Prescribing Guidance for Oral Anticoagulants in Non-Valvular AF
<table>
<thead>
<tr>
<th>Version Number</th>
<th>Date</th>
<th>Amendments made</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version 1.1</td>
<td>Nov 13</td>
<td>Updated contraindications and warnings for all three drugs issued by MRHA October 2013</td>
</tr>
<tr>
<td>Version 1.2</td>
<td>Dec 13</td>
<td>- Rivaroxaban dose amended from 5mg to 15mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Apixaban renal function creatinine clearance amended from 30+ ml to &gt;30 ml / min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dronedarone included on the contra-indications for Dabigatran.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Box 2 page 3 extended to complete the sentence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (SEE) removed as always used in full</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Guidelines put into Standard Guidelines covers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Review date amended to November 2016</td>
</tr>
<tr>
<td>Version 2.0</td>
<td>March 16</td>
<td>- Purpose &amp; Scope of guidance clarified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Information on edoxaban incorporated as per NICE TA 355.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Renal section updated with information on CrCl vs eGFR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Serious drug interactions updated as per BNF 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Contraindications updated as per SPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Use of DOACs with antiplatelets considered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prescribing information section updated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Information on dabigatran reversal incorporated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dabigatran discontinuation information updated as per the SPC</td>
</tr>
<tr>
<td>Version 3.0</td>
<td>November 2016</td>
<td>- Oral anticoagulant consensus statement, decision aid incorporated with the DOAC guidance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dabigatran (Pradaxa) information updated in line with SPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- References checked and updated.</td>
</tr>
<tr>
<td>Version 3.1</td>
<td>May 2018</td>
<td>Reference to Cockcroft Gault equation - may underestimate Creatinine Clearance in overweight patients.</td>
</tr>
<tr>
<td>Review date</td>
<td>November 2019</td>
<td></td>
</tr>
</tbody>
</table>
Guidance for prescribing Oral Anticoagulants in Patients with Non-Valvular AF

1. Introduction
Atrial fibrillation (AF) is the most common cardiac arrhythmia and is a major cause of ischaemic stroke. Anticoagulation to reduce the risk of stroke is an essential part of AF management but patients are not always appropriately anticoagulated.\(^1\) NICE Guidance emphasises the importance of undertaking a stroke risk assessment for all patients with AF and anticoagulating, where safe and appropriate. All people with AF should be offered a personalised package of care which includes up-to-date, comprehensive information and practical advice on their anticoagulation in line with recommendations made in NICE CG144 section 1.3.1.\(^2\)

The recent availability of Non-Vitamin K Antagonist Oral Anticoagulants (DOACs), has led to a major change in the management of stroke prevention in atrial fibrillation (AF). At the same time there is greater understanding of how to manage warfarin, with the importance of the average time in therapeutic range (TTR) increasingly recognised.

2. Purpose
The aim of this guidance is to summarise key information around the assessment of patients with Non-Valvular AF (NVAF) and to compare oral anticoagulant options, thereby providing support for patients and clinicians to make informed choices about which anticoagulant is most appropriate. Additionally, prescribing information is provided which offers further advice on the management of anticoagulant therapy in particular clinical scenarios.

3. Scope
This guidance outlines the assessment of patients with NVAF to determine if anticoagulation is needed. It also summarises and compares key prescribing considerations for oral anticoagulants when used for stroke prevention in patients with NVAF. It should be read in conjunction with the relevant Summary of Product Characteristics.

This guidance does not:
- Provide oral anticoagulant dosing information for other indications
- Provide information on use of heparins or Low Molecular Weight Heparins.
4. Guidance

4.1 Assessing the Need for Oral Anticoagulant Drugs in adults with NVAF: Oral Anticoagulant Consensus Statement (See also Appendix 1)

4.1.1 Assess stroke risk using CHA²DS₂VASc in patients with:
- Symptomatic or asymptomatic paroxysmal, persistent or permanent AF or
- Atrial flutter, or
- Continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

**CHA²DS₂VASc**: The CHA²DS₂VASc score is used to estimate the 1 year risk of stroke or thromboembolic event in a non-anticoagulated patients with NVAF.

<table>
<thead>
<tr>
<th>Calculating CHA²DS₂VASc</th>
<th>Annual stroke/VTE risk associated with CHA²DS₂VASc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
<td>Score</td>
</tr>
<tr>
<td>C: Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>H: Hypertension History</td>
<td>1</td>
</tr>
<tr>
<td>A: Age 65-74yrs</td>
<td>1</td>
</tr>
<tr>
<td>A: Age &gt;75yrs</td>
<td>2</td>
</tr>
<tr>
<td>D: Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S: Stroke/TIA/Thromboembolism history</td>
<td>2</td>
</tr>
<tr>
<td>Va: Vascular Disease History</td>
<td>1</td>
</tr>
<tr>
<td>Sex Category: Female</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CHA²DS₂VASc Annual event risk %</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

4.1.2 Use the HAS-BLED score to assess bleeding risk in patients who are starting/have started anticoagulation. Offer modification and monitoring of the following risk factors; uncontrolled hypertension, poor control of international normalised ratio (INR), concurrent medication (e.g. aspirin or NSAIDs) and harmful alcohol consumption.

<table>
<thead>
<tr>
<th>Calculating HAS-BLED</th>
<th>Annual Risk of Major Bleed associated with HAS-Bled score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td>Score</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1</td>
</tr>
<tr>
<td>Stroke history</td>
<td>1</td>
</tr>
<tr>
<td>Prior major bleeding or predisposition to bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>1</td>
</tr>
<tr>
<td>Medication usage predisposing to bleeding e.g. NSAIDs, Aspirin</td>
<td>1</td>
</tr>
<tr>
<td>Harmful alcohol usage</td>
<td>1</td>
</tr>
</tbody>
</table>

**HAS-BLED**: The HAS-BLED score is designed to help clinicians to make an informed assessment of bleeding risk and identify correctable risk factors e.g. uncontrolled hypertension, concomitant use of NSAIDs, etc. It cannot be used in isolation to exclude anticoagulation or to confer the absence of risk. Prescribers must continue to make a careful assessment of the risks Vs benefits of treatment for each individual patient and take measures to address correctable risk factors when possible.
If, on discussion, anticoagulation is rejected because of bleeding risks or other factors review the decision annually & document the reasoning.

**Offer anticoagulation to males & females with CHA\textsubscript{2}DS\textsubscript{2}VASc score≥2** (take bleeding risk into account).

