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NHS
West Suffolk
Clinical Commissioning Group

Dabigatran, rivaroxaban and apixaban, the new oral anticoagulants (NOACS), for the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation

Implementation of NICE TA 249, 256, and 275

References to warfarin in this document also relate to other vitamin K analogues, i.e. acenocoumarol and phenindione

Contents

The licensed information in this guideline is based on the following Summaries of Product Characteristics:

- Pradaxa® (dabigatran) 150mg hard capsules (Boehringer Ingelheim); date of review 08/2013
- Xarelto® (rivaroxaban) 20mg film-coated tablets (Bayer); date of review 06/2013
- Eliquis® (apixaban) 5mg film-coated tablets (Bristol-Myers Squibb); date of review 19/09/2013

This guideline will be reviewed annually; **it is the responsibility of the prescriber to consult the most up-to-date prescribing information before prescribing a NOAC**. Current Summaries of Product Characteristics can be accessed via the electronic Medicines Compendium (eMC) http://www.medicines.org.uk/EMC/default.aspx

1. Introduction

This guideline has been produced to help identify those patients who are most likely to benefit from dabigatran, rivaroxaban or apixaban, and to provide advice on using these new drugs in the safest possible manner. The guideline covers both newly identified AF patients and existing AF patients currently taking warfarin. It does not and should not over-ride the NICE Technology Appraisals 249, 256 and 275; a clinician may initiate dabigatran, rivaroxaban or apixaban for any patient within the Technology Appraisals' (TAs) criteria. The guideline includes the expert advice and opinions of local clinicians following a detailed review of the NOAC clinical trial papers: RE-LY, ROCKET AF, and ARISTOTLE (see Appendix 5, p.30).

For the purposes of this guideline, 'non-valvular' atrial fibrillation is defined as rhythm disturbance occurring in the absence of rheumatic mitral stenosis or a prosthetic heart valve[◊].

[◊] *ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation. Circulation 2001;104:2118-2150*

2. Definition of abbreviations and authors/contributors

Abbreviation	Definition
AF	Atrial fibrillation
$CHADS_2$	Stroke risk assessment: **C**ardiac failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke (doubled)
CHA_2DS_2-VASc	Extended stroke risk assessment: **C**ongestive heart failure, **H**ypertension, **A**ge ≥75 (doubled), **D**iabetes, **S**troke (doubled), **V**ascular disease, **A**ge 65-74, **S**ex **c**ategory (female)
eGFR	Estimated glomerular filtration rate [mL/minute/1.73m^2] (taken to be approximately 10mL/minute greater than the calculated creatinine clearance to provide a safety margin); degrees of renal impairment are detailed in section 6 of this guideline (see p.19)
FBC	Full blood count
GI	Gastro-intestinal
HAS-BLED	Bleeding risk assessment: **H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding, **L**abile INR, **E**lderly, **D**rugs/alcohol
LFTs	Liver function tests
NOAC	New oral anticoagulant (dabigatran, rivaroxaban, or apixaban)
SPC	Summary of Product Characteristics
TTR	Time in therapeutic range
U&Es	Urea and electrolytes
WSCCG	NHS West Suffolk Clinical Commissioning Group

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3. Initiation of a NOAC

Applies to newly diagnosed AF patients and to existing AF patients who are not able to take warfarin.

- **Oral anticoagulation is indicated for patients with a $CHADS_2$ or a CHA_2DS_2-VASc score ≥2** (see Appendix 1, p.20)
- **Warfarin remains a suitable first-line option for patients who require an oral anticoagulant, particularly in those with:**
  - eGFR <40
    Patients with a baseline eGFR of 40-50 are at risk of progressive/acute renal dysfunction and the potential risks of bleeding with a NOAC should be weighed on an individual basis
  - a history of significant peptic ulcer disease
  - significant ischaemic heart disease

Physicians should carefully consider whether NOACs are appropriate replacements for warfarin. Following prescribing guidelines and keeping a vigilant eye on medication safety literature should guide the management of individual patients receiving newly approved medications with potential life-threatening side effects.

