NEW ORAL ANTICOAGULANT DRUGS (NOAC) AND THEIR USE IN THE MANAGEMENT OF ATRIAL FIBRILLATION IN SALFORD PATIENTS

Version 2
December 2012

1. Background

Three new oral anticoagulants (NOAC) drugs dabigatran, rivaroxaban and apixaban have been licensed in the UK for the management of patients with Atrial Fibrillation (AF).

NICE have reviewed two of the currently licensed drugs:

- Dabigatran (Pradaxa®) – NICE TA249: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation
- Rivaroxaban (Xarelto®) – NICE TA256: Rivaroxaban for the prevention of stroke and stroke and systemic embolism in atrial fibrillation

NICE guidance on Apixaban (Eliquis) is due April 2013.

These drugs are new to market and the potential long-term side effects are not yet fully known. Concerns also include that the optimal method of emergency reversal of the anticoagulant effects of these agents is currently unclear in those patients who present with major bleeding. There are also concerns, highlighted by the MHRA regarding dabigatran use in renal insufficiency as exposure is substantially increased in these patients. The benefits of dabigatran and rivaroxaban over warfarin decline as INR control on warfarin increases. In patients where warfarin is well controlled (time in therapeutic range [TTR] >65%), the use of dabigatran or rivaroxaban may be less favourable. On this basis, the use of these drugs should be implemented carefully and targeted to those patients that are likely to gain the most benefit from them i.e. patients poorly controlled on warfarin or those eligible for, but choose not to be anti coagulated with warfarin.

2. Implementation in Salford

The Greater Manchester and Cheshire Cardiac and Stroke Network (GMCCSN) have produced guidance to ensure there is a planned introduction for these drugs. Guidance documents have been developed and full documents are available on the GMCCSN website. This guidance has warfarin as first line treatment unless commencement of a NOAC is clinically appropriate or it is the patients choice to commence NOAC (within licensed indications). This is in line with NICE TA 249 and NICE TA 256. All patients commencing anticoagulant treatment must have a CHA2DS2-VASC ≥ 1.

Further clarification on CHA2DS2-VASC of 1

It is advised by the European Society Group who developed the 2010 ESC guidance on AF that scoring 1 point for female sex should be applied only to females aged 65 or over.

3. Managed entry of New Oral Anticoagulants (NOAC) – initiating and switching anticoagulant therapy safely

To ensure that prescribing of these new drugs is controlled and appropriate, all new initiations of NOAC will be monitored by the NHS Salford CCG locality medicines management team. There will be no formal gatekeeper role, but these drugs have not been approved for any off label use in primary care except in line with the cardiac network algorithm (see figure 1).
3.1 Acute setting (SRFT)

Patients who are diagnosed with AF whilst an inpatient at SRFT, may be commenced on warfarin as per existing protocols. If, after an in depth discussion with the consultant, they request a NOAC then SRFT will be responsible for ensuring all elements of the prescribing checklist (appendix 4) are completed and that this is communicated to the GP. Patients who are commenced on anticoagulation for AF should have a CHA2DS2-VASC score >1

3.2 Patients with a diagnosis of AF already prescribed warfarin (under the care of the anticoagulant clinic)

The anticoagulant clinic will review patients currently prescribed warfarin/sinthrome to identify those patients who are currently inadequately controlled and meet the criteria as specified by the cardiac network guidance:

- The INR % of time in the therapeutic range of 2-3 less that 65% (unexplained) (as determined by the Rosendaal method) and/or
  - INR >5 more than 2 time (in 12 months) (unexplained) and/or
  - Other clinical consideration e.g. intolerance that must be specified in the referral to the GP

Following review, these patients will be highlighted and a communication letter (see appendix 3) will be sent from the anticoagulant clinic to the GP. This will be to advise the GP to:

1. Undertake a CHA2DS2-VASC score
2. Follow the appropriate algorithm (see figure 1 below) dependent upon the patient’s score.
3. If the patient’s CHA2DS2-VASC score is >1 and warfarin/sinthrome* treatment has not led to adequate control (as per GM criteria), a new oral anticoagulant agent (NOAC) should be commenced.
4. Patient’s medical history (e.g. renal impairment), concomitant drugs/interactions e.g. verapamil should be reviewed prior to commencing NOAC.
5. In the majority of cases, patients will already be prescribed warfarin and will need to have therapy switched over. This will require liaison with the anticoagulant clinic as warfarin/sinthrome* is withdrawn.
6. To aid switching of anticoagulation to NOAC or commencement of NOAC, patient information leaflets are available for dabigatran and rivaroxaban, both containing a patient alert card that the patient is advised to keep on their person and show to healthcare professionals prior to treatment. Anticoagulant clinics have stocks of these or they can be obtained directly from the manufacturer. In addition, to ensure safe changeover of medication from warfarin/sinthrome* to NOAC, a summary checklist can be found in appendix 2.
7. A summary of the oral anticoagulants currently available for this indication can be found in appendix 5 to support treatment choice.