Do NOT withhold anticoagulation solely because the person is at risk of having a fall.

Do NOT offer anticoagulation to people <65yrs with AF & no risk factors other than sex i.e. with a CHA\textsubscript{2}DS\textsubscript{2}VASc score of 0 for men & 1 for women. This patient group is defined in NICE CG180 as having very low risk of stroke.

Do NOT offer aspirin monotherapy solely for stroke prevention in AF. For patients currently taking aspirin, consider anticoagulation, taking account of co-morbidities & other reasons for using aspirin.

The *decision about which oral anticoagulant to start* should be based on the patient’s clinical features and preferences. There should be an informed discussion between the clinician and patient, with consideration of the risks & benefits of different therapies. (See Decision Aid in Appendix 2)

**Options for oral anticoagulation include:** Warfarin (or other vitamin K antagonist) or the Non-vitamin K antagonist Oral Anticoagulants (DOACs) i.e. Apixaban, Dabigatran, Rivaroxaban and Edoxaban.

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

**DOACs** do not need INR monitoring, however careful initiation and management is essential. There is no standard measure to assess compliance with DOACs. In addition, whilst DOACs have a shorter half-life compared to warfarin, there is only an established antidote for dabigatran i.e. Idarucizumab (licensed December 2015). Apixaban, rivaroxaban and edoxaban are currently black triangle drugs.

For patients taking warfarin (or other vitamin K antagonist), assess anticoagulation control. Poor control can be identified by unexplained INRs outside the normal range and is classed as either; TWO INRs >5 or <1.5 or ONE INR >8 within the past 6 months, or a Time in Therapeutic Range (TTR) < 65%.

NB. Out of range INRs may sometimes be explained by drug interactions e.g. antibiotic therapy

TTR should be calculated at each INR testing, using a validated methodology. Exclude measurements taken during the 1st SIX weeks of treatment and calculate the TTR over a maintenance period of ≥ SIX months. TTRs should be provided to GPs to allow for clinical evaluation.

If poor control is identified where possible take measures to address: cognitive function, adherence, illness, interacting medications and lifestyle factors e.g. diet and alcohol consumption.

If anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss with the person. NB. If poor control is as a result of non-compliance switching to a different agent is unlikely to address the issue.
**Figure 1: AF Patient Assessment**

**START:** Patient has Atrial Fibrillation, atrial flutter or risk of arrhythmia recurrence following cardioversion

Is the patient already taking anticoagulation?

- **Yes**
  - For all patients on anticoagulation
    - Assess:
      - Compliance
      - Cognitive function
      - Concurrent illness
      - Interacting drug therapy
      - Bleeding risk using HAS-BLED
      - Lifestyle factors; diet & alcohol consumption
    - Where possible take measures to address the above

- **No**
  - Assess stroke risk using CHA₂DS₂VASc
    - **Yes**
      - Assess bleeding risk using HAS-BLED
        - If the patient is male & CHA₂DS₂VASc = 1
          - Consider ANTICOAGULATION taking bleeding risk into account
        - If the patient is either male or female & CHA₂DS₂VASc = 2 or more
          - Offer ANTICOAGULATION taking bleeding risk into account
          - If poor control is a result of non-compliance switching to a different agent is unlikely to resolve this

  - **No**
    - **Is the patient: Female & CHA₂DS₂VASc ≥2? Or Male & CHA₂DS₂VASc ≥1?**
      - **Yes**
        - Evaluate risks & benefits of alternative stroke prevention strategies and discuss with the patient.
      - **No**
        - For patients taking Warfarin or another Vitamin K Antagonist
          - Assess INR control. Poor control is indicated by:
            - TTR ≤65% which cannot be accounted for or
            - Two or more unexplained INRs > 5 or <1.5 in the last 6 months or
            - A single unexplained INR >8 in the last 6 months
          - Good control
            - Continue on Current Therapy
          - Poor control
            - Take measures to address

**Discuss the risks & benefits of each stroke prevention strategy. Choice of anticoagulant should be based on clinical features & patient preferences.** Anticoagulation options:
- Warfarin as per CG180
- Dabigatran as per TA249 & CG180
- Rivaroxaban as per TA256 & CG180
- Apixaban as per TA275 & CG180
- Edoxaban as per TA 355

**NB.** Whilst NOACs do not need INR monitoring, careful initiation & management is essential.

See also decision aid Appendix 2.

**Reassess anticoagulation annually or more frequently if clinically indicated**

Read code for annual warfarin assessment = 66QB
4.2. Oral Anticoagulants Prescribing Information.

Vitamin K antagonists (VKAs) have been the main agents for antithrombotic prevention in atrial fibrillation (AF) for >60 years and have had an unquestionable impact on stroke prevention. More recently, a range of Non-Vitamin K Antagonist Oral Anticoagulants have been licensed. This has led to increased anticoagulant options and a need to provide supporting guidance around use.

NICE TA 249,3 256,4 2755 and 3556 recommend dabigatran*, rivaroxaban, apixaban* and edoxaban respectively, as options for prevention of stroke in non-valvular Atrial Fibrillation (NVAF) if patients have one or more of the following risk factors:

- Previous stroke or TIA
- Age 75 Years or older
- Congestive heart failure
- Hypertension
- Diabetes.

*For Dabigatran, NICE and SPC stipulates: heart failure of NYHA class 2 or above and age of over 65 with diabetes, CAD or hypertension.

*For Apixaban, NICE and SPC stipulates: heart failure of NYHA class 2 or above

As per NICE CG 1807 (Atrial Fibrillation Management), treatment may also be with a vitamin K antagonist such as warfarin. The clinician should discuss the risks and benefits of treatment options before considering initiation or switching. For patients with a stable INR already on warfarin or coumarin it may be appropriate to remain on current drug.