A NOAC can be offered as an alternative *option* to warfarin for the prevention of stroke and systemic embolism provided that NICE criteria are satisfied (see Table 1a below). Further recommendations are provided in Table 2a (p.4) to help identify those patients who are most likely to benefit from a NOAC, and to provide advice on using the NOACs in the safest possible manner.

Table 1a
NICE criteria to be met when initiating a NOAC for the prevention of stroke and systemic embolism in AF

Dabigatran is an option if:	Rivaroxaban is an option if:	Apixaban is an option if:
Nonvalvular AF and NICE TA 249 criteria are satisfied, i.e. one or more of the following risk factors: • Previous stroke, TIA or systemic embolism • Left ventricular ejection fraction below 40% • Symptomatic heart failure of New York Heart Association 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	Nonvalvular AF and NICE TA 256 criteria are satisfied, i.e. one or more risk factors such as: • Congestive heart failure • Hypertension • Age 75 years or older • Diabetes mellitus • Prior stroke or TIA	Nonvalvular AF and NICE TA 275 criteria are satisfied, i.e. one or more risk factors such as: • Prior stroke or TIA • Age 75 years or older • Hypertension • Diabetes mellitus • Symptomatic heart failure

NICE TAG 249 (dabigatran): http://publications.nice.org.uk/dabigatran-etexilate-for-the-prevention-of-stroke-and-systemic-embolism-in-atrial-fibrillation-ta249

NICE TAG 256 (rivaroxaban): http://publications.nice.org.uk/rivaroxaban-for-the-prevention-of-stroke-and-systemic-embolism-in-people-with-atrial-fibrillation-ta256

NICE TAG 275 (apixaban): http://publications.nice.org.uk/apixaban-for-preventing-stroke-and-systemic-embolism-in-people-with-nonvalvular-atrial-fibrillation-ta275

A clinician may choose to prescribe a NOAC for any patient who satisfies the relevant NICE TA criteria, however, careful consideration of the points in Table 2a are strongly recommended.

Table 2a
Further recommendations to consider when initiating a NOAC for the prevention of stroke and systemic embolism in AF

It is recommended that:
1. $CHADS_2$ or CHA_2DS_2-VASc score ≥2 (see Appendix 1, p.20)
2. eGFR >40 for dabigatran; eGFR >25 for rivaroxaban; eGFR >25 for apixaban. • Dabigatran is principally renally excreted; doses may therefore accumulate and increase the risk of bleeding. • Dabigatran is contraindicated in patients with creatinine clearance <30mL/min; in patients with creatinine clearance 30-50mL/min the dose of dabigatran (150mg twice daily or 110mg twice daily) should be selected based on an individual assessment of both thromboembolic and bleeding risk. • Rivaroxaban is not recommended if creatinine clearance <15mL/min. It should be used with caution in patients with creatinine clearance 15-29mL/min; in patients with creatinine clearance 15-49mL/min, a low dose of 15mg once daily is recommended. • Apixaban is not recommended if creatinine clearance <15mL/min. A low dose of 2.5mg twice daily is recommended in patients with creatinine clearance 15-29mL/min, or with a serum creatinine ≥133micromole/L associated with age ≥80 years or bodyweight ≤60kg, or in patients with at least two of the following characteristics: age ≥ 80 years, body weight ≤60kg, or serum creatinine ≥133micromole/L. • Extreme caution is advised when prescribing a NOAC to a patient with any degree of renal impairment (particularly if eGFR <50). The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients who are acutely unwell can deteriorate very quickly. • Prescribers should also be alert to the risks associated with using the NOACs in the event of an acute decline in renal function due to an acute co-morbidity (e.g. dehydration, shock, or the initiation of nephrotoxic medicines such as NSAIDs, ACE inhibitors, or aminoglycosides).
3. No history of significant peptic ulcer disease. • Low dose dabigatran (110mg twice daily) is not known to cause an increase in the incidence of GI bleeding compared to warfarin, but it is associated with increased GI side effects. • In patients with gastritis, oesophagitis, or gastro-oesophageal reflux, the dose of dabigatran (150mg twice daily or 110mg twice daily) should be selected based on an individual assessment of both thromboembolic and bleeding risk. • Rivaroxaban is associated with more GI bleeding than warfarin. • There is no difference in the frequency of GI bleeds with apixaban compared to warfarin. • NOACs should usually be avoided in patients with a history of peptic ulcer disease due to the increased risk of bleeding.
4. No significant ischaemic heart disease. • A small but significant increased risk of myocardial infarction (MI) was seen in trials with dabigatran standard dose (150mg twice a day) compared with warfarin, which may reflect a possible clinical benefit of warfarin. • The long term effects of NOACs with regard to MI are not known and it is therefore advised that all NOACs should be avoided in patients with significant ischaemic heart disease. ***Continued on next page***

