Frequently Asked Questions about the Direct Oral Anticoagulants (DOACs) (prev NOAC)

NHS Wiltshire Clinical Commissioning Group

The following FAQs are covered in this document:

- These frequently asked questions are not meant as a guideline or protocol. All doctors retain responsibility for their own prescribing and have to bear in mind licensing issues as well as evidence base.
- This FAQ only addresses the use of Apixaban, Dabigatran and Rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular AF and also the use of Rivaroxaban for the treatment of DVT and PE and prevention of recurrent VTE in adults
- PLEASE NOTE Information about the DOAC Edoxaban which has is recommended as an option by NICE for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation and also for treating and preventing recurrent deep vein thrombosis or pulmonary embolism will be added to this document shortly.

Any potential use of DOACs outside of NICE and the license should be discussed on an individual case by case basis with the consultant

1. What are the DOACs licensed and NICE approved for?

Apixaban

- The NICE TA275 (published February 2013) allows Apixaban to be used as an option in stroke prevention in AF as per the license below.
- Apixaban is licensed for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:
  - **Previous stroke or transient ischemic attack**
  - **Age 75 years**
  - **Diabetes mellitus, symptomatic heart failure (NYHA ≥ 2) or hypertension**
- Apixaban is also licensed for prevention of venous thromboembolism (VTE) in adult patients who have undergone elective hip or knee replacement surgery, but this is dealt with as a RED drug in our local formularies and so no prescribing of this drug for this indication should take place in primary care.
- Apixaban is licensed for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults, and was NICE (TA341) approved in June 2015.

Dabigatran

- NICE TA249 (published March 2012) allows Dabigatran to be used as an option in stroke prevention in AF
- Dabigatran is licensed for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:
- **Previous stroke or transient ischemic attack**
- **Symptomatic heart failure, New York Heart Association (NYHA) Class 2**
- **Age ≥75 years**
- **Diabetes mellitus or hypertension**
  - *NOTE: The license for Dabigatran has slightly changed since the NICE TA249 was published, hence the NICE TA249 refers to the old license wording*
- Dabigatran is also licensed for prophylaxis of venous thromboembolism in adults after total hip or total knee replacement surgery but this is dealt with as a RED drug in our local formularies and so no prescribing of this drug for this indication should take place in primary care
- Dabigatran is licensed for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults and was NICE approved in December 2014 (TA327).
- It is expected however that Rivaroxaban will continue to be the first-line choice for this indication with Dabigatran providing an alternative option for those patients who don't tolerate or can't have Rivaroxaban

Rivaroxaban

- NICE TA256 allows Rivaroxaban to be used as an option in stroke prevention in AF as per the license as follows:
- Rivaroxaban is licensed for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:
  - **Previous stroke or transient ischemic attack**
  - **Age 75 years**
  - **Diabetes mellitus, congestive heart failure or hypertension**
- NICE TA261 allows Rivaroxaban to be used as an option for the treatment of DVT and prevention of recurrent DVT and PE after a diagnosis of acute DVT in adults (TA261)
- NICE TA287 recommends rivaroxaban as a possible treatment for adults with pulmonary embolism and to prevent a further deep vein thrombosis or pulmonary embolism (TA287)
- Rivaroxaban is also licensed for prophylaxis of venous thromboembolism in adults after total hip or total knee replacement surgery but this is dealt with as a RED drug in our local formularies and so no prescribing of this drug for this indication should take place in primary care

Frequently Asked Questions about the Direct Oral Anticoagulants (DOACs) (prev NOAC)

NHS Wiltshire Clinical Commissioning Group

2. My patient is elderly and I am worried about the falls risk when prescribing DOACs

- The fear of falls may be overstated, as a patient may need to fall ~300 times per year for the risk of intracranial haemorrhage to outweigh the benefit of oral anticoagulants in stroke prevention.[7] It is assumed that a similar risk would apply to the DOACs.
- Therefore, the risk of falls is not a contraindication to initiating oral anticoagulation. Falls should therefore be considered but as part of a full risk/benefit review