3.3 Patients with a new diagnosis of AF, identified by the GP

Patients who have a new diagnosis of AF (with a CHA2DS2-VASC score >1) should be commenced on warfarin if not contraindicated, unless after an in depth discussion with the GP, they request a NOAC. If a NOAC is to be commenced, follow the flow chart in appendix 1.

If warfarin is to be commenced, refer immediately to the anticoagulant clinic for commencement of warfarin.

If after 3 months the patient has:

- The INR % of time in the therapeutic range of 2-3 less that 65% unexplained (as determined by the Rosendaal method) and/or
- INR >5 more than 2 times unexplained (in 12 months)

Then they should be reviewed as above in section 3.2
3.4 Patients with a new diagnosis of AF, identified by secondary care out patients

Patients who have a new diagnosis of AF (with a CHA2DS2-VASC score >1) should be commenced on warfarin unless contraindicated or after an in depth discussion with the consultant they request a NOAC. Patients should be informed that their GP will need to review them for appropriateness of a NOAC. Secondary care should then request that the GP reviews the patients and, if appropriate after a further informed discussion commences a NOAC. If a NOAC is to be commenced, ensure the prescribing checklist is completed (appendix 4). Secondary care do not need to inform the locality medicines management team at the CCG as there is no longer a gate keeper role.

If the patient is to be commenced on warfarin, the GP should refer the patient through to the new start anticoagulation clinic ASAP and inform the patient’s secondary care consultant that the patient has been anti-coagulated. The GP will then prescribe warfarin as per current arrangements. The anticoagulation of these patients (with either warfarin or a NOAC) remains the responsibility of the GP to arrange in a timely manner without delay.

3.5 Patients with a diagnosis of AF who are not anticoagulated

GPs should review all patients on their AF registers and identify those patients who are not on any treatment or who have chosen to take aspirin. These patients should be reviewed and if their CHA2DS2-VASC >1 and they decide that they do not wish to take warfarin then the option to take a NOAC should be discussed with the patient, bearing in mind several of the contraindications to warfarin also apply to the NOAC drugs (see appendix 5).

4. Miscellaneous information

4.1 NOAC general safety information

The MHRA issued a drug safety update for Dabigatran in December 2011 after a number of serous and fatal haemorrhages were reported in elderly patients with renal impairment. They also released a further drug safety update in July 2012 which clarifies the type of clinical conditions and medicines that are contraindicated for use with dabigatran, to help minimise the known risk of haemorrhage.

Dabigatran is also now contraindicated with dronedarone, and with the use of other anticoagulant agents, except when switching therapy to or from dabigatran, or with the use of unfractionated heparin for maintenance of venous or arterial catheter patency. It also reminds prescribers about the importance of monitoring renal function in patients who receive dabigatran.

Cardiology have advised that due to a lack of data it is advisable to avoid the use of NOACs in combination with aspirin >100mg and dual anti platelet therapy. In addition, coumarins rather then NOACs should be used in all patients with rheumatic heart disease causing any degree of mitral stenosis and those with severe aortic stenosis of any cause.

4.2 NOAC use in patients with reduced renal or hepatic function

They recommended that renal function should be assessed in all patients before commencing dabigatran treatment and at least once a year in patients older than 75 or those with suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (CR Cl < 30 ml/min). Patients with elevated liver enzymes > 2 ULN were excluded from the study investigating the prevention of stroke and SEE associated with atrial fibrillation. No treatment experience is available for this subpopulation of patients, and therefore the use of dabigatran is not recommended in this population.

For rivaroxaban, caution is required in patients with severe renal impairment (creatinine clearance <30 mL/min) or moderate hepatic impairment. It is not recommended in patients with a creatinine clearance of less than 15 mL/min. Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased therefore, rivaroxaban to be used with caution in these patients. Rivaroxaban is also contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, and is not recommended in those also taking strong inhibitors of cytochrome P 3A4 enzyme or P-glycoprotein, such as the azole-antimycotics (eg, ketoconazole) or HIV protease inhibitors (eg, ritonavir).

4.3 NOACs in monitored dosing systems (MDS)

Dabigatran must remain in its original packing up until it is taken to protect it from moisture. If it was to go into an MDS, then the whole blister would need to go in and the patient would have to peel the backing off prior to taking (not push it through
as this may damage the coating). In practice this is not workable and the size would limit it going into most of the MDS systems that community pharmacists use.

Rivaroxaban does not have any specific storage requirements and so may be an option if the patient requires an MDS.