Table 2a continued

5. At least one of these:
   - Warfarin is contraindicated.
   - Venous access for INR monitoring is not possible.
   - There are insurmountable difficulties with safe compliance of INR monitoring and dose adjustments, e.g. due to cognitive impairment.
   - HAS-BLED score ≥3 (see Appendix 2, p.21), where apixaban or low-dose dabigatran (110mg twice daily) may be appropriate. Apixaban and low-dose dabigatran are associated with a reduced risk of major bleeding.
   - Warfarin has been stopped due to intolerance, poor response, or a significant bleed while taking warfarin. Apixaban and low-dose dabigatran are associated with a reduced risk of major bleeding.

6. No other contraindications.
   The current SPCs containing the full contraindications for Pradaxa® (dabigatran etexilate), Xarelto® (rivaroxaban), and Eliquis® (apixaban) can be accessed via the electronic Medicines Compendium (eMC) http://www.medicines.org.uk/EMC/default.aspx

7. The special warnings, precautions, and drug interactions that apply have been considered.
   The current SPCs containing the full special warnings, precautions and drug interactions for Pradaxa® (dabigatran etexilate), Xarelto® (rivaroxaban), and Eliquis® (apixaban) can be accessed via the electronic Medicines Compendium (eMC) http://www.medicines.org.uk/EMC/default.aspx

8. An informed discussion has taken place between the clinician and the patient about the risks and benefits of NOACs compared to warfarin. Refer to Tables 3a (p.9) and 3b (p.12).

4. Conversion from warfarin to a NOAC

Applies to existing AF patients who are currently prescribed warfarin.

- **Warfarin remains a suitable first-line option for patients who require an oral anticoagulant, particularly in those who are currently well controlled and tolerant of warfarin**

Physicians should carefully consider whether NOACs are appropriate replacements for warfarin. Following prescribing guidelines and keeping a vigilant eye on medication safety literature should guide the management of individual patients receiving newly approved medications with potential life-threatening side effects.

Conversion to a NOAC is an alternative *option* to warfarin for the prevention of stroke and systemic embolism provided that NICE criteria are satisfied (see Table 1b below). Further recommendations are provided in Table 2b (p.7) to help identify those patients who are most likely to benefit from a NOAC and to provide advice on using the NOACs in the safest possible manner.

Table 1b
NICE criteria to be met when converting from warfarin to a NOAC for the prevention of stroke and systemic embolism in AF

Conversion to dabigatran is an option if:	**Conversion to rivaroxaban is an option if:**	**Conversion to apixaban is an option if:**
Nonvalvular AF and NICE TA 249 criteria are satisfied, i.e. one or more of the following risk factors: • Previous stroke, TIA or systemic embolism • Left ventricular ejection fraction below 40% • Symptomatic heart failure of New York Heart Association 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	Nonvalvular AF and NICE TA 256 criteria are satisfied, i.e. one or more risk factors such as: • Congestive heart failure • Hypertension • Age 75 years or older • Diabetes mellitus • Prior stroke or TIA	Nonvalvular AF and NICE TA 275 criteria are satisfied, i.e. one or more risk factors such as: • Prior stroke or TIA • Age 75 years or older • Hypertension • Diabetes mellitus • Symptomatic heart failure

