



**Implementation of NICE TAs 249, 256 and 275**  
**Dabigatran, Rivaroxaban and Apixaban**  
**for the prevention of stroke and systemic embolism in**  
**atrial fibrillation**

**April 2013**

## **Contents**

Executive summary	Page 3
1. Introduction	Page 4
2. The new oral anticoagulants licensed for stroke prevention in AF	Page 5
3. Guidance aims and choice of new OAC	Page 8
4. Selection of appropriate patients	Page 13
5. Pathway for initiation	Page 14
6. Shared Care Guidance	Page 15
Appendix 1	Page 16
Letter to Primary Care following initiation of Dabigatran for Stroke Prevention in AF	
Appendix 2	Page 18
Letter to Primary Care following initiation of Rivaroxaban for Stroke Prevention in AF	
Appendix 3	Page 20
Letter to Primary Care following initiation of Apixaban for Stroke Prevention in AF	

### **Guidance authors –**

Dr Matthew Lyttelton, Consultant Haematologist, Kettering General Hospital  
Dr Karyn Longmuir, Consultant Haematologist, Kettering General Hospital  
Sue Smith, Head of Prescribing and Medicines Management, Nene and Corby Clinical Commissioning Groups, Northamptonshire

### **With contributions from - Dr**

Suchitra Krishnamurthy, Consultant Haematologist, NGH Stroke & Care of the Elderly Consultants, Cardiologists NGH Scott Savage, Chief Pharmacist, KGH	Junie, Gupta, Formulary Pharmacist, NGH Professor Tom Robinson, Stroke Lead, East Midlands Cardiovascular Network
Dr Jonathan Shribman, GP and primary care East Midlands Cardiovascular Network representative	Dr Richard Andrews, Cardiac Lead, East Midlands Cardiovascular Network Bayer
Dr Yassir Javaid, GP Northampton	Boehringer Ingelheim

### **Approved by -**

Northamptonshire Prescribing Advisory Group April 2013  
Review date June 2014  
(Revision of original version approved March 2012)

## **Executive summary**

- <sup>3/4</sup> NICE has issued single Technology Appraisals for dabigatran (Pradaxa ▼), for rivaroxaban (Xarelto ▼) and for apixaban (Eliquis ▼) for the prevention of stroke and systemic embolism in atrial fibrillation (TAs 249, 256 and 275). This guidance has been produced to help identify those patients who are most likely to benefit from dabigatran, rivaroxaban or apixaban for this indication and to provide advice on using these new drugs in the safest possible manner. The guidance does not and should not over-ride the NICE TAs. A clinician may choose to initiate dabigatran, rivaroxaban or apixaban for any patient within the Technology Appraisals' criteria if clinically appropriate.
- <sup>3/4</sup> Dabigatran, rivaroxaban and apixaban are orally active antithrombotic agents. Dabigatran is a direct thrombin inhibitor and rivaroxaban and apixaban are oral direct factor Xa inhibitors. They will be referred to as the NOACs (New Oral Anti-Coagulants) throughout this document. The NOACs have the potential advantage over warfarin of not requiring INR blood monitoring, but other factors about the NOACs need to be taken into consideration when deciding whether one of the drugs is appropriate for an individual patient.
- <sup>3/4</sup> These factors include
- Unknown long term safety profile of the NOACs. All 3 are “black triangle drugs”.
  - Lack of reversibility of the NOACs.
  - Consideration of the patient's current INR control on warfarin.
  - Renal function.
  - Bleeding risk, especially GI bleeding risk.
  - Drug interactions
  - Compliance.
- <sup>3/4</sup> The choice of NOAC is the decision of the prescriber and there are pros and cons to each agent. Guidance is provided both for patients newly diagnosed with AF and for existing patients currently taking warfarin.
- <sup>3/4</sup> In Northamptonshire it is recommended that the NOACs should be initiated only by a secondary care consultant (haematologist, cardiologist or stroke physician as appropriate) with the support of their anticoagulant clinics. Prescribing can then be passed to the GP with shared care advice (amber 2 status). This pathway for initiation will be reviewed once experience with these new drugs becomes more established.
- <sup>3/4</sup> **Warfarin remains a suitable first-line oral anticoagulant for most patients.**

## **1. Introduction**

**NICE issued a Technology Appraisal (TA 249) “Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation” in March 2012.**