All patients receiving oral anticoagulants should be referred for an urgent review if presenting with unexplained iron deficiency anaemia or drop in Hb. Thresholds for referral are:

- Male Hb <11g/dl
- Post-menopausal Female Hb <10g/dl

SEE individual SPCs and Appendix 2 Oral Anticoagulant Decision Aid for Cautions and Contra-indications

4.2.1 Anticoagulant Dose For Stroke Prevention in NVAF 8,9,10,11&12

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Once daily dosing. Initiation as per local organisation guidance, different people will required different doses pre-existing conditions may make people more or less sensitive to warfarin Dose adjusted based on the INR (Computerised Decision Support Software, should be used where available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>&lt; 80yrs:150mg Twice daily*</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCL: &gt;49mL/min: 20mg Once daily 30-49mL/min: 15mg Once daily 15-29mL/min: 15mg Once daily</td>
</tr>
<tr>
<td>Apixaban</td>
<td>CrCl: &gt;29ml/min: 5mg Twice daily* 15–29ml/min: 2.5mg Twice daily</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Dose = 60mg* Once Daily</td>
</tr>
</tbody>
</table>
| *2.5mg twice daily if two of the following: Age ≥ 80years Weight ≤ 60kg Serum Cr ≥ 1.5mg/dl (133micromol /L) | *For the following patient groups the daily dose of 300mg or 220mg should be based on an assessment of the thromboembolic Vs bleeding risk 75-80yrs 75-80yrs Moderate renal impairment (CrCl 30-49ml/min) Increased risk of bleeding e.g. gastritis, esophagitis or reflux, high HAS-BLED |}

*30mg Once daily if one or more of the following: CrCl 15-50ml/min Weight ≤ 60Kg Concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole
4.2.2 Renal Dose Adjustments

Before initiation of an anticoagulant, patients must have an up to date renal function test, the results may affect treatment choice and the dose used.

| CrCl > 50 ml/min | Warfarin can be used. 
All 4 DOACs may be used. 
NB. Edoxaban should only be used in patients with NVAF and high CrCl after careful evaluation of the individual thromboembolic and bleeding risk (there is a trend towards decreasing efficacy with increasing CrCl compared to well-managed warfarin). |
| CrCl 30-49 ml/min | Warfarin can be used: More frequent INR monitoring may be required 
All 4 DOACs may be used. 
Dabigatran - dose reduction should be considered 
Rivaroxaban and edoxaban - dose adjustment required |
| CrCl 15-29 ml/min | Warfarin can be used: More frequent INR monitoring may be required 
Dabigatran - contraindicated 
Rivaroxaban, apixaban and edoxaban - dose adjustment required |
| CrCl < 15 ml/min | Warfarin can be used: More frequent INR monitoring may be required 
Dabigatran - contraindicated 
Rivaroxaban - use not recommended 
Apixaban - no clinical experience, use not recommended 
Edoxaban - use not recommended |

NB. Renal function can decline while on treatment, monitor annually or more frequently in high-risk patients or when a change in renal function is suspected during treatment (e.g. hypovolaemia, dehydration).

4.2.3 Use of Creatinine Clearance (CrCl) Vs eGFR

- The BNF and SPCs use CrCl as the basis of dose adjustment for the DOACs. The SPCs for dabigatran and edoxaban specifically state that CrCL should be used to assess renal function.
- CrCl and eGFR are calculated using different formulas and they are not routinely interchangeable.
- Because renal function in adults is increasingly being reported on the basis of eGFR, the BNF now provides information on dosage adjustment in terms of eGFR rather than CrCl for most drugs.
- In practice, for most drugs and for most patients (over 18 years) of average build and height, the eGFR can be used to determine dosage adjustments in place of CrCl. Exceptions being for toxic drugs or drugs with a narrow therapeutic index and in patients at extremes of weight (BMI < 18.5 kg/m² & > 30 kg/m²).
- Therefore, although eGFR can be used in place of CrCl to determine dose adjustments in most patients, DOAC dosing should be based on CrCl where possible. For patients at increased risk of toxicity or adverse events, CrCl or absolute GFR should always be used.

Cockcroft-Gault Equation

The Cockcroft Gault equation may underestimate creatinine clearance in overweight patients and caution should be used when DOAC adjustment is being considered

*Use ideal body weight (IBW) if actual weight is greater than 120% IBW (or if the BMI > 30)

IBW (kg) = (number of inches over 5ft x 2.3) + 50 (males) or 45.5 (females)

Or consider using https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation
4.3 DOACs Frequently Asked Questions

4.3.1 Concomitant use of DOACs and Antiplatelets\textsuperscript{14,15}

The co-prescription of an antiplatelet agent with a DOAC confers an additional bleeding risk. If a patient is on an antiplatelet because of pre-existing ischaemic heart disease (or cerebrovascular disease), the antiplatelet agent should be reviewed with a view to discontinuation. As summarised by UKMI this is a complex area because:

- Dual antiplatelet therapy reduces the risk of ischaemic cardiac events but not AF related thrombotic stroke.
- Anticoagulants reduce the risk of AF related thrombotic stroke but not of cardiac ischaemic events.
- The combination of dual-antiplatelet therapy plus anticoagulant (referred to as “triple oral antithrombotic therapy” or “triple therapy”) increases the risk of bleeding events by about 2-4 times compared to anticoagulant or aspirin alone.

The optimal strategy to balance the risk of bleeding events and recurrent ischaemic events in people needing antiplatelets and anticoagulants is subject to debate because specifically designed and powered studies are not available. The choice of therapy and its duration should be individualised, based on atherothrombotic risk, cardio-embolic risk, and bleeding risk.

European guidelines advise the following:

- Patients with stable coronary artery disease (i.e. no acute ischaemic events or PCI/stent in the preceding 12 months) and concurrent AF can be managed with anticoagulation alone.
- Gastroprotection with a proton pump inhibitor should be considered in all patients on any combination of antiplatelets.
- The routine use of P2Y12 inhibitors (prasugrel and ticagrelor) in combination with a NOAC is not recommended due to the increased risk of major bleeding.
- Where a NOAC is used with an antiplatelet, the lowest effective dose to reduce the risk of stroke should be considered.
- The period of dual antiplatelet therapy plus anticoagulant should be as short as possible (e.g. not exceeding 6 months for patients at low risk of bleeding or 4 weeks for patients at high risk of bleeding). This can be followed by single antiplatelet therapy plus anticoagulant for up to 12 months then lifelong anticoagulant.

Further information is available from UKMI.

If there are concerns about stopping the antiplatelet then cardiology advice should be sought.

4.3.2 DOAC Monitoring Requirements\textsuperscript{8,10,11,12,16}

There are no specific monitoring requirements outlined in the SPCs with the exception of:

- **Dabigatran where the** manufacturer recommends that renal function should be checked at least once a year.
- **Edoxaban where** renal function should be checked at beginning of treatment then as clinically indicated. If treatment is beyond 1 year hepatic function should be tested periodically.

Patients at high risk of bleeding should be monitored for signs and symptoms of bleeding complications and anemia after initiation of anticoagulation. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

It is good practice to reassess anticoagulation annually or more frequently if clinically indicated. The annual check should be used as an opportunity to check adherence and reassess whether an anticoagulant/DOAC prescription is still appropriate, if the patient has any adverse effects and if any new interacting medicines have been started.

