**Implementation of NICE TA 249 and NICE TA 256**

**Dabigatran and rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation Version 1.0**

**Background**

NICE has recently issued guidance that these new oral anticoagulants (OACs) are an option for stroke prevention in patients with atrial fibrillation.

The new OACs have caused considerable interest because they offer an alternative to warfarin which does not need monitoring with blood tests.

However this "headline" advantage has to be balanced by some key considerations:

- There is very little, if any advantage over warfarin in terms of stroke prevention
- There is no check on patient concordance since the new OACs are not monitored
- There are safety concerns particularly about severe haemorrhage and possibly myocardial infarction – warnings by the regulatory bodies continue to be issued
- The new OACs cannot be reversed in practical terms, presenting problems in emergencies
- Renal function needs to be assessed and monitored – see the NHS Suffolk guidance
- Bleeding risk needs to be carefully assessed
- All are Black Triangle drugs

Page 11 of this guidance summarises the pros and cons of the new OACs and warfarin.

All clinicians need to be aware of the disadvantages of the new OACs, in order to make an informed decision about which patients might be suitable. NHS Suffolk has therefore produced this paper which explains a rational way to implement NICE’s guidance, and most importantly gives guidance on patient selection. The paper is based very closely on work done by NHS Northamptonshire, which included consultation with the relevant pharmaceutical companies.

I would draw your attention particularly to the fact that the complexity of the situation has led NHS Suffolk to give the new OACs a Traffic Light status of “Green – Hospital Initiated, GP prescribed”.

This is a developing area and further changes may be necessary particularly as more safety data become available – however we will inform you of significant changes.

*This is an NHS Suffolk document that has been adopted by the WSCCG*
Some patients are understandably keen to switch to a drug which does not need monitoring. However, most will not be aware of the full implications of taking the new OACs. We as clinicians need to explain this clearly to make sure that patients are fully informed.

Finally, as clinical commissioners, we need to be cost-aware. I believe that the reasons for treading carefully with the new OACs are clinical. However, it is also necessary to realise that widespread use will cause very significant cost pressures on our healthcare system in Suffolk, particularly since the warfarin monitoring service will need to be maintained for the foreseeable future. In order to obtain the maximum clinical advantage, we need to use the new drugs in situations where there are real clinical problems with using warfarin.
Executive summary

NICE has issued Technology Appraisals for dabigatran (Pradaxa▼) and for rivaroxaban (Xarelto▼) for the prevention of stroke and systemic embolism in atrial fibrillation (TA 249 and TA 256). This guidance has been produced to help identify those patients who are most likely to benefit from dabigatran or rivaroxaban 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 chose to initiate dabigatran or rivaroxaban for any patient within the Technology Appraisals’ criteria if clinically appropriate.

Dabigatran and rivaroxaban are orally active antithrombotic agents. Dabigatran is a direct thrombin inhibitor and rivaroxaban is an oral direct factor Xa inhibitor. Both drugs have the potential advantage over warfarin of not requiring INR blood
monitoring, but other factors about both drugs need to be taken into consideration when deciding whether either drug is appropriate for an individual patient.

- These factors include
  - Unknown long term safety profile of the new agents. Both are “black triangle drugs”.
  - Lack of reversibility of the new agents.
  - Consideration of the patient’s current INR control on warfarin.
  - Renal function. The MHRA update for Dabigatran (July 2012) states;
    - We previously advised on the importance of renal function monitoring in patients who receive dabigatran, as systemic exposure to dabigatran is substantially increased in patients with renal insufficiency (see December 2011 Drug Safety Update)
    - Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min)

For rivaroxaban, the SPC states

- In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min

- Bleeding risk, especially GI bleeding risk. MHRA update, Dabigatran (July 2012) states;
  - current or recent gastrointestinal ulceration
  - malignant neoplasms
  - recent brain or spinal injury
  - recent brain, spinal or ophthalmic surgery
  - recent intracranial haemorrhage
  - oesophageal varices
  - arteriovenous malformations
  - vascular aneurysms
  - major intraspinal or intracerebral vascular abnormalities

For Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- 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

Drug interactions

Dabigatran
http://www.medicinescomplete.com/mc/bnf/current/41001i1120.htm

Rivaroxaban
http://www.medicinescomplete.com/mc/bnf/current/41001i1136.htm

Compliance.