<http://guidance.nice.org.uk/TA249>

*1.1 Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:*

- *previous stroke, transient ischaemic attack or systemic embolism*
- *left ventricular ejection fraction below 40%*
- *symptomatic heart failure of New York Heart Association (NYHA) class 2 or above*
- *age 75 years or older*
- *age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.*

*1.2 The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control.*

**NICE issued a Technology Appraisal (TA 256) “Rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation” in May 2012.**

<http://guidance.nice.org.uk/TA256>

*1.1 Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:*

- *congestive heart failure*
- *hypertension*
- *age 75 years or older*
- *diabetes mellitus,*
- *prior stroke or transient ischaemic attack.*

*1.2 The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.*

**NICE issued a Technology Appraisal (TA 275) “Apixaban for the prevention of stroke and systemic embolism in atrial fibrillation” in February 2013.**

<http://guidance.nice.org.uk/TA275>

*1.1 Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with 1 or more risk factors such as:*

- *prior stroke or ischaemic attack*
- *age 75 years or older*
- *hypertension*
- *diabetes mellitus*
- *symptomatic heart failure.*

*1.2 The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control.*

## **2. The new oral anticoagulants licensed for stroke prevention in AF**

### **2.1 Dabigatran**

Dabigatran (more correctly called dabigatran etexilate – a prodrug of dabigatran) is an orally active antithrombotic agent. It is a direct thrombin inhibitor, which has the potential advantage over warfarin of not requiring blood monitoring, and may have fewer clinically important drug interactions.

The RE-LY study was a Phase III clinical study which evaluated the non-inferiority of two doses of dabigatran compared with warfarin in people with AF who were at moderate to high risk of stroke. The primary efficacy endpoint of the trial was incidence of stroke (including haemorrhagic) and systemic embolism. The primary safety endpoint was major bleeding.

The study found that the lower dose of dabigatran (110mg bd) was non-inferior to warfarin at reducing the risk of stroke and systemic embolism in people with AF (RR 0.91; 95% CI 0.74 to 1.11;  $p < 0.001$  for non-inferiority). The higher dose (150mg bd) was found to be statistically significantly more effective than warfarin (RR 0.66; 95%CI 0.53 to 0.82;  $P < 0.001$ ; NNT172 over one year).

The mean rates for major bleeding were 2.71% per year for low dose dabigatran, 3.11% per year for high dose dabigatran and 3.36%/year for warfarin. Whereas low-dose dabigatran was associated with a reduced risk of major bleeding ( $P = 0.003$ ; NNT 154 over one year), there were no significant differences between the high-dose dabigatran and warfarin in this respect.

Dabigatran has thus demonstrated superiority to warfarin in preventing strokes, particularly haemorrhagic strokes, in people with AF who are at moderate or high risk of strokes. This finding, taken together with no greater risk of major bleeding, suggests a possible role as an alternative to warfarin in such patients.

## **2.2 Rivaroxaban**

Rivaroxaban is an oral direct factor Xa inhibitor administered as a fixed-dose that does not require laboratory monitoring and, unlike warfarin, has no known food and few drug interactions.

The ROCKET AF study was a randomized, double blind, double dummy, sham INR trial which compared rivaroxaban with warfarin. In this study, the per-protocol, as treated primary analysis was designed to determine whether rivaroxaban was non-inferior to dose adjusted warfarin (target INR of 2.0 -3.0) in preventing stroke or systemic embolism among patients with non-valvular atrial fibrillation. Over a median 590 days of treatment exposure in the per-protocol treatment group, the event rates for stroke and systemic embolism were 1.7% per year in the rivaroxaban daily group and 2.2% per year in the warfarin group (HR 0.79; 95% CI 0.66 to 0.96;  $p < 0.001$  for non-inferiority)

In the intention to treat (ITT) population as part of sensitivity analysis, the event rate for stroke and systemic embolism was 2.1% per year for rivaroxaban and 2.4% per year for warfarin (HR 0.88; 95% CI 0.75 to 1.03;  $p < 0.001$  for non-inferiority and  $p = 0.12$  for superiority)

Clinically relevant bleeding event rate was 14.9% with rivaroxaban as against 14.5% per year in the warfarin group, intracranial haemorrhage occurred less frequently with rivaroxaban (0.5% v/s 0.7% per year;  $p = 0.02$ ) as did fatal bleeding (0.2% v/s 0.5% per year  $p = 0.003$ )

Rivaroxaban was thus shown to be non-inferior to warfarin in preventing strokes or systemic embolism in people with atrial fibrillation who are at moderate to high risk for a stroke, while demonstrating a comparable risk of major and non-major clinically significant bleeding. Intracranial haemorrhage occurred less frequently than with warfarin, but the incidence of gastrointestinal bleeding increased.

