Implementation of NICE TA 249 and NICE TA 256

Dabigatran and Rivaroxaban

for the prevention of stroke and systemic embolism in atrial fibrillation

June 2012
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Approved by -
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East Midlands Cardiovascular Network June 2012
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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.
  - Bleeding risk, especially GI bleeding risk.
  - Drug interactions
  - 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 (OAC), 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 Northamptonshire 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 shared care advice (amber 2 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.

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.

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

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 TTR.

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 trial was 71 and in ROCKET AF was 73; 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.

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 rivaroxaban, 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><strong>Overall no difference</strong></td>
<td>Superior (150mg bd dose)</td>
<td>Overall no difference</td>
</tr>
<tr>
<td><strong>Non-inferior (110mg bd dose)</strong></td>
<td>Non inferior (ITT analysis)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reduced risk of bleeding compared to warfarin</th>
<th>Evidence for reduced bleeding risk at lower dose.</th>
<th>Equivalent to warfarin (except reduced ICH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NB Increased risk of GI bleed than warfarin at higher dose which is the usual dose.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall reduced intra cranial haemorrhage (ICH)</strong></td>
<td></td>
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</table>

| Reversibility | Uncertain. | 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) |

| Dialysable | Yes, but will need to be carried out for at least 6 hours in order to ensure adequate drug clearance | No |

| Dosing | bd | od |

<table>
<thead>
<tr>
<th>Drug interactions</th>
<th>P- glycoprotein substrates</th>
<th>Simultaneous PGP &amp; CYP-3A4</th>
</tr>
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</table>

| Drug cautions (increased bleeding risk) | Antiplatelet agents, NSAIDs, SSRIs or SNRIs | Antiplatelet agents, NSAIDs |

| Use in patients with swallowing difficulties | Cannot be crushed | May be crushed and put through NG tube |

| Suitability for MDS | Not suitable | Suitable |

| Cost / year (Costs may vary in different settings because of negotiated procurement discounts) | £803 | £767 |

| Possibility of using in other conditions | NICE approved for orthopaedic prophylaxis. Phase III data shows efficacy in DVT but no NICE appraisal currently planned | 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. |

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, thromboprophylaxis)
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\_2 or CHA\_2DS\_2-VASc > or \(=\) 2 requiring oral anticoagulant stroke thromboprophylaxis. This can be found at [AF Pathway](#) or at appendix 4.

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
- 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 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 NPC 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 Midlands Cardiovascular Network guideline for selection of patients with a CHADS\_2 or CHA\_2DS\_2-VASc > or \(=\) 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)
• requiring domiciliary phlebotomy

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

The NPC 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
• CHADS\(_2\) / CHA\(_2\)DS\(_2\)VaSc
• refer to anticoagulant department (or cardiologist or stroke physician if appropriate) for counselling, 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 Counseling</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>
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</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 CHADS$_2$ or CHA$_3$DS$_2$VaSc $\geq$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 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 h/o significant bleeding or high HASBLED
- 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%
  - 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

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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. 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.
- It interacts with P glycoprotein substrates and its use is contraindicated with:
  - ketoconazole
  - quinidine
  - ciclosporin
  - tacrolimus
- 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.

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%
  - H/o significant bleeding on warfarin
  - H/o stroke or TIA on warfarin

CHADS2 __________ 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 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:
  - 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.

For further information or advice please contact the KGH Anticoagulant service on 01536 492000 bleep 541 or NGH Anticoagulant service on 01604 525707
Appendix 3

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

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.
Appendix 4

EAST MIDLANDS CARDIOVASCULAR NETWORK PATHWAY FOR THE MANAGEMENT OF ATRIAL FIBRILLATION IN PRIMARY CARE

For details, please refer to relevant national clinical guidelines:
http://www.nice.org.uk/CG315

1. Patients aged 65 and older should have a manual pulse palpation at least annually and any irregularity should be followed up with a 12-lead ECG.

2. Consider emergency hospital admission for patients with hemodynamic instability, heart failure, chest pain, breathlessness at rest, light-headedness or syncope, stroke, rates in excess of 180 bpm and wide QRS complexes. Patients considered for immediate cardioversion (clear history of AF, onset within 48 hrs).

3. Physical examination including manual BP evaluation, 12 lead ECG if not already carried out, FBC, U&Es, TFTs and LFTs. BNP if patient is breathless.

4. Consider echocardiogram for patients with suspected structural heart disease (murmur, abnormal ECG etc.) OR when echocardiogram may alter clinical management.

5. Assess Stroke Risk (CHADS2 / CHA2DS2-VASC) and initiate appropriate stroke prevention therapies (See page 2 for details).

6. Structural heart disease includes valve disease, heart failure, cardiomyopathy.

7. Target heart rate at rest < 50 bpm (<110 during exertion in sedentary individuals and 200 – age in active individuals).
   First-line treatment: either beta-blockers or rate limiting calcium-channel blockers, i.e. bisoprolol 1.25-10mg once daily or diltiazem 60-120bd (use branded MR product not generic) or verapamil 40-120mg tds (remember more negatively inotropic than diltiazem, particularity of echo confirms LV dysfunction). If still poor rate control add digoxin to either or acp BNP (Section 2.11).

8. Provision of primary AF services vary across the network and may be provided by specialist nurses, GPwSI or within cardiology departments.

9. Annual Review to include review of stroke prevention therapy and compliance and the appropriateness of the rate/rhythm strategy.