➢ The choice of agent is the decision of the prescriber and there are pros and cons to each agent. A third new oral anticoagulant, apixaban, is expected to be licensed for this indication later in 2012 and considered by NICE in February 2013.

➢ Guidance is provided both for patients newly diagnosed with AF and for existing patients currently taking warfarin.

➢ In Suffolk it is recommended that both drugs 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 an advisory letter (Green Status). This pathway for initiation will be reviewed once experience with these new drugs becomes more established.

➢ 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.


1.3 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.

1.4 The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the patient 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.

The third new agent, apixaban, anticipates a licence for this indication in late 2012 and a NICE TA is expected in February 2013.

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](http://www.npc.nhs.uk/rapidreview/?p=4580)

There are a number of issues raised by both studies which need to be considered when putting the results in the context of normal clinical practice. These relate to the level of anticoagulant control in the warfarin groups, long-term safety and tolerability of dabigatran, and limitations in the study methodology.

Many of these issues have been considered by NICE.

3. **Guidance aims and choice of new OAC**
   This guidance has been produced to help identify those patients who are most likely to benefit from dabigatran or rivaroxaban and to provide advice on using these new drugs 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 or rivaroxaban 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 time in therapeutic range (TTR).

   • The average TTR at Ipswich hospital is 70.92% and at West Suffolk hospital it is 71.95%.

   • The average age of the patients in the RE-LY trial was 71 and in ROCKET AF was 73; some of our Suffolk 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.

• The best method for reversing either dabigatran or rivaroxaban is not known. Studies in human volunteers have shown that Prothrombin Complex Concentrate (PCC) can reverse the laboratory abnormalities caused by rivoroxaban, but not dabigatran. However both drugs are associated with a non linear relationship between 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. rVIIa and PCC (Beriplex/Octaplex) have been found to be ineffective 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.

• For Rivaroxaban, the high degree of albumin binding in plasma means that it is not dialysable. All its measurable (laboratory) anticoagulant effects are reversed by PCC (Beriplex/Octaplex). Clinical data is lacking but it seems reasonable to give a dose of 25IU/kg of PCC in case of acute bleeding. PCC works in this setting because it provides additional factor II, VII, IX and X and the Xa inhibitor (Rivaroxaban) is overcome.

• There are currently no tests to assess the level of anticoagulation (under or over) being achieved.

• Dabigatran is not suitable for patients with CrCl < 30 and requires regular tests of renal function.

• Rivaroxaban is to be used with caution in patients with CrCl 15 - 29 ml/min

• A small but significantly greater rate of myocardial infarction with high-dose dabigatran seen in RE-LY is a signal of potential long-term safety which will need to be considered. The absolute differences in this study were small; results suggest that 476 patients, like those in this study, would need to be treated with dabigatran for one year for one of them to have a myocardial infarction who would not have done if they had received warfarin. This observation may reflect a clinical benefit of warfarin rather than an adverse effect of dabigatran. Nevertheless, this raises particular concerns about the use of dabigatran in people who are at high risk of coronary heart disease. No increase in myocardial infarctions was seen.
with rivaroxaban vs warfarin in ROCKET-AF or any other studies involving rivaroxaban

- Long term safety and tolerability of these new agents is not yet known. Both 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 may be put into an MDS.