The trial methodology increases the complexity in interpreting the efficacy data – see <http://www.npc.nhs.uk/rapidreview/?p=4580>

## **2.3 Apixaban**

Apixaban is an oral direct factor Xa inhibitor administered as a fixed-dose that does not require laboratory monitoring and, unlike warfarin, has no known food and few drug interactions.

The ARISTOTLE was a double blind, double dummy randomized controlled trial which examined the effects of apixaban on the risk of stroke or systemic embolism in patients with AF. It compared apixaban 5 mg twice a day with adjusted-dose warfarin (target INR 2.0 to 3.0) in 18,201 patients with AF and at least one additional risk factor for

stroke (mean CHADS<sub>2</sub> score 2.1), over a median follow-up of 1.8 years. The trial was designed to test for non-inferiority, but demonstrated the superiority of apixaban (a pre-specified analysis).

The rate of the primary outcome (ischaemic or haemorrhagic stroke or systemic embolism) was 1.27% per year in the apixaban group compared with 1.60% per year in the warfarin group (HR with apixaban 0.79, 95% CI 0.66 to 0.95,  $p < 0.001$  for non-inferiority;  $p = 0.01$  for superiority, NNT over 1.8 years 168, 95%CI 95 to 773).

The rate of major bleeding was 2.13% per year in the apixaban group and 3.09% per year in the warfarin group (HR 0.69, 95%CI 0.60 to 0.80  $p < 0.001$ , NNT over 1.8 years 66, 95%CI 48 to 110), and the rates of death from any cause were 3.52% and 3.94%, respectively (HR 0.89, 95%CI 0.80 to 0.998,  $p = 0.047$ , NNT over 1.8 years 132, 95%CI 67 to 6951).

The risk of the composite outcome of stroke, systemic embolism, MI or death from any cause was reduced in the apixaban group: HR 0.88 (95%CI 0.80 to 0.97,  $p = 0.01$ , NNT over 1.8 years 91, 95%CI 51 to 406). The risk of the net clinical outcome of stroke, systemic embolism, major bleeding or death from any cause was also reduced in the apixaban group: HR 0.85 (95%CI 0.78 to 0.92,  $p < 0.001$ , NNT over 1.8 years 56, 95%CI 36 to 117).

Statistical analysis is not presented, but the adverse event rates appear similar in both study groups, including the rates for disturbances of liver function tests. Fewer patients in the apixaban group discontinued the study drug before the end of the study: 25.3% (3.6% due to death) versus 27.5% (3.8% due to death) in the warfarin group,  $p = 0.001$ .

## **Study Comparisons**

Differences among study populations, study designs, and times within target INR range (for patients randomised to warfarin) limit the comparisons which can be drawn between apixaban, dabigatran and rivaroxaban. For example, patients in ROCKET AF (rivaroxaban) had a higher risk of stroke at baseline than those in other studies. As an editorial accompanying ARISTOTLE points out, in all the studies the reductions in the primary efficacy end point — which included haemorrhagic as well as ischaemic stroke — were greatly influenced by a marked reduction in the risk of haemorrhagic stroke. Of the three drugs, only dabigatran at a dose of 150 mg also significantly reduced the risk of ischaemic stroke compared with warfarin. Point estimates for reduction in risk of stroke and reduction in all-cause mortality were similar in all studies. However, only apixaban has so far been shown to exhibit the combination of being significantly superior to warfarin in terms of stroke reduction; all-cause mortality; and fatal, major, and non-major bleeding; with no statistically significant increase in risk of MI.

The NICE Committee concluded that the network meta-analysis results, submitted by the manufacturer of apixaban, should be interpreted with caution (for example, because of the differences in baseline characteristics between the study populations) and were not sufficiently robust to reliably differentiate between apixaban, rivaroxaban and dabigatran. The Committee also concluded that there was insufficient evidence to

distinguish between the cost effectiveness of apixaban, dabigatran and rivaroxaban at this time.

Probably the biggest gap in the evidence relating to all these drugs, including apixaban, is the limited long term safety and efficacy data. The long term effects of dabigatran are being evaluated in an ongoing follow-up study (RELY-ABLE) of patients enrolled in RELY. Long term effects of apixaban are similarly being investigated in the Long Term Open label extension of AVERROES (a trial versus aspirin).