### 4.3 Opening of Dabigatran capsules

The oral bioavailability may be increased by 75% compared to the reference capsule formulation when the pellets are taken without the Hydroxypropylmethylcellulose (HPMC) capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and to take the pellets alone (e.g., not sprinkled over food or into beverages).

### 4.5 NOAC discontinuation

In the RE-LY study more dabigatran subjects discontinued study medication due to adverse effects compared with warfarin subjects. Gastrointestinal adverse events (e.g., dyspepsia, gastrointestinal haemorrhage, nausea) occurred more frequently with dabigatran vs. warfarin (35% vs. 24%) and were the most frequently reported adverse events resulting in treatment discontinuation. The risk of dyspepsia with dabigatran was highest within the first few weeks of treatment. **Dyspepsia can be reduced by taking dabigatran with food, but it is not improved by adding a PPI.**

For rivaroxaban, in ROCKET—AF the total number of subjects who permanently discontinued study drug was similar between the two treatment groups: rivaroxaban subjects 35.44% and warfarin subjects 34.64%. The Kaplan-Meier estimated cumulative discontinuation rates at 1 and 2 years were 21.83% and 34.72% for rivaroxaban and 21.12% and 33.52% for warfarin, respectively.

The number of subjects receiving rivaroxaban who permanently discontinued study drug for bleeding adverse events: 304 (4.28%) subjects in the rivaroxaban group compared with 219 (3.07%) subjects in the warfarin group.

**Patients on dabigatran or rivaroxaban should therefore, be advised to take these medications with food, to increase absorption and reduce heartburn.**

### 4.6 Missed doses

Dabigatran is taken twice a day and the advice on missed doses is: a forgotten dose can still be taken up to 6 hours prior to the next due dose. A missed dose should be omitted if the remaining time is below 6 hours prior to the next due dose. Do not take a double dose to make up for missed individual doses.

Rivaroxaban is taken once daily and patients are advised if they have missed a dose, take it as soon as they remember. Do not take more than one tablet in a single day to make up for a forgotten dose. Take the next tablet on the following day and then carry on taking one tablet once a day.

### 4.7 Pre operative management of patients taking NOACs

**Dabigatran**

The time to stopping treatment prior to surgery depends on the patient’s renal function and is detailed in the SPC and is summarised below.

<table>
<thead>
<tr>
<th>Renal function (CrCl in ml/min)</th>
<th>Estimated half life</th>
<th>High risk of bleeding or major surgery</th>
<th>Standard risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>Approx 13 hrs</td>
<td>2 days before</td>
<td>24 hours before</td>
</tr>
<tr>
<td>≥ 50&lt;80</td>
<td>Approx 15 hrs</td>
<td>2-3 days before</td>
<td>1-2 days before</td>
</tr>
<tr>
<td>&gt;30&lt;50</td>
<td>Approx 18 hrs</td>
<td>4 days before</td>
<td>2-3 days before</td>
</tr>
</tbody>
</table>

**Rivaroxaban**

If an invasive procedure or surgical intervention is required, rivaroxaban should be stopped 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. Rivaroxaban should be restarted after the invasive procedure or surgical intervention as soon as possible, provided the clinical situation allows and adequate haemostasis has been established.
Bridging therapy
Occasionally some patients may require bridging therapy with LMWH. Secondary care will advise regarding this on a case by case basis.

4.8 Switching patients from NOACs back to warfarin
Some patients may not be able to tolerate a NOAC and so may have to convert back to warfarin

Dabigatran to warfarin
When converting from dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:
- CrCL ≥50 ml/min, start warfarin 3 days before discontinuing dabigatran.
- CrCL ≥30-< 50 ml/min, start warfarin 2 days before discontinuing dabigatran.

Because 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.

Rivaroxaban to warfarin
When converting from rivaroxaban to warfarin, warfarin should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing guided by INR testing. While patients are on both rivaroxaban and warfarin, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban.

Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.

Patients who have discontinued warfarin and moved onto NOAC treatment who then need to revert back to warfarin treatment will need to go back into the anticoagulant service as a new start as they will have been discharged from this service.
Figure 1: GM&C Cardiac Network algorithm following CHA2DS2-VASC
Appendix 1: Patient flow chart for switching from warfarin to a NOAC

Patient reviewed in primary care. Patient unable to achieve INR control and is under coagulated INR <2 on warfarin/sinthrome at present.

Patient reviewed in anticoagulant clinic (ACC). Patient inadequately controlled on warfarin/Sinthrome at present.