- The effects of non-compliance with both dabigatran and rivaroxaban 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 new OAC for SPAF:

<table>
<thead>
<tr>
<th>Efficacy in stroke prevention compared to warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall no difference</td>
<td>Superior (150mg bd dose) The NNT to prevent one systemic embolism or stroke/year = 172</td>
<td>Overall no difference Non inferior (ITT analysis)</td>
</tr>
<tr>
<td>Reduced risk of bleeding compared to warfarin</td>
<td>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)</td>
<td>Equivalent to warfarin (except reduced ICH)</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Uncertain.</td>
<td>Uncertain (possible data supports use PCC which may reverse the laboratory abnormalities of clotting but this may not translate into stopping the actual bleeding event)</td>
</tr>
<tr>
<td>Dialysable</td>
<td>Yes, but will need to be carried out for at least 6 hours in order to ensure adequate drug clearance</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>bd</td>
<td>od</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P- glycoprotein substrates</td>
<td>Simultaneous PGP &amp; CYP-3A4</td>
</tr>
<tr>
<td>Drug cautions (increased bleeding risk)</td>
<td>Antiplatelet agents, NSAIDs, SSRIs or SNRIs</td>
<td>Antiplatelet agents, NSAIDs</td>
</tr>
<tr>
<td>Use in patients with swallowing difficulties</td>
<td>Cannot be crushed</td>
<td>May be crushed and put through NG tube</td>
</tr>
<tr>
<td>Suitability for MDS</td>
<td>Not suitable</td>
<td>Suitable</td>
</tr>
<tr>
<td>Cost / year (Costs may vary in different settings because of negotiated procurement discounts)</td>
<td>£803</td>
<td>£767</td>
</tr>
<tr>
<td>Possibility of using in other conditions</td>
<td>NICE approved for orthopaedic prophylaxis. Phase III data shows efficacy in DVT but no NICE appraisal currently planned</td>
<td>NICE approved for orthopaedic prophylaxis. Licensed for treatment of DVT, and the prevention of recurrent DVT and PE following an acute DVT in adults. DVT NICE FAD issued on 1st June 2012.</td>
</tr>
</tbody>
</table>

Choice of new OAC will need to be reviewed with further data expected in the next 12-24 months, especially regarding reversibility, other new OACs, and the opportunity to adopt a single drug across a wide variety of indications (SPAF, VTE treatment and thromboprophylaxis)
4. **Selection of appropriate patients**

4.1 **Newly diagnosed AF patients**

This should be used in conjunction with the East of England Guidelines for selection of patients with a CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc $\geq$ 2 requiring oral anticoagulant stroke thromboprophylaxis.

**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  
  (NB Patients with a baseline eGFR of 30-40 are at risk or progressive/acute renal dysfunction and the potential risks of bleeding with dabigatran or rivaroxaban 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 **New OAC may be the preferred option in patients:**

- predicted to have variable interacting medications e.g. recurrent antibiotics
- with known excess use of ethanol
- 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 new OACs
- issues concerning reversibility
- NICE guidance and evidence base on dabigatran / rivaroxaban
- principles used in patient selection
- patient will be converted to new OAC if TTR < 60% after 4 months in presence of compliance

The NICE decision aid can be used to explain the risks and benefits to patients. *Add weblink when available.*

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

This should be used in conjunction with the East of England guidelines for selection of patients with a CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc $\geq$ 2 requiring oral anticoagulant stroke thromboprophylaxis.

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

4.2.1 **Conversion to new OAC 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 new OAC may be considered for patients:
- with history of significant bleed on warfarin (dabigatran 110mg bd preferred)
- with history of stroke or TIA while taking warfarin (providing no evidence non compliance)

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

The NICE decision aid can be used to explain the risks and benefits to patients. Add weblink when available.

5. Pathway for initiation

5.1 Newly diagnosed AF patients

5.1.1 GP or referring clinician to check
- FBC U&E clotting screen
- CHADS2 / CHA2DS2-VaSc
- refer to anticoagulant department (or cardiologist or stroke physician if appropriate) for counseling, induction and selection of preferred anticoagulant agent.