### **3. Guidance aims and choice of NOAC**

This guidance has been produced to help identify those patients who are most likely to benefit from a NOAC in this clinical situation and to provide advice on using the NOACs in the safest possible manner. The guideline covers both newly identified patients and existing patients currently taking warfarin.

**The guidance does not and should not over-ride the NICE TAs. A clinician may initiate dabigatran, rivaroxaban or apixaban for any patient within the Technology Appraisals' criteria (as per section 1 above).**

The guidance is based on the NICE TAs but includes the advice and opinions of local clinicians.

Additional guidance to that provided by the NICE TA is offered in order to take into account some of the following issues -

- In RE-LY, the INR was within the therapeutic range for 64% of the time. Although, this seems low, this is similar to other contemporary trials of warfarin and, in this trial, may reflect the high proportion of people in the study who had not received warfarin previously. Nevertheless, some patients will have been more controlled than others, and the study does not address the issue of whether dabigatran would be as effective as warfarin in those people who were well controlled on warfarin.
- In ROCKET AF, among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR.
- In ARISTOTLE, the INR was within the therapeutic range for a mean of 62.2% of the time.
- The average TTR at Kettering General hospital is 68% and at NGH it is 71%.
- The average age of the patients in the RE-LY, ROCKET AF and ARISTOTLE was 71, 73 and 69 respectively; the average age of patients taking warfarin in the North Northamptonshire population is 77 and South Northamptonshire for females is 73 and males is 71. Some of these patients may therefore have different risk/ benefit profiles relating to these drugs than the trial patients.
- More patients discontinued treatment with dabigatran than warfarin during the RE-LY study, which might be due to poorer tolerability. A higher incidence of discontinuations that were a result of serious side effects supports this view. Annual



discontinuation rates in ROCKET AF were similar between warfarin and rivaroxaban (22.2% vs 23.7%).

- Although, major bleeding was no more frequent between groups overall, the higher risk of GI side effects (both doses) and GI bleeding with dabigatran at the 150mg dose compared with warfarin raises questions about its use in people who are at high risk of these effects. This was despite the fact that RE-LY excluded patients with a previous GI bleed.
- Major bleeding from a gastrointestinal site was also more common in the rivaroxaban group than the warfarin group in ROCKET AF. One of the advantages of the NOACs is that they do not require routine monitoring; however one of the drawbacks is the lack of readily available tests to quantify the degree of under or over coagulation. Specific tests are becoming available. A normal thrombin time and a normal APTT would indicate that a high level of dabigatran is unlikely in the patient. A calibrated diluted thrombin time may provide further information regarding the degree of anticoagulation with dabigatran and a specific anti-Xa assay calibrated for rivaroxaban or apixaban can help determine the degree of anticoagulation associated with the oral factor X inhibitors.
- Given that rivaroxaban and apixaban have a high degree of albumin binding in plasma they are not dialysable. Whereas the clearance of dabigatran can be enhanced by dialysis if it available.
- Dabigatran is not suitable for patients with CrCl < 30 ml/min and requires regular tests of renal function.
- Rivaroxaban and apixaban should be used with caution in patients with CrCl 15 - 29 ml/min and are not suitable for patients with a CrCl <15 ml/min
- The best method for reversing the NOACs is not known. Studies in human volunteers have shown that Prothrombin Complex Concentrate (PCC) can reverse the laboratory abnormalities caused by rivaroxaban, but not dabigatran. However both drugs are associated with a nonlinear relationship between the prolongation of coagulation tests and bleeding tendency and drug levels, and it remains uncertain whether PCC is a clinically effective method of reversing these drugs.
- All the measurable (laboratory) anticoagulant effects of rivaroxaban are reversed by PCC (Beriplex/Octaplex). Clinical data is lacking but it seems reasonable to give a dose of 25 IU/kg of PCC in cases of acute uncontrollable bleeding. PCC works in this setting because it provides additional factor II, VII, IX and X and the Xa inhibitor (rivaroxaban) is overcome.
- The product literature for apixaban suggests considering recombinant factor VIIa (rVIIa) in the setting of uncontrolled life threatening bleeding associated with apixaban. Clinical evidence for reversal of apixaban is lacking but, given the common mode of action, it would be expected that reversal would be along the lines of that advised for rivaroxaban.
- PCC (Beriplex/Octaplex) and rVIIa have not been found to be effective in dabigatran reversal. This may be explained by the fact that dabigatran inhibits the last enzymatic step of the coagulation cascade. Any agent that replaces coagulation

factors proximal to thrombin will not compensate for the profound terminal defect in haemostasis. Activated PCC (FEIBA) may improve haemostasis by providing small amounts of thrombin, however clinical data to date is lacking. In the absence of an effective antidote and until new data are available it would seem reasonable to offer PCC, rVIIa or activated PCC to patients with life threatening bleeding associated with dabigatran after evaluation of the risk versus benefit in an individual case.

