| Risk of dyspepsia/upper GI side effects compared to warfarin | Non-reported (ARISTOTLE)\(^\text{12}\) | Dyspepsia was significantly more common with both doses of dabigatran (RE-LY)\(^\text{13}\) | Similar risk of dyspepsia (ROCKET-AF)\(^\text{14}\) |

| Risk of MI compared to warfarin | Reduced risk (ARISTOTLE)\(^\text{12}\) | Increased risk but trend did not reach statistical significance (RE-LY)\(^\text{13}\) | Reduced risk but trend did not reach statistical significance (ROCKET-AF)\(^\text{14}\) |

### Reversibility

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<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. Administration of activated charcoal reduces apixaban exposure.</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. Therefore the use of idarucizumab or haemodialysis can be used in the case of uncontrolled bleeding associated with dabigatran therapy.</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. The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.</td>
</tr>
</tbody>
</table>

### Conversion from warfarin to NOAC (consult locally agreed pathways if available)

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<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</td>
<td>Discontinue warfarin and start rivaroxaban when: - INR ≤3.0 for prevention of stroke and systemic embolism. - Caution: INR values will be falsely elevated after the intake of rivaroxaban.</td>
</tr>
</tbody>
</table>

### Conversion from NOAC to warfarin/alternative NOAC (consult locally agreed pathways if available)

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<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 apixaban6.</td>
<td>CrCl ≥50mL/min – Start warfarin 3 days before discontinuing dabigatran. CrCl ≥30- &lt;50mL/min – Start warfarin 2 days before discontinuing dabigatran(^\text{7}). 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>Co-administer rivaroxaban and warfarin until INR&gt;2.0. Test INR 24hours after previous dose but prior next dose of rivaroxaban. Start warfarin as standard initial dosing followed by dosing guided by INR testing. Once rivaroxaban is discontinued, INR testing may be done reliably at least 24hours after the last dose.</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.

---

Management of Atrial Fibrillation (AF)
Updated: September 2014
Review date: August 2016
Page 20 of 26
<table>
<thead>
<tr>
<th>Before surgery (see SPC for details)</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. Discontinue at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding.</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>
<td>If possible, based on the clinical judgement of the physician, discontinue 24 hours before surgery or invasive procedure.</td>
</tr>
</tbody>
</table>

Table adapted from and thanks to Greater Manchester Commissioning Support Unit Medicines Optimisation Team
Appendix 6: 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?
  - Yes
  - Warfarin
  - No
  - Consider a NOAC
Consider a NOAC

Drug Interactions: See BNF or SPC for details of interactions. In most cases patients taking drugs that may interfere with anticoagulants would be better taking warfarin so that INR can be monitored and dose adjusted accordingly.

Clinical Considerations

- Please note that there have been no head-to-head trials between NOACs and the following are only recommendations made using indirect comparisons.

Logistical Considerations

- Patient needs once daily dosing and unable to take warfarin. Other NOACs appear to be more effective but rivaroxaban is non-inferior to warfarin.

**Apixaban and rivaroxaban 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 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>CHA2DS2-VASc Score</th>
<th>n</th>
<th>Events per 100 patients/year</th>
<th>Ischaemic stroke</th>
<th>Stroke/TIA/peripheral emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5343</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6770</td>
<td>0.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11,240</td>
<td>2.5</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17,689</td>
<td>3.7</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>19,091</td>
<td>5.5</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14,488</td>
<td>8.4</td>
<td>11.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9577</td>
<td>11.4</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4465</td>
<td>13.1</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1559</td>
<td>12.6</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>268</td>
<td>14.4</td>
<td>20.3</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 8: 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
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.