Patient meets Greater Manchester criteria for new oral anticoagulants (NOAC) (see GMCCN guidance)

Yes

Patient suitable for NOACs

No

GP Actions
- Checks renal function
- Checks CHADS-2 score and that patient fits licence criteria or GMCCN guidance for NOAC
- Sees patient and discusses pros & cons on treatment, side effects, importance of compliance
- Dabigatran: If INR > 2 Issue ACUTE prescription for 1/12 NOAC – Dabigatran to be taken when INR < 2 managed by ACC
- Rivaroxaban: If INR > 3 Issue ACUTE prescription for 1/12 NOAC – Rivaroxaban to be taken when INR < 3 managed by ACC
- If INR <2 NOAC can be commenced by GP and patient discharged from ACC
- Checks no interacting drugs
- Book F/U appointment for 1/12

Anticoagulation clinic
- Monitor INR until < 2 or 3 and patient can commence NOAC
- Reinforce counselling around NOAC
- Discharge from A/C clinic

Patient commences NOAC

GP
- Seen again at 1/12
- Compliance, side effects reviewed
- NOAC issued monthly on repeat

GP annual review to monitor renal function and concordance

Patient unable to tolerate NOAC
- Consider an alternative NOAC
- If goes back on warfarin manage as in text re-refer to anticoagulation clinic as new start

ACC: Refer back to GP to discuss options with patient
Appendix 2: Guideline for switching from vitamin K antagonists (VKA) e.g. warfarin to a new oral anticoagulant therapy (NOAC)
(In addition see patient flow chart)

GP is to discuss possible change with patient and explain reason – risks/benefits
Consult with anticoagulant clinics if oral anticoagulant switching is required

If patient consents to change:

- Check renal function / LFT required
- Consider dose to be prescribed based on patient age / renal function – see SPC/appendix 4
- Review medications for potential drug interactions
- Contact anticoagulant clinic and inform them of impending conversation and be advised to stop warfarin when patient attends and when the clinic will check INR
- Give patient an acute prescription so that pharmacist can arrange supply
- Vitamin K antagonist to be discontinued for 2 days
- Patient’s INR monitored at clinic
- INR to be taken after 2 days omission
- For dabigatran if INR <2 NOAC can commence
- For rivaroxaban if INR <3 NOAC can commence
- Give the patient an alert card and patient information leaflet for the NOAC
- Ensure patient / carers are aware to send redundant warfarin supply back to the pharmacy for safe destruction
- Ensure recall for annual U&E is on the clinical system.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Boehringer Ingelheim – Drug safety on 0800 328 1627 (free phone) for dabigatran or Bayer plc on 01635 63500 for rivaroxaban.
Appendix 3 – Template letter sent from anticoagulation clinic to GP

Community anticoagulation service

Dr B Thinner
The Practice
Salford
M5 6FW
Date

Dear Dr B Thinner

Re: Mr I R Beat 24A Cleveleys Avenue, Swinton, Salford M27 OLL

Hosp No: 1000000
NHS No: 6000000000
Date of Birth: 2/7/1945

This patient is currently under our care for monitoring of warfarin therapy. For the reasons highlighted below, we are requesting a GP review of this patient’s anticoagulation therapy needs in order to decide which drug is best for optimal stroke prevention in this individual.

| The INR % of time in the therapeutic range of 2-3 less than 65% (TTR should be measured for individual patients using the Rosendaal Method) | Y / N |
| Unexplained INR >5 more than 2 times (in 12 months) | Y / N |
| Other clinical considerations | Y / N |
| • Intolerance to warfarin | |
| • Newly diagnosed patient for advice | |
| • New referral post stroke / TIA | |
| • Other – please state | |

Review of anticoagulation therapy should be undertaken in line with Greater Manchester treatment algorithms, including a review of the individual’s CHADS2 /VASC score which will determine if a new oral anticoagulant drug e.g. dabigatran / rivaroxaban is indicated as a replacement for warfarin.

A detailed guide on how to manage the transition of these patients is available on the PCT intranet at http://nww.salford-pct.nhs.uk/MedicinesManagement/documents/NOAC.pdf

We would be grateful if you would inform us as soon as possible of your decision. Please feel free to contact me on (insert contact number) if you wish to discuss this matter. Further information can also be obtained from the CCG medicines management team.