4.3.4 DOACs and Heart Murmurs/Valvular AF\textsuperscript{16}

DOACs are not indicated (or licensed), for use in patients with rheumatic mitral stenosis, mechanical prosthetic heart valves or who have had a valve repair or tissue valve replacement. If a patient has a heart murmur and new AF, initiation of an anticoagulant should not be delayed whilst waiting for the cause of the murmur to be established. If valvular heart disease is later diagnosed (e.g. from an echocardiogram) the patient should be referred to cardiology who will review the medicines as appropriate.
### 4.3.5 Conversions between DOACs and Warfarin

<table>
<thead>
<tr>
<th>Conversion from DABIGATRAN to WARFARIN</th>
<th>Conversion from WARFARIN to DABIGATRAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjust the starting time of warfarin based on CrCl as follows:</strong></td>
<td><strong>Discontinue warfarin and start dabigatran when the INR is below 2.0</strong></td>
</tr>
<tr>
<td>• CrCl &gt; 50mL/min, start warfarin 3 days before discontinuing dabigatran.</td>
<td>(This usually occurs 3-5 days after discontinuing warfarin)</td>
</tr>
<tr>
<td>• CrCl 31-50mL/min, start warfarin 2 days before discontinuing dabigatran.</td>
<td>Care is needed when converting patients from Warfarin to Dabigatran that the patient fully understands the process. DOAC</td>
</tr>
<tr>
<td>• CrCl 15-30mL/min, start warfarin 1 day before discontinuing dabigatran</td>
<td></td>
</tr>
<tr>
<td>• CrCl &lt; 15mL/min, no recommendations can be made – consult with on call haematologist.</td>
<td></td>
</tr>
</tbody>
</table>

Dabigatran can contribute to an elevated INR, the INR will better reflect warfarin’s effect after dabigatran has been stopped for at least 2 days.

<table>
<thead>
<tr>
<th>Conversion from RIVAROXABAN to WARFARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin should be given concurrently until the INR is ≥ 2.0.</strong></td>
</tr>
<tr>
<td>(Use standard initial dosing for the first two days, after which the warfarin dose should be guided by INR testing).</td>
</tr>
</tbody>
</table>

**NB** rivaroxaban can contribute to an elevated INR. Once rivaroxaban is discontinued INR testing may be done reliably after at least 24hrs from the last dose.

<table>
<thead>
<tr>
<th>Conversion from APIXABAN to WARFARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continue apixaban for at least 2 days after starting warfarin therapy and then check the INR.</strong></td>
</tr>
<tr>
<td><strong>Continue co-administration of apixaban and warfarin until the INR is 2 or more</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conversion from EDOXABAN to WARFARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For patients on a 60mg dose</strong>, give 30mg once daily together with an appropriate dose of warfarin.</td>
</tr>
<tr>
<td><strong>For patients on a 30mg dose</strong>, give 15mg once daily together with an appropriate dose of warfarin. <strong>A loading dose of warfarin should not be taken.</strong></td>
</tr>
<tr>
<td>Once an INR ≥2.0 is achieved, stop edoxaban. <strong>(85% of patients should achieve this within 14 days of concomitant administration).</strong> Measure the INR at least 3 times during these 14 days of concomitant usage, (just prior to taking the daily dose of edoxaban to minimise the influence of edoxaban on the INR)</td>
</tr>
</tbody>
</table>

### 4.4 Further DOAC Drug Specific Prescribing Guidance

(To be read in conjunction with SPCs)

#### 4.4.1 DABIGATRAN (Pradaxa)

**Missed dose:** A forgotten dose of dabigatran etexilate may still be taken up to 6 hours before the next scheduled dose. From 6 hours before the next scheduled dose on, the missed dose should be omitted. No double dose should be taken to make up for missed individual doses.

**Special Patient Populations** (See section 4.2.1-2 for renal dose adjustments and contraindications)
- **Patients between 75-80 years**: Treat with 150mg twice daily. A dose of 110mg twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.
- **For patients with gastritis, oesophagitis, or gastroesophageal reflux**, a dose of 110 mg twice daily may be considered due to the elevated risk of major gastro-intestinal bleeding with dabigatran.
- As with warfarin, co-administration of aspirin, clopidogrel or NSAID increases risk of bleeding. (See section 4.3.1)
- **Patients with elevated liver enzymes > 2 upper limit of normal** were excluded from the study investigating the prevention of stroke and systemic embolism associated with atrial fibrillation. Experience of treatment with this subpopulation of patients is lacking therefore the use of dabigatran is not recommended in this population.
- **Pregnancy** There are limited data from the use of dabigatran in pregnant women.
- Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. The SPC states dabigatran ‘should not be used during pregnancy unless clearly necessary’.
- **Breastfeeding** There are no clinical data on the effect of dabigatran in infants during breastfeeding. The SPC states breastfeeding should be discontinued during treatment.

**When clinically relevant bleeding occurs**: In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. As dabigatran is excreted predominantly by the renal route, adequate diuresis must be maintained. Depending on the clinical situation, appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber’s discretion.

**Reversal of anticoagulant effects**: Idarucizumab (Praxbind®) is a specific reversal agent for dabigatran and is indicated in patients treated with dabigatran when rapid reversal of its anticoagulant effect is needed e.g. for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding (use is restricted to hospital). Refer to the SPC.

### DISCONTINUATION of DABIGATRAN (If an invasive procedure or surgical intervention is required)

<table>
<thead>
<tr>
<th>Renal function (CrCl mL/min)</th>
<th>Estimated half-life (hrs)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≥ 80</td>
<td>~13</td>
<td>24 hours</td>
</tr>
<tr>
<td>CrCl ≥ 50 to &lt; 80</td>
<td>~15</td>
<td>1-2 days before</td>
</tr>
<tr>
<td>CrCl &gt;30 to &lt; 50</td>
<td>~18</td>
<td>2-3 days before (&gt;48hrs)</td>
</tr>
<tr>
<td>CrCl ≤30</td>
<td></td>
<td>Dabigatran is contraindicated if CrCl ≤30</td>
</tr>
</tbody>
</table>

* Types of surgery associated with a high risk of bleeding (or in major surgery where complete haemostasis may be required) include but are not limited to; cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease), low body weight (< 50kg) and concomitant use of antiplatelet therapy.