10. For consideration of pulmonary vein isolation, pacemaker (AV node ablation or surgery).
**STROKE PREVENTION IS ARGUABLY THE MOST IMPORTANT ASPECT OF ATRIAL FIBRILLATION MANAGEMENT**

**Warfarin is highly effective in reducing stroke risk but is greatly underused.**

### Background

**AF as a Cause of Stroke**

**National Data**

- The annual risk of stroke is 5.6 times greater in AF patients than in people with normal heart rhythm.
- 18% of patients presenting with stroke are in AF. This equals to 19,000 strokes in England, of which 12,500 are thought to be directly attributable to AF.
- Warfarin is highly effective in preventing stroke in AF, reducing risk of stroke by 64% compared to placebo.
- Aspirin only reduces stroke risk by 22%.
- Only 12% of patients at high risk of stroke need to be treated with warfarin for one year to prevent one stroke, compared to 40.5% of patients taking aspirin.
- There is no statistical difference in the risk of major haemorrhage for warfarin and aspirin in elderly patients (1.9% vs. 2.0% per year, DMTA 2001)
- If annual stroke risk is >2.6%, the benefit of warfarin exceeds bleeding risk when well controlled (2006 Loewe of therapeutic range >80%)

The 2008 NICE guidance on AF concluded that 56% of patients who were receiving warfarin were not.

### Assessing Stroke Risk in AF Patients

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>CHA2DS2-VASc Score</th>
<th>Stroke Risk %</th>
<th>Recommended Stroke Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.4</td>
<td>Oral anticoagulation (OAC)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1.3</td>
<td>Either OAC or aspirin 75-325 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2.2</td>
<td>Either aspirin or no antithrombotic therapy</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3.2</td>
<td>Either aspirin or no antithrombotic therapy</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4.0</td>
<td>Either aspirin or no antithrombotic therapy</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5.9</td>
<td>Either aspirin or no antithrombotic therapy</td>
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<tr>
<td>6</td>
<td>6</td>
<td>8.5</td>
<td>Either aspirin or no antithrombotic therapy</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>12.5</td>
<td>Either aspirin or no antithrombotic therapy</td>
</tr>
</tbody>
</table>

### Risk Stratification

- **High Risk**
  - CHF, diabetes, age ≥ 65
- **Moderate Risk**
  - Age ≥ 65 or history of vascular disease
- **Low Risk**
  - No risk factors and age < 65

### Treatment

**Warfarin should be considered first line for all patients including the elderly unless absolutely contraindicated.**

Contraindications include recent life threatening haemorrhage, pregnancy and known hypersensitivity to warfarin. (See DMTA for complete list.)

**Target INR 2.5 (range 2.0-3.5).**

Assess bleeding risk (see below) and exercise caution and review regularly if score ≥ 5.

If very few patients and on specialist advice concomitant use of antiplatelet agents and warfarin may be appropriate.

**FAILS ARE NOT A MAJOR RISK FACTOR FOR BLEEDING IN ANTICOAGULATED PATIENTS**

<table>
<thead>
<tr>
<th>HAS-BLED Major Bleeding Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Letter</strong></td>
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<tr>
<td>H</td>
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<tr>
<td>A</td>
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<td>E</td>
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<tr>
<td>D</td>
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</tbody>
</table>

**HAS-BLED Notes**

- Hypertension: diastolic blood pressure ≥ 100 mmHg. Renal function: creatinine ≥ 250 or dialysis. Liver function: Child-Pugh score (e.g. decompensation ≤ 9, or ≤ 11 with ALT ≤ 2× upper limit normal). Bleeding: previous bleeding, bleeding diathesis or unexplained anemia. Labile INR: Time in Treatment Range < 65%. Drugs: concurrent use of drugs, e.g. amiodarone and non-steroidal anti-inflammatory drugs, Alcohol, excessive alcohol intake.

**Use of New Oral Anticoagulants**

NICE has published prescribing guidance on the use of dabigatran and rivaroxaban. It is anticipated that local (and regional) guidance will be agreed and published by the end of June 2013. Until local guidance has been published, it is recommended that patients are referred to local Haemostasis departments for advice and initiation of these products.

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**Find further information at:**
- www.strokefirst.org.uk
- www.stroke.org.uk

**GRASP-AF Query and risk stratification tools are FREE and available for use with all GP clinical systems in England**

GRASP-AF provides a set of 6 QUEST questions to identify, for your practice, patients with a diagnosis of AF who are not on warfarin.

It calculates the risk of stroke using a validated CHA2DS2-VASc scoring system and highlights patients with a CHA2DS2-VASc score of 3 or more who are not on warfarin and would benefit from a risk review to assess the issue of anticoagulation.

To find out more about this new tool and to sign up to receive the updates, simply go to [www.improvement.nhs.uk/grasp](http://www.improvement.nhs.uk/grasp)

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**Important Questions and Information to tell your Patients Taking Anticoagulation Therapies:**

- **Do they know why they are taking warfarin, their target INR and the importance of attending for INR checks?**
- **Do they know the importance of asking an expert card/yellow book (warfarin and newer agents)?**
- **Is it important that they tell their doctor and dentist that they are taking warfarin?**
- **Before buying any medicines including alternative remedies they should tell their pharmacist that they are taking warfarin?**
- **Any significant changes to your patient’s medication should be communicated to the Anticoagulation Clinic.**
- **You should explain to them that any major changes to their diet may affect how their body responds to warfarin.**
- **If this occurs a few days they should have an INR test.**
- **Chamomile and grapefruit can affect their INR and should be avoided.**
- **It is dangerous to binge drink whilst taking anticoagulants.**

**Ensure patients are given written information leaflets and understand the information in it.**