NICE TAG 249 (dabigatran): http://publications.nice.org.uk/dabigatran-etexilate-for-the-prevention-of-stroke-and-systemic-embolism-in-atrial-fibrillation-ta249

NICE TAG 256 (rivaroxaban): http://publications.nice.org.uk/rivaroxaban-for-the-prevention-of-stroke-and-systemic-embolism-in-people-with-atrial-fibrillation-ta256

NICE TAG 275 (apixaban): http://publications.nice.org.uk/apixaban-for-preventing-stroke-and-systemic-embolism-in-people-with-nonvalvular-atrial-fibrillation-ta275

A clinician may choose to prescribe a NOAC for any patient who satisfies the NICE TA criteria, however, careful consideration of the points in Table 2b are strongly recommended.

Table 2b
Further recommendations to consider when converting from warfarin to a NOAC for the prevention of stroke and systemic embolism in AF

It is recommended that:
1. $CHADS_2$ or CHA_2DS_2-VASc score ≥2 (see Appendix 1, p.20).
2. eGFR >40 for dabigatran; eGFR >25 for rivaroxaban; eGFR >25 for apixaban. • Dabigatran is principally renally excreted; doses may therefore accumulate and increase the risk of bleeding. • Dabigatran is contraindicated in patients with creatinine clearance <30mL/min; in patients with creatinine clearance 30-50mL/min the dose of dabigatran (150mg twice daily or 110mg twice daily) should be selected based on an individual assessment of both thromboembolic and bleeding risk. • Rivaroxaban is not recommended if creatinine clearance <15mL/min. It should be used with caution in patients with creatinine clearance 15-29mL/min; in patients with creatinine clearance 15-49mL/min a low dose of 15mg once daily is recommended. • Apixaban is not recommended if creatinine clearance <15mL/min. A low dose of 2.5mg twice daily is recommended in patients with creatinine clearance 15-29mL/min, or with a serum creatinine ≥133micromole/L associated with age ≥80 years or bodyweight ≤60kg, or in patients with at least two of the following characteristics: age ≥ 80 years, body weight ≤60kg, or serum creatinine ≥133micromole/L. • Extreme caution is advised when prescribing a NOAC to a patient with any degree of renal impairment (particularly if eGFR <50). The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients who are acutely unwell can deteriorate very quickly. • Prescribers should also be alert to the risks associated with using the NOACs in the event of an acute decline in renal function due to an acute co-morbidity (e.g. dehydration, shock, or the initiation of nephrotoxic medicines such as NSAIDs, ACE inhibitors, or aminoglycosides).
3. No history of significant peptic ulcer disease. • Low dose dabigatran (110mg twice daily) is not known to cause an increase in the incidence of GI bleeding compared to warfarin, but it is associated with increased GI side effects. • In patients with gastritis, oesophagitis, or gastro-oesophageal reflux the dose of dabigatran (150mg twice daily or 110mg twice daily) should be selected based on an individual assessment of both thromboembolic and bleeding risk. • Rivaroxaban is associated with more GI bleeding than warfarin. • There is no difference in the frequency of GI bleeds with apixaban compared to warfarin. • NOACs should usually be avoided in patients with a history of peptic ulcer disease due to the increased risk of bleeding.
4. No significant ischaemic heart disease. • A small but significant increased risk of myocardial infarction (MI) was seen in trials with dabigatran standard dose (150mg twice a day) compared with warfarin, which may reflect a possible clinical benefit of warfarin. • The long term effects of NOACs with regard to MI are not known and it is therefore advised that all NOACs should be avoided in patients with significant ischaemic heart disease ***Continued on next page***