Yours sincerely

Anticoagulant Clinic
Appendix 4: Prescribing checklist for dabigatran and rivaroxaban

<table>
<thead>
<tr>
<th>Patient name:</th>
<th>DOB:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS Number:</td>
<td>Address:</td>
</tr>
</tbody>
</table>

**A) NICE Criteria for DABIGATRAN use (all must be met – tick all applicable)**

<table>
<thead>
<tr>
<th>1. Non Valvular Atrial Fibrillation(AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine echocardiography is not required prior to initiation of dabigatran. It is not recommended in patients with known haemodynamically significant valvular heart disease or in patients with prosthetic heart valves</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. eGRF &gt;30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N.B. If eGFR is not available e.g. inpatient – the Creatinine Clearance should be calculated instead (using Cockcroft formula).)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Does the patient have a CHAD2SVAS2C score of ≥1?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>4. No contraindicated concomitant medications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole, cyclosporine A,itraconazole and tacrolimus, dronedarone</td>
</tr>
<tr>
<td>Caution should be exercised with other P-gp inhibitors / inducers (e.g. amiodarone, quinidine or verapamil, clarithromycin, rifampicin, carbamazepine, phenytoin). This list is not exhaustive – refer to BNF / manufacturer’s datasheet for further details.</td>
</tr>
</tbody>
</table>

**(B) General Assessment**

<table>
<thead>
<tr>
<th>5. Ability to comply with medication dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.B. Due to the short half life of dabigatran compared to warfarin erratic compliance could result in worse anticoagulation. Dosing is twice daily.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. No other contradictions to anticoagulation (not listed above)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Major bleeding potential or tendency e.g. severe haemophilia</td>
</tr>
<tr>
<td>• Active peptic ulcer, oesophageal varices, aneurysm, proliferative retinopathy</td>
</tr>
<tr>
<td>• Recent organ biopsy</td>
</tr>
<tr>
<td>• Recent trauma or surgery to the head, orbit or spine</td>
</tr>
<tr>
<td>• Recent stroke (usually &lt;2 weeks)</td>
</tr>
<tr>
<td>• Confirmed intracranial or intraspinal bleed (usually within last 4 weeks although requires individual assessment)</td>
</tr>
<tr>
<td>• Uncontrolled hypertension</td>
</tr>
<tr>
<td>• Infective Endocarditis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. Baseline bloods satisfactory:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not recommended if</td>
</tr>
<tr>
<td>• FBC: Platelet &lt;70 x 10^9/L</td>
</tr>
<tr>
<td>• eGFR: see above</td>
</tr>
<tr>
<td>• LFT: Liver enzymes elevated &gt;2 x normal</td>
</tr>
</tbody>
</table>
8. **Explain purpose of anticoagulation / dabigatran**
   - Avoidance of embolic stroke / peripheral emolisation secondary to atrial fibrillation

9. **Explain Serious Side Effects: Bleeding**
   Seek urgent medical attention if develops new:
   - Blood in urine, faeces, vomit or sputum, vaginal bleeding (other than regular period)
   - Severe unusual headache (particularly if following head trauma)

10. **Explain**
   - Need to inform anyone prescribing medications that they are on dabigatran and to confirm that it does not interact
   - Explain need for annual review / blood test to assess renal function or if change
   - Dyspepsia and GI bleeding were the only adverse events noted to be statistically more common with dabigatran than warfarin. Dyspepsia may be ameliorated by taking medication with food. Caution should be exercised if symptoms persist / recent history of peptic ulcer disease
   - **There is no known antidote to dabigatran (unlike warfarin).** In the event of life threatening bleeding or need for emergency surgery stop dabigatran – anticoagulant effect will wear off after approximately 24 - 36 hours post last dose
   - Although there are no anticipated long term adverse effects from the large multinational study there is no long data currently available. Dabigatran has black triangle status – prescribers are required to complete a yellow card for any suspected adverse drug reactions
   - Renal function should be assessed at least once a year in patients treated with dabigatran or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain co-medications, etc)
   - Dabigatran is not suitable for monitored dose systems (e.g. dosette boxes) and must be stored in original packaging. Once a bottle is opened the tablets must be finished within 4 months (SPC)
   - Standard coagulation tests e.g. INR and APTT may be prolonged by dabigatran but are not predictable and should not be routinely monitored

- Coagulation Screen: APTT > 1.5 x normal; INR > 1.4
**Dosing Recommendation:**

1. 150mg bd PO – Standard dose
2. 110mg bd PO – Suitable patients:
   - All patients aged >80y
   - Selected patients aged >75y if bleeding risk
   - Other high risk bleeding patients, especially if borderline renal function
   - Concomitant verapamil

If patients are switching from warfarin commence dabigatran when INR <2.

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

**Authorisation:**

Signature of medical practitioner undertaking assessment: ........................................

Print Name: ........................................