- Long term safety and tolerability of these new agents is not yet known. All 3 are “black triangle” drugs.
- Non-compliant patients were excluded from RE-LY, and they might receive less (if any) benefit from dabigatran, because the long half-life of warfarin could provide them with a more consistent anticoagulant effect.
- Warfarin cannot usually be put into a Monitored Dosage System due to the need for dose adjustments. Dabigatran is unstable after being removed from the blister pack and is therefore also not suitable for administration using MDS boxes. Rivaroxaban and apixaban may be put into an MDS.
- The effects of non-compliance with the NOACs might be more significant because of their short half-lives compared to warfarin.

In summary the following factors need to be considered in selecting a NOAC for SPAF

<i>(Note that the trials compared different levels of INR rates – TTR was 64% in RE-LY, 62% in ARISTOTLE and 55% in ROCKET AF)</i>	<b>Dabigatran</b>	<b>Rivaroxaban</b>	<b>Apixaban</b>
<b>Efficacy in stroke prevention compared to warfarin</b>	Overall no difference  Superior (150mg bd dose)  Non-inferior (110mg bd dose)	Overall no difference  Non inferior (ITT analysis)	Overall superior  Superior for haemorrhagic stroke  No difference for ischaemic and uncertain type stroke
<b>Reduced risk of bleeding compared to warfarin</b>	Evidence for reduced bleeding risk at lower dose.  NB Increased risk of GI bleed than warfarin at higher dose which is the usual dose.  Overall reduced intra cranial haemorrhage (ICH)	Equivalent to warfarin (except reduced ICH)	Superior
<b>Reversibility</b>	Uncertain.  If last dose taken in last 2 hours consider oral activated charcoal.  PCC, rVII or activated PCC can be considered after risk v benefit assessment	Uncertain  PCC, rVII or activated PCC can be considered after risk v benefit assessment	Uncertain  Area Under Curve may be reduced using activated charcoal  PCC, rVII or activated PCC can be considered after risk v benefit assessment
<b>Dialysable</b>	Yes, but will need to be carried out for at least 6 hours in order to ensure adequate drug clearance	No	No
<b>Dosing</b>	bd	od	bd
<b>Drug interactions</b>	P- glycoprotein substrates	Simultaneous PGP & CYP-3A4	Simultaneous PGP & CYP-3A4
<b>Drug cautions (increased bleeding risk)</b>	Other anticoagulants (except during switching) Antiplatelet agents, NSAIDs, SSRIs or SNRIs	Other anticoagulants (except during switching), Antiplatelet agents, NSAIDs	Other anticoagulants (except during switching), Antiplatelet agents, NSAIDs

<b>Use in patients with swallowing difficulties</b>	Cannot be crushed	May be crushed and put through NG tube but this is outside of license	May be crushed and put through NG tube but this is outside of license
<b>Suitability for MDS</b>	Not suitable	Suitable	Suitable
<b>Cost / year (Costs for dabigatran and rivaroxaban may vary in different settings because of negotiated procurement discounts)</b>	£803*	£767*	£803
<b>Possibility of using in other conditions</b>	NICE approved for orthopaedic prophylaxis. Phase III data shows efficacy in DVT but no NICE appraisal currently planned	NICE approved for orthopaedic prophylaxis. NICE approved for the treatment of DVT, and the prevention of recurrent DVT and PE following an acute DVT in adults.	NICE approved for orthopaedic prophylaxis.

#### **4. Selection of appropriate patients**

##### **4.1 Newly diagnosed AF patients**

This should be used in conjunction with the East Midlands Cardiovascular Network guideline for selection of patients with a CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥ 1 requiring oral anticoagulant stroke thromboprophylaxis.

This can be found at [AF Pathway](#).