5.1.2 If new OAC preferred agent (selection criteria above), anticoagulant department will:
- deliver induction counselling
- supply initial 4 week prescription
- enter on acute trust database
- refer back to Primary Care for further prescriptions and monitoring

<table>
<thead>
<tr>
<th>Content of Induction Counselling</th>
</tr>
</thead>
<tbody>
<tr>
<td>effect of drug</td>
</tr>
<tr>
<td>risks (and benefits) of drug</td>
</tr>
<tr>
<td>risk /benefit of new OAC vs warfarin</td>
</tr>
<tr>
<td>advice re platelet antagonists</td>
</tr>
<tr>
<td>Importance of compliance</td>
</tr>
<tr>
<td>notification of health professionals / use of alert card</td>
</tr>
<tr>
<td>Management of procedures</td>
</tr>
<tr>
<td>information leaflet including list of known drug interactions</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

5.1.3 When patient is referred from cardiology department with planned cardioversion
• New OAC will be started in Cardiology. There is no data on rivaroxaban in 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 CHADS₂ or CHA₂DS₂VaSc >=1
• history of stroke / TIA on warfarin

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 new OAC
  3. start new OAC 3 days after discontinuation (INR to be rechecked until INR <2 if concerns about patient) with 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 a history of significant bleeding or high HASBLED
• uncertainty about compliance

6. Care Guidance for GPs

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. History of stroke / TIA
  2. check HASBLED incl 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%
  - h/o significant bleeding on warfarin
  - h/o stroke or TIA on warfarin

CHADS2 _______ HASBLED_________ 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

• At standard dose (150mg bd) it has the same risk of major bleeding (but not intracranial haemorrhage) as warfarin.

• Dabigatran T1/2 is 12-14 hours only, in presence of normal renal function. Therefore compliance is critical 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.

• It interacts with P glycoprotein substrates and its use is contraindicated with:
  o ketoconazole
  o quinidine
  o ciclosporin
  o tacrolimus
  • dronedarone and other anticoagulants

• It should be used with caution with other p glycoprotein substrates e.g. verapamil, amiodarone, clarithromycin) with at least 2 hour gap between taking dabigatran and these drugs

• It causes prolongation of APTT and TT which are not however measures of degree of anticoagulation. A normal Thrombin time 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.
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%
  - H/o significant bleeding on warfarin
  - H/o stroke or TIA on warfarin

CHADS2 ________ or HASBLED ________ eGFR_______

Your patient has been prescribed:

Rivaroxaban 20mg od

Your patient:

- Has been counseled 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 15-30ml/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 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 has a T1/2 of 5-9 hours in young patients and 11-13 hours in elderly patients. **Therefore compliance is critical as protection from stroke may be lost with omission of only one dose (in contrast to warfarin).**
- In the event of surgery or procedures, Rivaroxaban should be stopped 24 hours prior to the intervention.
- It interacts with the following drugs:
  - Azole antifungals: Ketoconazole, Voriconazole, Itraconazole, Posaconazole
  - HIV protease inhibitors
  - Rifampicin
  - Phenytoin, Carbamazepine, Phenobarbital
  - 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.
Appendix 3

On 25th May 2012 the European Medicines Agency updated the Patient and Prescriber information for dabigatran (Pradaxa▼).

Dabigatran Q&A May 2012.pdf
Dabigatran SPC.pdf

This includes updated advice for patients and prescribers

• 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.

• Patients taking other anticoagulants (medicines to prevent blood clotting) must not take Pradaxa except during a period where their treatment is being switched to or from Pradaxa.

• Prescribers are reminded of the need to follow all the necessary precautions with regard to the risk of bleeding with Pradaxa, including the assessment of kidney function before treatment in all patients and during treatment if a deterioration is suspected, as well as dose reductions in certain patients.

• Pradaxa must not be used in patients with a lesion or condition putting them at significant risk of major bleeding (see the revised product information for details).

• Pradaxa must not be used in patients using any other anticoagulant, unless the patient is being switched to or from Pradaxa (see the revised product information for details).

A European Commission decision on this opinion will be issued in due course.

In July 2012, the MHRA issued a drug safety update; Dabigatran: risk of serious haemorrhage- contraindications clarified and reminder to monitor renal function. Full details are available at

http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON175429