**Restart** as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established.

Peak plasma concentrations are reached at 6 hours following administration in a postoperative period due to contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It has been demonstrated that slow and delayed absorption is usually only present on the day of surgery. On subsequent days, absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.

### 4.4.2 RIVAROXABAN (Xarelto▼)

**Missed dose**: If a dose is missed the patient should take rivaroxaban immediately and then continue the following day with once daily intake as before. No double dose should be taken to make up for a missed dose.

**Special Patient Populations** (See 4.2.1 for renal dose adjustments)
- **Elderly** No dose adjustment needed
- **For patients with gastritis, oesophagitis, or gastroesophageal reflux**, the lower dose of 15mg may be considered due to the elevated risk of major gastro-intestinal bleeding.
As with warfarin, co-administration of aspirin, clopidogrel or NSAID increases risk of bleeding. (See section 4.3.1)

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C - contraindicated

Pregnancy Studies in animals have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and evidence that rivaroxaban crosses the placenta, rivaroxaban is contraindicated during pregnancy

Breastfeeding Rivaroxaban is contraindicated during breast feeding. Data from animals indicate that rivaroxaban is secreted into milk.

**DISCONTINUATION of RIVAROXABAN (If an invasive procedure or surgical intervention is required)**

Stop at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Restart as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established.

There is no antidote to rivaroxaban. When clinically relevant bleeding occurs:

Treatment should be interrupted. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets. If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). Refer to the SPC and local hospital protocols for more information.

4.4.3 APIXABAN (Eliquis)

**Missed dose** If a dose is missed, the patient should take apixaban immediately and then continue with twice daily intake as before.

**Special Patient Populations** (See 4.2.1-2 for renal dose adjustments & contraindications)

- Elderly – See Section 4.1; dose adjustment may be required for patients >80yrs
- As with warfarin, co-administration of aspirin, clopidogrel and NSAID increases risk of bleeding. (See section 4.3.1)
- Hepatic Disease Apixaban is contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). It should be used with caution in patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN as they were excluded from clinical trials.
- Pregnancy Not recommended during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
- Breastfeeding It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. A risk to newborns and infants cannot be excluded.

There is no antidote to apixaban. When clinically relevant bleeding occurs, discontinue treatment and investigate the source of bleeding. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered. If life-threatening bleeding cannot be controlled by the above measures, administration of prothrombin complex concentrates (PCC) or recombinant factor VIIa may be considered. Refer to the SPC and local hospital protocols for more information.

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.

**DISCONTINUATION of APIXABAN (If an invasive procedure or surgical intervention is required)**

Stop at least 48hrs prior to elective surgery or invasive procedures with a moderate or high risk of bleeding
Discontinued at least 24hrs prior to elective surgery or invasive procedures with a low risk of bleeding including interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding against the urgency of intervention.

**Restart** as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established.

4.4.4 EDOXABAN (Lixiana▼)

**Missed dose** If a dose is missed, it should be taken immediately and then continued the following day. The patient should not take double the prescribed dose on the same day to make up for a missed dose.

**Special Patient Populations** (See 4.2.1-2 for renal dose adjustments & contraindications)

- **Elderly** – No dose reduction required
- **Medicines or conditions which increase gastric emptying or motility** have the possibility of reducing dissolution and absorption, (edoxaban is predominantly absorbed in the upper GI tract).
- As with warfarin, co-administration of aspirin, clopidogrel or NSAID increases risk of bleeding. The administration of a PPI can be considered. In clinical studies, mucosal bleeding and anaemia was seen more frequently during long term edoxaban treatment compared with VKA treatment, therefore in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding. (See also section 4.3.1)
- **Hepatic Disease** Edoxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. (Liver function should be checked before initiation). It is not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild to moderate hepatic impairment (dose- 60mg once daily).
- Patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥ 1.5 x ULN were excluded in trials and so edoxaban should be used with caution in this population.
- **Pregnancy** Animal studies have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and evidence that edoxaban passes the placenta, it is contraindicated during pregnancy. Women of childbearing potential should avoid becoming pregnant during treatment.
- **Breastfeeding** Data from animals indicate that edoxaban is secreted into breast milk and therefore edoxaban is contraindicated during breastfeeding.

There is no specific antidote for edoxaban.

**When clinically relevant bleeding occurs.** Delay the next dose or discontinue as appropriate. Edoxaban has a half-life of ~10-14hrs. Management should be individualised according to severity and location of haemorrhage.

For life-threatening bleeding that cannot be controlled with measures such as transfusion or haemostasis, a 4-factor prothrombin complex concentrate at 50 IU/kg has been shown to reverse the effects of edoxaban 30mins after infusion. Refer to the SPC and local hospital protocols for more information.

**DISCONTINUATION of EDOXABAN** (If an invasive procedure or surgical intervention is required)

**Stop** as soon as possible and preferably at least 24 hours before the procedure.

When 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.

**Restart** as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established. The time to onset of the edoxaban anticoagulant therapeutic effect is 1-2 hours.
APPENDIX 1

Consensus statement for ORAL ANTICOAGULANT DRUGS for the prevention of stroke and systemic embolism in adults with Non-Valvular Atrial Fibrillation
(As per NICE CG180 recommendations)

The focus of Atrial Fibrillation (AF) management should be to undertake a stroke risk assessment and anticoagulate, where safe and appropriate. All people with AF should be offered a personalised package of care which includes up-to-date, comprehensive information and practical advice on their anticoagulation in line with recommendations made in NICE CG144 section 1.3.1.

Assess stroke risk using CHA2DS2VASc in patients with:
- Symptomatic or asymptomatic paroxysmal, persistent or permanent AF or
- Atrial flutter, or
- A continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

Use the HAS-BLED score to assess bleeding risk in patients who are starting/have started anticoagulation. Offer modification and monitoring of the following risk factors: uncontrolled hypertension, poor control of international normalised ratio (INR), concurrent medication (e.g. aspirin or NSAIDs) and harmful alcohol consumption.

When initiating anticoagulation, prescribers should be aware that the vitamin K antagonist warfarin has been in use for over 60 years, compliance is measurable and its effect can be reversed (e.g. if major bleeding occurs).

Consider anticoagulation for males with a CHA2DS2VASc score of 1 (take bleeding risk into account).

Offer anticoagulation to males & females with CHA2DS2VASc score≥2 (take bleeding risk into account).

If, on discussion, anticoagulation is rejected because of bleeding risks or other factors review the decision annually and document the reasoning.

Do NOT withhold anticoagulation solely because the person is at risk of having a fall.