**Warfarin remains a suitable first-line oral anticoagulant for most patients.**

##### **4.1.1 Warfarin should be the preferred option in patients:**

- with eGFR < 30 mls/min  
(NB Patients with a baseline eGFR of 30-40 mls/min are at risk or progressive/acute renal dysfunction and the potential risks of bleeding with NOACs should be weighed on an individual basis)
- with a history of significant peptic ulcer disease
- significant ischaemic heart disease in absence of other determining considerations

##### **4.1.2 NOACs may be the preferred option in patients:**

- predicted to have variable interacting medications e.g. recurrent antibiotics
- with known excess use of ethanol
- who would require domiciliary testing
- with high HASBLED score where dabigatran 110mg bd dosing should be considered

##### **4.1.3 In all other patients, warfarin is recommended as a first line treatment following discussion with patient explaining:**

- lack of long term data on NOACs
- issues concerning reversibility
- NICE guidance and evidence base on dabigatran / rivaroxaban / apixaban
- principles used in patient selection
- patient will be considered for a NOAC if TTR < 60% after 4 months in presence of compliance

#### **4.2 Existing patients currently taking vitamin K antagonists**

This should be used in conjunction with the East Midlands Cardiovascular Network guideline for selection of patients with a CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥1 requiring oral anticoagulant stroke thromboprophylaxis.

**Warfarin remains a suitable first-line oral anticoagulant for most patients.**

##### **4.2.1 Conversion to NOACs will be recommended for patients:**

- intolerant of vitamin K antagonists
- TTR < 60% after > 4 months (providing no evidence non-compliance)

#### **4.2.2 Conversion to NOAC may be considered for patients:**

- with history of significant bleed on warfarin (dabigatran 110mg bd or apixaban preferred)
- with history of stroke or TIA while taking warfarin (providing no evidence non-compliance)
- requiring domiciliary phlebotomy

#### **4.2.3 Other patients who are well controlled and tolerant of warfarin are not recommended to change.**

### **5. Pathway for initiation**

#### **5.1 Newly diagnosed AF patients**

##### **5.1.1 GP or referring clinician to check**

- FBC, U&E, LFT and a clotting screen
- CHADS<sub>2</sub> / CHA<sub>2</sub>DS<sub>2</sub>VaSc
- refer to anticoagulant department for counselling, induction and selection of preferred anticoagulant agent.

##### **5.1.2 If NOAC preferred agent (selection criteria above), the anticoagulant department will:**

- deliver induction counselling
- supply initial 4 week supply of NOAC
- enter on acute trust database
- refer back to Primary Care for further prescriptions and monitoring

#### **Content of Induction Counselling**

- effect of drug
- risks (and benefits) of drug
- risk /benefit of NOAC versus warfarin
- advice regarding platelet antagonists
- importance of compliance
- notification of health professionals / use of alert card
- management of procedures
- information leaflet including list of known drug interactions
- **patients should seek urgent medical attention if they fall or injure themselves during treatment, especially if they hit their head, due to the increased risk of bleeding.**

### **5.1.3 When patient is referred from cardiology department with planned cardioversion**

- New NOAC will be started in cardiology. Currently there is insufficient data on either rivaroxaban or apixaban in the setting of cardioversion so dabigatran is strongly preferred.
- A/C service will see within 5 working days to perform counselling, registration etc. (as above)
- Patients should be reviewed in Cardiology OP department 4-6 weeks post cardioversion to consider longer term choice of OAC

## **5.2 Patients currently taking vitamin K antagonists**

### **5.2.1 Anticoagulant department to screen database of existing patients for all patients:**

- with TTR < 60%
- history of major bleeding on warfarin with CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>VaSc ≥1
- history of stroke / TIA on warfarin
- in domiciliary testing service

### **5.2.2 These patients will be seen in nurse led A/C assessment clinic:**

- to establish compliance
- check U&E
- to explain rationale for conversion
- to manage conversion
  1. stop warfarin
  2. supply 4 weeks NOAC
  3. start NOAC after discontinuation of warfarin as per guidance in product literature, (instructions to be written in Warfarin book)
- letter to be sent to GP explaining outcome of above and recommendations concerning monitoring

### **5.2.3 The following patients will be referred from the nurse led clinic to haematology consultant led clinic:**

- patients with h/o significant bleeding or high HASBLED score
- uncertainty about compliance

## **6. Shared Care Guidance**

### **6.1 Information letter to be supplied to GP**

### **6.2 Recommended monitoring**

- twice yearly U&E if renal function normal
- 3 monthly U&E if renal function abnormal
- annual clinical review to assess risk / benefit
  1. h/o stroke / TIA
  2. check HASBLED including any bleeding episodes with a view to dose reduction or referral back to specialist clinic

## Appendix 1

### Letter to Primary Care following initiation of Dabigatran for Stroke Prevention in AF

Dear Dr

Your patient has today been started on dabigatran to prevent stroke associated with atrial fibrillation.