3. What about monitoring?

- One of the advantages of the DOACs is that they do not need routine anticoagulation monitoring for long term or short term treatment. However, it may be pertinent to check U&Es annually
- DABIGATRAN : The MHRA advised in 2011 that renal function should be checked in all patients prior to starting dabigatran[8] and at least once a year during continued treatment in those aged >75 years or those with suspected decline in renal function

4. What about adverse effects?

Apixaban

- Bleeding events, haematoma, haematuria, GI tract haemorrhage, epistaxis, confusion and hypersensitivity
- For full details please see the summary of product characteristics (SPC)

Dabigatran

- Bleeding events, anaemia, haematoma, haematuria, decreased haemaglobin, dyspepsia and gastrointestinal upsets
- For full details please see the summary of product characteristics (SPC)

Rivaroxaban

- Bleeding events, anaemia, haematoma, haematuria, GI tract haemorrhage, epistaxis, GI and abdominal pains, dyspepsia, dizziness, headache, nausea and constipation
- For full details please see the summary of product characteristics (SPC)

5. My patient is pregant or breastfeeding, what are the recommendations?

Apixaban

- Apixaban is not recommended in pregnancy
- It is unknown whether apixaban is excreted in breastmilk
- see SPC for further information

Dabigatran

- There are limited amount of data on the use of dabigatran in pregnant women
- Dabigatran should not be used during pregnancy unless clearly necessary
- There are no clinical data on the effect of Dabigatran on infants during breastfeeding
- Breastfeeding should be discontinued during treatment with Dabigatran
- See SPC for further information

Rivaroxaban

- Rivaroxaban is contra-indicated in pregnancy and breastfeeding
- see SPC for further information

6. What about the management of complications?

- Doses above the recommended dose will put the patient at risk of bleeding. Unlike warfarin there are no specific antidotes to apixaban or rivaroxaban. There is now an antidote for Dabigatran called Idarucizumab which is available via secondary care under the advice of a haematologist.
- In cases of suspected overdose it would be recommended to seek advice from secondary care as it would be advisable for the patient's anticoagulation status to be assessed.
- **Minor bleeding**[9] such as epistaxis, ecchymosis or menorrhagia can be managed with simple withdrawal of the anticoagulant for 1 or more days, allowing definitive interventions (where available) to be applied.
- For Dabigatran specifically, it could then be restarted at a lower dose (110mg bd) if the higher dose (150mg bd) was previously being used, for a short period of time.
- **Moderate bleeding**[9] (such as upper or lower GI bleeding) should be managed with withdrawal of the anticoagulant, careful clinical monitoring, interventions to identify and definitively treat the bleeding source, and consideration of an extended period of withdrawal of the oral anticoagulant (perhaps with the addition of a parenteral anticoagulant for patients at particularly high risk of thrombosis) to allow healing. Transfusion therapy with RBCs might be required to treat symptomatic anaemia.
- **Major and life-threatening bleeding**[9] should be treated in hospital with immediate anticoagulant withdrawal, aggressive clinical monitoring, transfusion of packed red blood cells in response to proven or anticipated severe anaemia, aggressive interventions to identify and treat the bleeding source (requiring endoscopy, interventional radiology, or surgery) and consideration of lifesaving therapies, such as inotropes, ventilation, and ICU admission to stabilize the patient. The new antidote for Dabigatran, Idarucizumab may be used if applicable.

Frequently Asked Questions about the Direct Oral Anticoagulants (DOACs) (prev NOAC)

NHS Wiltshire Clinical Commissioning Group

6. What about the management of complications (cont.)?

Apixaban

- Apixaban is highly plasma protein bound (87%)
- Haemodialysis is therefore unlikely to be effective in managing apixaban overdose
- The half-life of apixaban is 12hrs and so supportive treatment may not be needed for long – but any serious haemorrhage will need hospital treatment

Dabigatran

- Dabigatran is not highly protein bound and can therefore be dialysed
- As Dabigatran is primarily excreted by the renal route, adequate diuresis should be maintained
- The half-life of Dabigatran is 12-14hrs (this is prolonged if the patient has renal impairment) and so supportive treatment may not be needed for long – but any serious haemorrhage will need hospital treatment.