Do NOT offer anticoagulation to people <65yrs with AF and no risk factors other than gender i.e. with a CHA2DS2VASc score of 0 for men and 1 for women. This patient group is defined in NICE CG180 as having very low risk of stroke.

Do NOT offer aspirin monotherapy solely for stroke prevention in AF. For patients currently taking aspirin, consider anticoagulation, taking account of co-morbidities & other reasons for using aspirin.

The decision about which oral anticoagulant to start should be based on the patient’s clinical features and preferences. There should be an informed discussion between the clinician and patient, with consideration of the risks and benefits of different therapies.

OPTIONS FOR ORAL ANTICOAGULATION INCLUDE: Warfarin (or other vitamin K antagonist) or the non-vitamin K antagonist oral anticoagulants (DOACs) i.e. Apixaban, Dabigatran, Rivaroxaban and Edoxaban. Whilst DOACs do not need INR monitoring, careful initiation and management is essential. There is no standard measure to assess compliance with DOACs. In addition, whilst DOACs have a shorter half-life than warfarin, only dabigatran has an established antidote i.e. Idarucizumab (licensed December 2015). Apixaban, rivaroxaban and edoxaban are currently black triangle drugs.

For patients taking warfarin (or other vitamin K antagonist), assess anticoagulation control. Poor control can be identified by unexplained INRs outside the normal range and is defined as either; TWO INRs >5 or <1.5 or ONE INR >8 within the past 6 months, or a Time in Therapeutic Range (TTR) < 65%.

NB. Out of range INRs may sometimes be explained by drug interactions e.g. antibiotic therapy. TTR should be calculated at each INR testing, using a validated methodology. Exclude measurements taken during the first SIX weeks of treatment and calculate the TTR over a maintenance period of ≥ SIX months. TTRs should be provided to GPs to allow for clinical evaluation.

If poor control is identified, where possible take measures to address: cognitive function, adherence, illness, interacting medications and lifestyle factors e.g. diet & alcohol consumption.

If anticoagulation control cannot be improved, evaluate the risks & benefits of alternative stroke prevention strategies and discuss with the person. NB. If poor control is as a result of non-compliance switching to a different agent is unlikely to address the issue.
Summary of recommendations for use of ORAL ANTI-COAGULANT DRUGS for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation

Assess stroke risk using CHA₂DS₂-VASc

Is the patient: Female & CHA₂DS₂-VASc ≥2? Or Male & CHA₂DS₂-VASc ≥1?

Yes

No

Assess bleeding risk using HAS-BLED

If the patient is male & CHA₂DS₂-VASc = 1

If the patient is either male or female & CHA₂DS₂-VASc = 2 or more

Consider ANTI-THROMBOCOAGULATION taking bleeding risk into account

Offer ANTI-THROMBOCOAGULATION taking bleeding risk into account

Do not offer Anticoagulation This patient group is defined in NICE CG180 as having very low risk of stroke

Review when the patient reaches 65yrs or sooner if CHA₂DS₂-VASc changes

Assess INR control. Poor control is indicated by:
- TTR ≤65% or
- Two or more unexplained INRs > 5 or <1.5 in the last 6 months or
- A single unexplained INR >8 in the last 6 months

For patients taking Warfarin or another Vitamin K Antagonist

Evaluate risks & benefits of alternative stroke prevention strategies & discuss with the patient.

If poor control cannot be resolved despite

Reassess anticoagulation annually

Or more frequently if clinically indicated

Read code for annual warfarin assessment = 66QB

Calculating CHA₂DS₂-VASc

Risk factor Score
C: Congestive Heart Failure 1
H: Hypertension History 1
A: Age 65-74yrs 1
A: Age >75yrs 2
D: Diabetes Mellitus 1
S: Stroke/TIA/Thromboembolism history 2
Vª: Vascular Disease History 1
Sex Category: Female 1

Annual stroke/VTE risk associated with CHA₂DS₂-VASc

CHA₂DS₂ VASc Annual event risk %
1 2.01
2 3.71
3 5.92
4 9.27
5 15.26
6 19.74
7 21.50
8 22.38
9 23.64

Calculating HAS-BLED

Risk factor Score
Hypertension (uncontrolled, >160mmHg systolic) 1
Renal disease (diabetes, transplant, Cr>200µmol/L) 1
Liver disease (cirrhosis, bilirubin >2xnormal, AST/ALT/AP >3xnormal) 1
Stroke history 1
Prior major bleeding or predisposition to bleeding 1
Labile INR (unstable/high INR), TTR <60% 1
Age >65 1
Medication usage predisposing to bleeding e.g. NSAIDs, Aspirin 1
Harshful alcohol usage History ≥2 drinks/week 1

Annual stroke risk of major bleed

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

Extra caution & regular review is required if prescribing anticoagulants for patients at moderate or high risk of major bleed. Measures to address correctable risk factors should be taken when possible

The HAS-BLED score is designed to help clinicians to make an informed assessment of bleeding risk & identify correctable risk factors e.g. uncontrolled hypertension, concomitant use of NSAIDs etc. It cannot be used in isolation to exclude anticoagulation or to confer the absence of risk. Prescribers must continue to make a careful assessment of the risks vs benefits of treatment for each individual patient and take measures to address correctable risk factors when possible

References:
1. NICE CG180, CG144, TA249, TA256, TA275 accessed 21/7/2014
3. SPC for each drug at http://www.medicines.org.uk/emis/
4. NICE TA355 accessed 4/1/16

November 2014, Updated Nov 2016 (Edoxaban & dabigatran antidote added)
Review November 2019
Appendix 2: Anticoagulation Decision Support Tool: Stroke Prevention in adults with Non-Valvular Atrial Fibrillation (NVAF) (Version 2.0)

**Scope:** To be used to help prescribers pick the most appropriate oral anticoagulant (after patient assessment has established that anticoagulation is appropriate)

- For information on assessment for anticoagulation see the LMMG Oral Anticoagulant Consensus Statement or NICE CG180
- For further prescribing information see the LMMG DOAC Prescribing Guide or the relevant SPC

### Table 1. NVAF Anticoagulant Decision Support Tool

Prescribers must be able to answer yes to all questions prior to initiating therapy

(Refer to the SPC for Further Information about the Individual Medications)