Optional CHAD2S – VAS2c Score | Score (circle)
--- | ---
Congestive heart failure / LV dysfunction | 1
Hypertension | 1
Age ≥75y | 2
Diabetes mellitus | 1
Stroke/TIA/TE | 2
Vascular Disease (MI/PVD/Aortic Plaque) | 1
Age 65-75 | 1
Sex Category i.e. female | 1

**TOTAL …..**

**Reference:**

2. NICE TA249 (15th March 2012) dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation
A) NICE Criteria \[^{[2]}\] for RIVAROXABAN use (all must be met – tick all applicable)  

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Non Valvular Atrial Fibrillation (AF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Routine echocardiography is not required prior to initiation of rivaroxaban. It is not recommended in patients with known haemodynamically significant valvular heart disease or in patients with prosthetic heart valves</td>
<td></td>
</tr>
<tr>
<td>2. eGFR &gt;15 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If eGFR &lt; 50 and ≥15 dose should be reduced to 15mg OD. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance &lt; 15 ml/min</td>
<td></td>
</tr>
<tr>
<td>3. Does the patient have a CHAD(_2)SVAS(_2)C score of ≥1?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. No contraindicated concomitant medications:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The use of Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). This list is not exhaustive – refer to BNF / manufacturer’s datasheet for further details.</td>
<td></td>
</tr>
</tbody>
</table>

(B) General Assessment  

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Ability to comply with medication dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N.B. Due to the short half life of Rivaroxaban compared to warfarin erratic compliance could result in worse anticoagulation. Dosing is once daily.</td>
<td></td>
</tr>
</tbody>
</table>

6. Other contradictions to anticoagulation (not listed above)  

- congenital or acquired bleeding disorders  
- uncontrolled severe arterial hypertension  
- active ulcerative gastrointestinal disease  
- recent gastrointestinal ulcerations  
- vascular retinopathy  
- recent intracranial or intracerebral haemorrhage  
- intraspinal or intracerebral vascular abnormalities  
- recent brain, spinal or ophthalmological surgery  
- bronchiectasis or history of pulmonary bleeding.
7. **Baseline bloods satisfactory:**
   Not recommended if
   - Creatinine clearance <15 ml/min (eGFR <15ml/min/1.73 m2)

8. **Explain purpose of anticoagulation / rivaroxaban**
   - Avoidance of embolic stroke / peripheral embolisation secondary to atrial fibrillation

9. **Explain Serious Side Effects: Bleeding**
   Seek urgent medical attention if develops new:
   - Blood in urine, faeces, vomit or sputum, vaginal bleeding (other than regular period)
   - Severe unusual headache (particularly if following head trauma)

10. **Explain**
    - Need to inform anyone prescribing medications that they are on rivaroxaban and to confirm that it does not interact
    - Explain need for annual review / blood test to assess renal function or if change
    - **There is no known antidote to rivaroxaban (unlike warfarin).** In the event of life threatening bleeding or need for emergency surgery stop rivaroxaban – anticoagulant effect will wear off after approximately 24 - 36 hours post last dose
    - Although there are no anticipated long term adverse effects from the large multinational study there is no long data currently available. Rivaroxaban has black triangle status – prescribers are required to complete a yellow card for any suspected adverse drug reactions
    - Renal function should be assessed at least once a year in patients treated with rivaroxaban or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain co-medications, etc)
    - Standard coagulation tests e.g. INR and APTT may be prolonged by rivaroxaban but are not predictable and should not be routinely monitored
**Dosing Recommendation:**

(3) 20mg once daily PO – Standard dose  
(4) 15mg once daily PO – Suitable patients:

Patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment

If patients are switching from warfarin commence rivaroxaban when INR <3.

**Missed doses:** Rivaroxaban is taken once daily and patients are advised if they have missed a dose, take it as soon as they remember. Do not take more than one tablet in a single day to make up for a forgotten dose. Take the next tablet on the following day and then carry on taking one tablet once a day.

**Authorisation:**

Signature of medical practitioner undertaking assessment: ........................................

Print Name: ........................................

Optional CHAD2SVAS2C Score          Score (circle)

Congestive heart failure / LV dysfunction   1
Hypertension                              1
Age ≥75y                                  2
Diabetes mellitus                         1
Stroke/TIA/TE                             2
Vascular Disease (MI/PVD/Aortic Plaque)   1
Age 65-75                                 1
Sex Category i.e. female                  1

TOTAL .....  

**Reference:**

(1) NICE TA256 (May 2012) Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation
Appendix 5 – Choice of oral anticoagulant e.g. warfarin, dabigatran, rivaroxaban

This summary provided an overview of the various oral anticoagulants now available. The individual Summary of Product characteristics should be accessed for full prescribing information when a specific drug is selected for prescribing.