Rivaroxaban

- Due to the high plasma protein binding rivaroxaban is not expected to be dialysable
- The half-life of Rivaroxaban is 5-13hrs and so supportive treatment may not be needed for long – but any serious haemorrhage will need hospital treatment

Advice can be sought from secondary care where appropriate

7. My patient has forgotten to take their DOAC, what should I tell them?

Apixaban

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

Dabigatran

- A forgotten dabigatran dose may still be taken up to six hours prior to the next scheduled dose. From six hours prior to the next scheduled dose on, the missed dose should be omitted

Rivaroxaban

- **Once daily:** The patient should be told to take it as soon as they remember but should not take more than one tablet in a single day to make up for a forgotten dose
- Instead they should take the next tablet on the following day and then carry on taking one tablet once a day
- **Twice daily (if on the loading phase for DVT treatment):** If a dose is missed, the patient should take rivaroxaban immediately to ensure intake of 30mg rivaroxaban per day (2 x 15mg tablets may be taken at once if necessary). Continue with the regular 15mg twice daily intake on the following day

8. What are the key counselling points?

- The need for careful follow up in the first few weeks to reinforce the importance of taking this medication as well as to discuss any concerns is essential
- Other counselling includes the following points:
  - There is no antidote to the DOACs and hence supportive measures are used instead. This could present problems in patients who need emergency surgery
  - Apixaban should be swallowed whole with or without food
  - Dabigatran should be swallowed whole with water, with or without food (**do NOT open the capsule**)
  - Rivaroxaban should be swallowed whole with water and food
- As this medicine prevents blood clotting, the most common side effects associated with treatment involve bruising or bleeding. Not all patients will experience side effects. However, patients should be aware that they should contact their doctor straight away if they notice any sign of bruising or bleeding while taking this medicine. This includes any signs of blood in the urine, or any sign of bleeding from the stomach or intestine, for example vomiting blood and/or passing black/tarry/blood stained stools
- It is also important that **patients inform other health professionals treating them**, including their dentist and pharmacist that they are taking this medicine. A patient alert card for all the DOACs is available from pharmacies or from the manufacturers websites (see links on decision aid document) and patients should carry this with them at all times
- If the patient is due to have any surgery it is also important to talk to their doctor in advance. For some surgery it may be safe to keep taking the DOAC, whereas for surgery with a higher risk of bleeding the patient may have to stop taking the DOAC before the surgery
- Patients should take care when buying over the counter medicines and avoid those that have the potential to interact such as NSAID medications or herbal products such as St John's Wort without discussing with their doctor
- Lifestyle advice regarding contact sports or extreme sports should be included in the counseling where appropriate as an injury whilst taking a DOAC could cause serious bruising or bleeding
- Dabigatran contains sunset yellow food colouring, which may cause allergic reactions in some people
- The DOACs do not require routine anticoagulation monitoring. However, it should be emphasized that poor compliance with any oral anticoagulant agent will reduce benefits but may increase risks associated with use. Therefore, it is essential that DOACs are taken on a regular basis

Frequently Asked Questions about the Direct Oral Anticoagulants (DOACs) (prev NOAC)

NHS Wiltshire Clinical Commissioning Group

9. My patient is going to have surgery, what should I do?

Apixaban

- Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding
- This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable
- Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding
- This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled
- If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding
- This risk of bleeding should be weighed against the urgency of intervention
- Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established
- The haematologist will be able to advise as to whether high risk patients may need bridging therapy with a parenteral anticoagulant

Dabigatran

- Patients on dabigatran who undergo surgery or invasive procedures are at increased risk of bleeding, therefore for surgical interventions the patient may require temporary discontinuation
- Patients undergoing brain, spinal or ophthalmic surgery are at a high risk of bleeding
- The length of time the dabigatran needs to be stopped prior to surgery will depend on risk of bleeding and the patient's renal function as well as how quickly the procedure is needed
- **Summary of discontinuation rules before invasive or surgical procedures:**
- **N.B**. Since patients with renal impairment may exhibit elevated concentrations of Dabigatran, it may be beneficial to check serum creatinine several days prior to elective surgery andDAQs for N calculate creatinine clearance **(**See table below)**
- The haematologist will be able to advise as to whether high risk patients may need bridging therapy with a parenteral anticoagulant
- If acute surgery is required, the surgery or intervention should be delayed if possible for at least 12 hrs after the last dose
- When rapid reversal of the anticoagulation effect is required the specific reversal agen (Praxbind® , idarucizumab) to Pradaxa is available.
- If surgery cannot be delayed the risk of bleeding may be increased
- This risk of bleeding should be weighed against the urgency of the intervention
- In the post-procedural period, Dabigatran treatment can be re-instated as soon as clinically indicated