<table>
<thead>
<tr>
<th>Yes/No</th>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No</td>
<td>1.</td>
<td>The patient has Non-valvular Atrial Fibrillation (AF)</td>
</tr>
<tr>
<td>Yes/No</td>
<td>2.</td>
<td>CHA²DS²-VASc is 1 or more (Men) or 2 or more (Women)</td>
</tr>
<tr>
<td>Yes/No</td>
<td>3.</td>
<td>Bleeding risk has been assessed using HAS-BLED &amp; correctable risk factors addressed when possible</td>
</tr>
<tr>
<td>Yes/No</td>
<td>4.</td>
<td>Contra-Indications and cautions to anticoagulant therapy have been excluded e.g. known hypersensitivity, clinically-significant active bleeding, or concomitant use of an alternative anticoagulant.</td>
</tr>
</tbody>
</table>

#### Drug Specific Contra-Indications

<table>
<thead>
<tr>
<th>Warfarin (Marevan®)</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
<th>Edoxaban (Lixiana®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 48 hours postpartum</td>
<td>CrCl less than 30mL/min</td>
<td>Pregnancy &amp; breast feeding</td>
<td>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C</td>
<td>Pregnancy and breast feeding</td>
</tr>
<tr>
<td>Pregnancy (1st &amp; 3rd trimesters)</td>
<td>Hepatic impairment or liver disease expected to have any impact on survival</td>
<td>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk</td>
<td>Lesion or condition considered significant risk factor for major bleeding</td>
<td>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>Contraindicated for use for prosthetic heart valves</td>
<td>Lesion or condition considered significant risk factor for major bleeding*</td>
<td>Lesion or condition considered significant risk factor for major bleeding*</td>
<td>Uncontrolled severe hypertension</td>
</tr>
</tbody>
</table>

*Significant risk factors for bleeding include: current or recent GI ulceration, malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities

#### Use Not Recommended

**Dabigatran:** SPC states not to be used in pregnancy unless clearly necessary, breast feeding to be discontinued during treatment

**Rivaroxaban:** Not recommended if CrCl less than 15mL/min

**Apixaban:** Not recommended if CrCl less than 15mL/min or if undergoing renal dialysis

**Edoxaban:** Not recommended if CrCl less than 15mL/min or if undergoing renal dialysis

#### Cautions

**Liver Function**

All anticoagulants should be used with caution in mild- moderate liver impairment & avoided in severe impairment (especially if the baseline prothrombin time is prolonged).

**Full Blood Count**

All anticoagulants should be used with caution in patients with anaemia or low platelets.

Active bleeding should be ruled out prior to initiation and more frequent monitoring may be required.
5. Potential interactions with other medications or foods have been considered. NB – For all anticoagulants, caution should be exercised with drugs that affect haemostasis, e.g. NSAIDS, aspirin & clopidogrel

<table>
<thead>
<tr>
<th>Interactions&lt;sup&gt;5,12&lt;/sup&gt;</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple interactions requiring increased INR monitoring.</td>
<td>Contraindicated with Strong P-gp inhibitors e.g. ketoconazole, ciclosporine, itraconazole &amp; dronedarone. Concomitant treatment with tacrolimus, is not recommended.</td>
<td>Avoid concomitant treatment with strong inhibitors of CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors.</td>
<td>Avoid concomitant use with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole, voriconazole or HIV protease inhibitors.</td>
<td></td>
<td>P-gp inhibitors. Contraindicated use with ciclosporin, dronedarone, erythromycin or ketoconazole requires dose reduction to 30mg once daily. Concomitant use with P-gp inhibitors quinidine, verapamil or amiodarone does not require dose adjustment. Caution with P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John’s wort (may lead to reduced apixaban concentrations) No known food interactions.</td>
</tr>
<tr>
<td>Cranberry juice. alcohol, foods with high amounts of Vitamin K e.g. leafy green veg such as cabbage, spinach, brussel sprouts and broccoli</td>
<td>Caution with mild to moderate P-gp inhibitors: e.g. amiodarone, clarithromycin, verapamil and quinidine. Caution with mild to moderate P-gp inducers: rifampicin, phenytoin and carbamazepine. Caution with SSRIs &amp; SNRIs- increased risk of bleeding</td>
<td>Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John’s wort (may lead to reduced rivaroxaban concentrations) No known food interactions</td>
<td>Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John’s Wort (may lead to reduced apixaban concentrations) No known food interactions</td>
<td>No known food interactions</td>
<td></td>
</tr>
</tbody>
</table>

6. Baseline bloods and other relevant parameters have been checked; the dose has been adjusted if needed

<table>
<thead>
<tr>
<th>Dose Adjustments&lt;sup&gt;5,12&lt;/sup&gt;</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin AF dose: As per INR</td>
<td></td>
<td>AF dose: 150mg Twice Daily</td>
<td>AF dose: 20mg Once Daily</td>
<td>AF dose: 5mg Twice Daily</td>
<td>AF dose: 60 mg once daily.</td>
</tr>
<tr>
<td>Renal Function</td>
<td>Can be used with caution in renal impairment. * As per NICE CG 182 for patients with CKD and a confirmed eGFR of 30–50 ml/min/1.73m² and 1 or more of the following risk factors: Prior stroke or transient ischaemic attack, 75 years or older, Hypertension, Diabetes mellitus or Symptomatic heart failure; apixaban may be considered in preference to warfarin.¹¹</td>
<td>CrCl &lt;30mL/min: Contraindicated The SPC States ‘The method used to estimate renal function (CrCL in mL/min) during clinical development was the Cockcroft-Gault method. This method is recommended when assessing patients’ CrCL prior to and during treatment.’</td>
<td>CrCl &lt;15ml/min: Not Recommended CrCl= 15-49ml/min: Reduce dose to 15mg once daily</td>
<td>CrCl &lt;15ml/min or on dialysis: Not Recommended CrCl ≥ 15-50ml/min: Reduce dose to 30 mg once daily</td>
<td>CrCl&gt;50-80 mL/min: 60 mg once daily Nb. There is a trend towards decreasing efficacy with increasing CrCl, therefore only use in patients with high CrCL after evaluation of the individual thromboembolic and bleeding risk. The SPC states Renal function should be assessed in all patients by calculating the CrCL prior to treatment. Renal function should also be assessed if a change is suspected (e.g. hypovolaemia, dehydration or concomitant use of certain medicines)</td>
</tr>
</tbody>
</table>