The decision to do so has been made on the basis of:

- predicted high risk on warfarin (polypharmacy, excess ethanol, high bleeding risk score)
- previous poor control on warfarin
  - Time in Treatment Range <60%
  - History of significant bleeding on warfarin
  - History of stroke or TIA on warfarin

CHADS<sub>2</sub> \_\_\_\_\_ or CHA<sub>2</sub>DS<sub>2</sub>VASc \_\_\_\_\_  
HASBLED \_\_\_\_\_ and eGFR \_\_\_\_\_

Your patient has been prescribed:

Dabigatran 150mg bd

OR

Dabigatran 110mg bd (preferred because of identified high risk of bleeding)

Your patient

- has been counselled about the safe use of dabigatran
- supplied with the attached information leaflet
- supplied with an alert card

The following monitoring is recommended for patients on dabigatran

U&E and FBC

- Normal renal function 6 monthly
- Abnormal or unstable renal function 3 monthly

Annual review

- History of any stroke / TIA or bleeding in last year
- recheck HASBLED
  - if HASBLED now high, or bleeding events, consider either reduction to 110 mg bd, or specialist assessment



## DABIGATRAN KEY POINTS

- It does not require INR monitoring
- It must be stopped if eGFR <30 mls/min
- At standard dose (150mg bd) it has **the same risk of major bleeding (but not intracranial haemorrhage) as warfarin.**
- Dabigatran T<sub>1/2</sub> is 12-14 hours only, in presence of normal renal function. Compliance is critical therefore, as protection from stroke will be lost with omission of only one dose (in contrast to warfarin).
- In the event of surgery or procedures, it will be necessary to omit the dose prior to the procedure. **See product SPCs for full details of timescales.**
- Dabigatran must not be used in patients with a lesion or condition putting them at significant risk of major bleeding (see SPC for details).
- Concomitant treatment with other anticoagulants is contraindicated while on dabigatran
- Its use is contraindicated with:
  - Ketoconazole, itraconazole, voriconazole, posaconazole
  - Ciclosporin
  - Tacrolimus
  - Dronedarone
  - Protease inhibitors
  - Rifampicin, carbamazepine, phenytoin and St. Johns wort
- It should be used with caution with other p glycoprotein substrates e.g verapamil (in which case the dose of dabigatran should be reduced to 110mg bd) and amiodarone, quinidine and clarithromycin especially if mild or moderate renal impairment.
- It causes prolongation of APTT and TT which are not however measures of the degree of anticoagulation. A normal TT will rule out the presence of any significant anticoagulant effect from dabigatran
- There is no established method acutely to reverse the effect of dabigatran. In the event of suspected overdose, activated charcoal should be administered within 2 hours of ingestion.
- As of February 2013 dabigatran is now contraindicated in patients with prosthetic heart valves requiring anticoagulant treatment. The existing warning in section 4.4 of the SPC not to use the drug in patients with prosthetic heart valves is strengthened to a contraindication based on the availability of new data from clinical trials.

**For further information or advice, please contact the KGH Anticoagulant service on 01536 492000 bleep 541 or the NGH Anticoagulant service on 01604 525707**

## Appendix 2

### Letter to Primary Care following initiation of Rivaroxaban for Stroke prevention in AF

Dear Dr

Your patient has today been started on rivaroxaban to prevent stroke associated with atrial fibrillation

The decision to do so has been made on the basis of:

- Predicted high risk on warfarin (polypharmacy, excess ethanol, high bleeding score)
- Previous poor control on warfarin
  - Time in treatment range <60%
  - History of significant bleeding on warfarin
  - History of stroke or TIA on warfarin

CHADS<sub>2</sub> \_\_\_\_\_ or CHA<sub>2</sub>DS<sub>2</sub>VASc \_\_\_\_\_  
HASBLED \_\_\_\_\_ and eGFR \_\_\_\_\_

Your patient has been prescribed:

Rivaroxaban 20mg od

OR

Rivaroxaban 15 mg od

Your patient:

- Has been counselled about the safe use of rivaroxaban
- Supplied with the attached information leaflet
- Supplied with an alert card

The following monitoring is recommended\* for patients on rivaroxaban

- Base line FBC, renal function, LFTs and clotting
- Renal function and LFTs monthly for first 3 months then 3 monthly