Rivaroxaban

- Patients on Rivaroxaban who undergo surgery or invasive procedures are at increased risk of bleeding, therefore for surgical interventions the patient may require temporary discontinuation
- The length of time the Rivaroxaban needs to be stopped prior to surgery will depend on risk of bleeding as well as how quickly the procedure is needed
- The SPC recommends that if an invasive procedure or surgical intervention is required, Rivaroxaban should be stopped at least 24hrs before the intervention, if possible and based on the clinical judgement of the patient's doctor
- If the procedure cannot be delayed the increased risk of bleeding due to Rivaroxaban should be assessed against the urgency of the intervention
- The haematologist will be able to advise as to whether high risk patients may need bridging therapy with a parenteral anticoagulant. Rivaroxaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established

**Surgical Procedures and Dabigatran in Renal Impairment

Renal function (Cr Cl ml/min)	Estimated half-life (hrs)	Stop Dabigatran before elective surgery	
		High risk of bleeding or major surgery	*Standard risk pts*
≥ 80	~13	2 days before	24 hrs before
≥ 50-<80	~15	2-3 days before	1-2 days before
≥30-<50	~18	4 days before	2-3 days before (>48 hrs)

10. How much do they cost? (28 day supply) May 2016

Apixaban	Dabigatran (110mg and 150mg)	Rivaroxaban
•£53.20	•£47.60	•£50.40

References

1. Apixaban versus warfarin in patients with AF (ARISTOTLE). Granger C et al. NEJM Sept 2011 365 (11): 981-992 http://www.nejm.org/doi/full/10.1056/NEJMoa1107039
2. Connolly SJ, Ezekowitz MD et al. Dabigatran versus warfarin in patients with atrial fibrillation (RELY). NEJM 2009; 361: 1139-51 http://www.nejm.org/doi/full/10.1056/NEJMoa0905561
3. Should dabigatran replace warfarin for stroke prevention in AF? Drug & Therapeutics Bulletin 2011; 49 (10): 114-7
4. Patel MR, Mahaffey KW et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation (ROCKET AF). NEJM 2011; 365: 883-91 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1009638
5. The EINSTEIN investigators. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. NEJM Dec 2010; 363:2499-2510
6. The EINSTEIN-PE Investigators. Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism. NEJM April 2012; 366: 1287-1297. http://www.nejm.org/doi/full/10.1056/NEJMoa1113572
7. 2012 focused update of the ESC guidelines for the management of atrial fibrillation. A. John Camm et al. http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/Guidelines_Focused_Update_Atrial_Fib_FT.pdf
8. MHRA, Drug Safety Update, Volume 5, Issue 5, December 2011 http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con137782.pdf
9. Schulman S & Crowther M. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 29 March 2012; 119 (13): 3016-3023

Other useful resouces

- Wallentin et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. The Lancet 2010; 376: 975–83
- NICE Clinical Guideline CG180 Atrial Fibrillation: The management of Atrial Fibrillation. June 2014 http://www.nice.org.uk/Guidance/CG180
- Keeling D, Baglin T et al; Guidelines on oral anticoagulation with warfarin – 4th Ed 2011; British Journal of Haematology 1365-2141. http://www.bcshguidelines.com/documents/warfarin_4th_ed.pdf
- Heidbuchel H et al. European heart rhythm association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace (2013) 15, 625-651. http://www.escardio.org/communities/EHRA/publications/novel-oral-anticoagulants-for-atrial-fibrillation/Documents/EHRA-NOAC-Practical-Full-EPEuropace-2013.pdf