Yes/No

Yes/No
## Dose Adjustments Continued

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF dose</strong>:</td>
<td>As per INR</td>
<td>150mg Twice Daily</td>
<td>20mg Once Daily</td>
<td>5mg Twice Daily</td>
<td>60 mg once daily.</td>
</tr>
<tr>
<td><strong>Age &amp; Weight</strong></td>
<td>No dose adjustment specified</td>
<td>≥ 80yrs: Reduce dose to 110mg twice daily</td>
<td>No dose adjustment specified</td>
<td>≥ 80yrs with a body weight ≤ 60kg: Reduce dose to 2.5mg twice daily</td>
<td>Low body weight ≤ 60 kg reduce to 30 mg once daily. No dose adjustment required for the elderly.</td>
</tr>
<tr>
<td>Others</td>
<td>If High Risk of Bleed or Treatment with Verapamil: Reduce to 110mg twice daily</td>
<td>Concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole: Reduce to 30 mg once daily.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 7. The patient’s ability to comply with medication dosing has been taken into account

#### Compliance Considerations

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable Dosing as Per INR</strong></td>
<td>Dosing is TWICE DAILY</td>
<td>Dosing is ONCE DAILY with food</td>
<td>Dosing is ONCE DAILY with food</td>
<td>Dosing is TWICE DAILY</td>
<td>Dosing is ONCE DAILY</td>
</tr>
<tr>
<td>Patients who forget doses may benefit from warfarin therapy because of its longer blood-thinning effect and the common use of Anticoagulation Management Services, which provide frequent reminders about medication adherence and follow-up with INR tests.</td>
<td>Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation</td>
<td>Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation</td>
<td>Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation</td>
<td></td>
<td>Shorter half-life compared to warfarin, erratic compliance could result in worse anticoagulation.</td>
</tr>
<tr>
<td><strong>Not stable in compliance aids/monitored dosage systems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 8. Safety information and comparative bleeding risks have been considered

#### Relevant Bleeding Risk

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding: No difference between dabigatran 150 mg BD and warfarin. Less common with dabigatran 110 mg BD than warfarin.</td>
<td></td>
<td></td>
<td></td>
<td>Major bleeding: Less common with apixaban than warfarin (p&lt;0.001)</td>
<td>Major bleeding: significantly reduced rate of major bleeding and of several secondary bleeding endpoints for 60mg/30mg edoxaban compared to warfarin (p≤0.01)</td>
</tr>
<tr>
<td>GI bleeding: More common with dabigatran 150mg BD than warfarin (p=0.0008). No difference between dabigatran 110mg BD and warfarin.</td>
<td></td>
<td></td>
<td></td>
<td>GI bleeding: No difference between apixaban and warfarin</td>
<td>Major GI bleeding: Occurred slightly more frequently in edoxaban 60mg/30mg than in warfarin p=0.03.</td>
</tr>
<tr>
<td>Intracranial bleeding: Less common with both doses of dabigatran than with warfarin (p&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td>Intracranial bleeding: Less common with apixaban than warfarin (p&lt;0.001)</td>
<td>In clinical studies mucosal bleedings and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment, therefore in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.</td>
</tr>
<tr>
<td>See respective agent for comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N.B. Falls are not a contraindication to the use of warfarin. Analytical models estimate that elderly patients would need to fall 295 times a year for their risk of developing subdural haematomas to outweigh the benefit of being anticoagulated with warfarin.</td>
<td>Major bleeding: No difference between rivaroxaban and warfarin.</td>
<td>GI bleeding: More common with rivaroxaban than warfarin (p=0.0008). No difference between rivaroxaban and warfarin.</td>
<td>Intracranial bleeding: less common with rivaroxaban than warfarin (p=0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term safety data based on over 50yrs use &amp; anticoagulant effects can be rapidly reversed in the event of major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No information available on long-term safety. Dabigatran is the only DOAC with an established antidote i.e. Idarucizumab (licensed December 2015).
<table>
<thead>
<tr>
<th><strong>Oral Anticoagulation Patient Counselling Checklist</strong></th>
<th><strong>Yes / No</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. An Anticoagulant Alert Card has been given to the patient</td>
<td></td>
</tr>
<tr>
<td>2. A medication specific patient information leaflet has been given to the patient</td>
<td></td>
</tr>
<tr>
<td>Links to Patient Information: warfarin, apixaban, rivaroxaban, dabigatran and edoxaban</td>
<td></td>
</tr>
<tr>
<td>3. The purpose of anticoagulation in AF has been explained</td>
<td></td>
</tr>
<tr>
<td>AF Patient Information Anticoagulation in AF Patient Information</td>
<td></td>
</tr>
<tr>
<td>4. The rationale for use of the chosen anticoagulant has been discussed and explained</td>
<td></td>
</tr>
<tr>
<td>5. The potential side effects have been explained. (Bleeding is common side effect for all anticoagulants). If taking a DOAC explain that there is no known antidote to the anticoagulant effects of apixaban, rivaroxaban or edoxaban unlike warfarin and dabigatran.</td>
<td></td>
</tr>
<tr>
<td>6. The patient understands that they should inform healthcare professionals, including doctors, pharmacists and dentists that they are taking an oral anticoagulant and to show their Patient Alert card. (Local organisations should have arrangements for sourcing and disseminating alert cards. Online cards are also available for printing from the AF association anticoagulant alert cards).</td>
<td></td>
</tr>
<tr>
<td>7. The need for an annual review/blood test to monitor renal function has been explained</td>
<td></td>
</tr>
<tr>
<td>8. The patient knows how to take the medication including:</td>
<td></td>
</tr>
<tr>
<td>• The frequency of administration</td>
<td></td>
</tr>
<tr>
<td>• To take with water, with or without food</td>
<td></td>
</tr>
<tr>
<td>• To take regularly</td>
<td></td>
</tr>
<tr>
<td>• What to do if a dose is missed</td>
<td></td>
</tr>
<tr>
<td>• If an extra dose is taken accidentally, advise patient to seek medical advice</td>
<td></td>
</tr>
<tr>
<td>• Remind patient not to stop taking the medication unless advised to do so by a healthcare provider</td>
<td></td>
</tr>
<tr>
<td>9. If initiating Warfarin; the patient has been informed if a LMWH is co-prescribed and arrangements have been made for the supply and administration of the LMWH (LMWH should be continued until the INR is in range for 2 consecutive days)</td>
<td></td>
</tr>
</tbody>
</table>
References

8. Warfarin SPC
14. UKMI. Medicines Q&A What are the risks of using antiplatelet agents in combination with NOACs in patients with atrial fibrillation, and how should the potential risks be managed. November 2015. Accessed vi
15. European Society Cardiology
This guidance does not override the individual responsibility of health professionals to make decisions in exercising their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. For full prescribing information please refer to the BNF and SPC.