Annual review

- History of any stroke/ TIA or bleeding in the last year
- Recheck HASBLED and eGFR
  - If HASBLED now high, or bleeding events or eGFR between 15-49 ml/min, dose of Rivaroxaban should be reduced to 15mg od or refer for specialist assessment

*\*local recommendation; not in SPC*

## RIVAROXABAN KEY POINTS

- It does not require INR monitoring
- If eGFR <15 mls/min rivaroxaban must not be initiated and if already initiated, must be stopped
- In patients with hepatic disease associated with coagulopathy and clinically significant bleeding risk, including cirrhotic patients rivaroxaban should not be prescribed
- Rivaroxaban must not be used in patients with a lesion or condition putting them at significant risk of major bleeding (see SPC for details).
- Concomitant treatment with other anticoagulants is contraindicated while on rivaroxaban
- Rivaroxaban has a t½ of 5-9 hours in young patients and 11-13 hours in elderly patients so compliance is crucial
- In the event of surgery or procedures, rivaroxaban should be stopped 24 hours prior to the intervention.
- It interacts with the following drugs:

### Contraindicated

- Azole antifungals: ketoconazole, voriconazole, itraconazole, posaconazole
- HIV protease inhibitors i.e. ritonavir
- Dronedarone

### Use with caution

- Rifampicin, Phenytoin, carbamazepine, phenobarbitol, St.John's wort

- Rivaroxaban causes an increase principally in PT, but this is not a measure of degree of anticoagulation
- There is no established method acutely to reverse the effect of rivaroxaban.

**For further information or advice please contact the KGH Anticoagulant service on 01536 492000 bleep 541 or the NGH Anticoagulant service on 01604 525707**

## Appendix 3

### Letter to Primary Care following initiation of Apixaban for Stroke prevention in AF

Dear Dr

Your patient has today been started on apixaban to prevent stroke associated with atrial fibrillation

The decision to do so has been made on the basis of:

- Predicted high risk on warfarin (polypharmacy, excess ethanol, high bleeding score)
- Previous poor control on warfarin
  - Time in treatment range <60%
  - History of significant bleeding on warfarin
  - History of stroke or TIA on warfarin

CHADS<sub>2</sub> \_\_\_\_\_ or CHA<sub>2</sub>DS<sub>2</sub>VASc \_\_\_\_\_  
HASBLED \_\_\_\_\_ and eGFR \_\_\_\_\_

Your patient has been prescribed:

Apixaban 5mg bd

OR

Apixaban 2.5 mg bd

(if CrCl 15-29 mls/min and in patients with either at least two of the following: (age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromole/l)

Your patient:

- Has been counselled about the safe use of apixaban
- Supplied with the attached information leaflet
- Supplied with an alert card

The following monitoring is recommended for patients on apixaban

- Base line FBC, renal function, LFTs and clotting
- Renal function and LFTs monthly for first 3 months then 3 monthly

Annual review

- History of any stroke/ TIA or bleeding in the last year
- Recheck HASBLED and eGFR
  - If HASBLED now high, or bleeding events or eGFR between 15-30ml/min, reduce dose to 2.5mg bd or refer for specialist assessment

## **APIXABAN KEY POINTS**

- It does not require INR monitoring
- If eGFR <15 mls/min apixaban must not be initiated and if already initiated, must be stopped
- In patients with hepatic disease associated with coagulopathy and clinically significant bleeding risk, including cirrhotic patients apixaban should not be prescribed
- Apixaban must not be used in patients with a lesion or condition putting them at significant risk of major bleeding (see SPC for details).
- Concomitant treatment with other anticoagulants is contraindicated while on apixaban
- Apixaban has a t<sub>1/2</sub> of approximately 12 hours in presence of normal renal function. Compliance is critical therefore, as protection from stroke will be lost with omission of only one dose (in contrast to warfarin).
- Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding.
- Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding.
- It interacts with the following drugs:

### Contraindicated

- Azole antifungals: ketoconazole, voriconazole, itraconazole, posaconazole
- HIV protease inhibitors i.e. ritonavir
- Dronedarone

### Use with caution

- Rifampicin, Phenytoin, carbamazepine, phenobarbital, St.John's wort

- Apixaban causes an increase principally in PT, but this is not a measure of degree of anticoagulation
- There is no established method acutely to reverse the effect of apixaban.

**For further information or advice please contact the KGH Anticoagulant service on 01536 492000 bleep 541 or the NGH Anticoagulant service on 01604 525707**