Indication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
</tr>
</thead>
</table>
| Indication (in relation to stroke prevention) | Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation | Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors:  
• Hypersensitivity to the active substance or to any of the recipients  
• Previous stroke, transient ischemic attack, or systemic embolism (SEE)  
• Left ventricular ejection fraction <40%  
• Symptomatic heart failure, New York Heart Association (NYHA) Class 2  
• Age 75 years  
• Age 65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension | Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors:  
• Congestive heart failure  
• Hypertension  
• Age >75 years  
• Diabetes mellitus  
• Prior stroke or transient ischaemic attack |

Dose, monitoring and formulation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban</th>
</tr>
</thead>
</table>
| Dose               | Variable dose (ONCE A DAY) generally at teatime. Dose dependent on INR and target range | 150mg TWICE A DAY  
150mg TWICE A DAY 75-80 years if bleeding risk is high and thromboembolic risk low – physician can consider 110mg BD  
110mg TWICE A DAY (aged 80 and over) | 20mg ONCE A DAY (taken with food) |
| Monitoring          | INR monitoring                                                          | Visible monitoring of the patient for signs of bleeding and anaemia. (No clinical monitoring available – INR not able to be used as different pathway action.) | Visible monitoring of the patients for signs of bleeding and anaemia (No clinical monitoring available; INR not able to be used as different pathway of action). |
| Formulation         | 0.5mg, 1mg, 3mg and 5mg tablet                                          | 110mg and 150mg tablet                                                              | 15mg and 20mg tablet                                                          |
## Contra-indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto®)</th>
</tr>
</thead>
</table>
| Contra-indications – See SPC for full details | • Known hypersensitivity to warfarin or to any of the excipients  
• Haemorrhagic stroke  
• Clinically significant bleeding  
• Within 72 hours of major surgery with risk of severe bleeding  
• Within 48 HOURS postpartum  
• Pregnancy (first and third trimesters)  
• Drugs where interactions may lead to a significantly increased risk of bleeding | • Hypersensitivity to active substance or to any of the excipients  
• Patients with severe renal impairments (CrCl <30ml/min)  
• Active clinically significant bleeding  
• Organic lesion at risk of bleeding  
• Spontaneous or pharmacological impairment of haemostasis  
• Hepatic impairment or liver disease expected to have any impact on survival  
• Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus, dronedarone. | • Hypersensitivity to the active substance or to any of the excipients  
• Clinically significant active bleeding  
• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C  
• Pregnancy and breast feeding |

## Cautions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban</th>
</tr>
</thead>
</table>
| Cautions/Special warning for use | Therapy should be reviewed on a regular basis (most ADRs are due to over anticoagulation). All patients should have a yellow anticoagulation booklet. Thrombophilia – patients with protein C or S deficiency. Thyroid disorders – closely monitor patients.  
The following may increase bleeding risk; loss of weight, acute illness, cessation of smoking (doses may need to be reduced)  
The following may reduce efficacy; weight gain, diarrhoea, vomiting (doses may need to be increased)  
Genetic conditions in relation to CYP2C9 and VKORC1 - closer monitoring required | Patient with elevated liver enzymes >2 ULN should not be prescribed dabigatran. Use with caution in conditions with an increased risk of bleeding | See SPC for information on converting from warfarin/synthrome to rivaroxaban  
**Renal impairment**  
Mild: (CrCl 50-80ml/min) no dose adjustment necessary  
Moderate: (CrCl 30-49ml/min) – 15mg ONCE A DAY  
Severe: (CrCl 15-29ml/min) – 15mg ONCE A Day (use caution in these patients)  
Very severe: CrCl <15ml/min – not recommended in this group of patients  
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased therefore, rivaroxaban to be used with caution in these patients. |
### Drug Interaction

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Dabigatran (Prada®)</th>
<th>Rivaroxaban (Xarelton®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug interactions (see individual SPCs for full details and action)</strong></td>
<td><strong>Pharmacodynamic and other interactions (avoid or use with cautions):</strong></td>
<td><strong>Generally interactions lead to an ↑ bleeding risk – patients should be monitored closely for signs of bleeding and anaemia</strong></td>
</tr>
<tr>
<td>- Care with concomitant including NSAIDs (including aspirin and COX-2) and platelet aggregation inhibitors (e.g. clopidogrel)</td>
<td>- Dipyridamole</td>
<td>- Caution with concomitant; systemic azole – antimycotics e.g. ketoconazole, itraconazole, voriconazole, HIV protease inhibitors</td>
</tr>
<tr>
<td>- Heparins (unless clinically indicated due to low INR)</td>
<td>- Sulfinpyrazone</td>
<td>- Concomitant use of strong P-gp inhibitors e.g. amiodarone, quinidine, verapamil</td>
</tr>
<tr>
<td>- Thrombin inhibitors e.g. bivalirudin, dabigatran</td>
<td>- Fondaparinux, rivaroxaban</td>
<td>- Concomitant use of amiodarone (nb: amiodarone has a long half life and interaction may exist for weeks after discontinuation, especially in patient with mid-renal impairment)</td>
</tr>
<tr>
<td>- Drugs inhibiting haemostasis, clotting or platelet actions</td>
<td>- Glycoprotein IIb / IIa receptor antagonists</td>
<td></td>
</tr>
<tr>
<td><strong>Generally interactions lead to an ↑ bleeding risk – patients should be monitored closely for signs of bruising, bleeding and anaemia (however will be guided by INR and anticoagulation clinic for dose variations)</strong></td>
<td>- SSRI / SNRI antidepressants</td>
<td>- Caution with concomitant use of quinidine especially in patients with mild-moderate impairment</td>
</tr>
<tr>
<td>- Azole antifungals (e.g. ketoconazole, fluconazole)</td>
<td>- Concomitant use of amiodarone – dose reduction advised from 150mg BD to 110mg BD in patients taking concomitant verapamil interaction more likely in patients with mild – moderate impairment)</td>
<td></td>
</tr>
<tr>
<td>- Paracetamol (prolonged use)</td>
<td>- Methylphenidate</td>
<td>- Caution with concomitant use of clarithromycin, especially in patients with mild – moderate renal impairment</td>
</tr>
<tr>
<td>- Allopurinol</td>
<td>- Zafirlukast</td>
<td>- Protease inhibitors (e.g. ritonavir containing products) should not be used</td>
</tr>
<tr>
<td>- Capecitabine</td>
<td>- Fibrates</td>
<td></td>
</tr>
<tr>
<td>- Erlotinib</td>
<td>- Statins (not pravastatin)</td>
<td></td>
</tr>
<tr>
<td>- Disulfiram</td>
<td>- Erythromycin</td>
<td></td>
</tr>
<tr>
<td>- Omeprazole</td>
<td>- Sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>- Propafenone</td>
<td>- Metronidazole</td>
<td></td>
</tr>
<tr>
<td>- Amiodarone</td>
<td>- Excessive alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>- Tamoxifen</td>
<td>- Cranberry juice should be avoided</td>
<td></td>
</tr>
<tr>
<td><strong>Interactions below lead to an ↑↓ in anticoagulant concentration therefore treatment may be suboptimal (however will be guided by INR and anticoagulation clinic for dose regulations</strong></td>
<td><strong>Caution concomitant use of strong CYP3A inducers e.g. Phenytoin Carbamezepine Phenobarbital St John’s Wort</strong></td>
<td><strong>Caution with concomitant use of clarithromycin, especially in patients with mild – moderate renal impairment</strong></td>
</tr>
<tr>
<td>- Barbiturates</td>
<td>- St John’s Wort – combination not supported</td>
<td></td>
</tr>
<tr>
<td>- Primidone</td>
<td>- Large amounts of food containing vitamin K – i.e. sudden changes in diet of these products may affect anticoagulant control</td>
<td></td>
</tr>
<tr>
<td>- Carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Griseofulvin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral contraception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Azathioprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Phenytoin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
prescribed concomitantly (due to lack of available safety data for this combination

- Interactions below lead to a ↓ in anticoagulant concentration therefore treatment may be suboptimal
- Caution with concomitant use of strong CYP344 inducers e.g. rifampicin, St John’s Wort, Carbamazepine, Phenytoin

### Relevant Resources

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant resources (e.g SPC)</td>
<td>Warfarin SPCs</td>
<td>SPC – 150mg tablets</td>
<td>SPC – 20mg tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SPC – 110mg tablets</td>
<td>SPC – 15mg tablets</td>
</tr>
</tbody>
</table>
Appendix 6: SRFT Guideline: Emergency reversal of anticoagulation in patients taking novel oral anticoagulants (eg. Dabigatran, Rivaroxaban etc…)

There is currently no reversal agent for any of these drugs.

Bleeding within 12 hours of ingestion of the drug (NB. longer if eGFR < 30 ml/min)

STOP THE DRUG

Check FBC, U&E, APTT

Minor Bleeding

Delay next dose and reassess indication for the drug

*Major Bleeding

Maintain blood volume with red cells (activate major haemorrhage protocol if appropriate)

Transxamic Acid **
1G I-V

Maintain platelets > 50
Maintain fibrinogen > 1.0

*Critical Site Bleeding

Consider oral liquid Charcoal if Dabigatran ingestion < 2 hours ago

Transxamic Acid **
1G I-V

If APTT ratio > 1.5 consider PCC 30U/kg

** Tranexamic acid can be obtained from Pharmacy if not available in your local area

* Major bleeding: Reduction in Hb≥2g/l, transfusion of ≥ units of red cells, hypotension
Bleeding in critical area: Intraocular, intracranial, intramuscular with compartment syndrome, retroperitoneal, intra-articular or pericardial bleeding