Table 2b continued

5. At least one of these:
   - Patient compliant with warfarin treatment, yet TTR <65% after 6 months. TTR figures are available from anticoagulant clinics**.**
   - History of a significant bleed on warfarin with $CHADS_2$ or CHA_2DS_2-VASc score ≥1 (see Appendix 1, p.20), where apixaban or low-dose dabigatran (110mg twice daily) may be appropriate. Apixaban and low-dose dabigatran are associated with a reduced risk of major bleeding.
   - History of ischaemic stroke or TIA while patient compliant with warfarin treatment, where apixaban or standard-dose dabigatran (150mg twice daily) may be appropriate. Apixaban or standard-dose dabigatran may be more effective than warfarin in preventing strokes in patients with AF.
   - Concurrent regular use of medicines that continue to cause wide INR fluctuation after a 3 month trial of warfarin, despite increased INR testing and warfarin dose adjustments. Interacting drugs can be co-prescribed with warfarin with care.
     For short courses of a new interacting drug, warfarin dose adjustment is not essential; for a drug change lasting >7 days, an INR test should be performed 3-7 days after starting the new medicine so that the warfarin dose can be adjusted on the basis of the INR result. [The British Committee for Standards in Haematology guidelines on oral anticoagulation with warfarin—fourth edition. Br J Haem 2011; 154 (3): 311-324].
   - HAS-BLED score ≥3 (see Appendix 2, p.21), where apixaban or low-dose dabigatran (110mg twice daily) may be appropriate. Apixaban and low-dose dabigatran are associated with a reduced risk of major bleeding.
   - Venous access for INR monitoring is difficult (consider using a finger prick near-patient testing device).
   - Increasing difficulties with safe compliance of INR monitoring and dose adjustments, e.g. due to cognitive impairment.

6. No other contraindications.
   The current SPCs containing the full contraindications for Pradaxa® (dabigatran etexilate), Xarelto® (rivaroxaban), and Eliquis® (apixaban) can be accessed via the electronic Medicines Compendium (eMC) http://www.medicines.org.uk/EMC/default.aspx

7. The special warnings, precautions, and drug interactions that apply have been considered.
   The current SPCs containing the full special warnings, precautions and drug interactions for Pradaxa® (dabigatran etexilate), Xarelto® (rivaroxaban), and Eliquis® (apixaban) can be accessed via the electronic Medicines Compendium (eMC)
   http://www.medicines.org.uk/EMC/default.aspx

8. An informed discussion has taken place between the clinician and the patient about the risks and benefits of NOACs and warfarin. Refer to Tables 3a (p.9) and 3b (p.12).

5. Disadvantages and advantages of NOACs compared to warfarin

The information provided in Table 3a should be used to enable an informed discussion to take place between clinician and patient regarding appropriate initiation of a NOAC. Table 3b (p.12) provides similar information, but is formatted to directly compare dabigatran, rivaroxaban, apixaban, and warfarin.

Table 3a: Disadvantages and advantages of NOACs compared to warfarin

Disadvantages
• NOACs are new drugs with a lack of long-term safety data; apixaban is a 'black triangle' drug. Warnings by the regulatory bodies continue to be issued. • No specific antidote for the NOACs. • Urgent medical attention is needed if the patient falls or suffers injury, particularly if their head is injured, due to the risk of bleeding. This also applies to warfarin however the anticoagulant effect of warfarin can be reversed, while the reversibility of NOAC anticoagulation is difficult and uncertain. • No difference in efficacy of stroke prevention for rivaroxaban or dabigatran low-dose (110mg twice daily), compared to warfarin. • The standard dose of dabigatran (150mg twice a day) was associated with a small but significant increased risk of MI, which may reflect a clinical benefit of warfarin. For every 476 people on dabigatran standard dose (150mg twice daily), one additional MI was observed. • Dabigatran standard dose (150mg twice daily) and rivaroxaban have a higher risk of GI bleeding. Rivaroxaban was associated with increased major GI bleeding compared to warfarin. Dabigatran (both doses) and rivaroxaban are both associated with increased GI side effects. There was no difference in the frequency of GI bleeds with apixaban compared to warfarin. • There is a risk of treatment failure unless patient compliance with NOAC treatment is consistently good. The half-life of dabigatran is 12-14 hours (if normal renal function). The half-life of rivaroxaban is 5-9 hours in young patients, and 11-13 hours in the elderly. The half-life of apixaban is 12 hours. Compliance is critical as protection from stroke will be lost with the omission of only one dose of a NOAC (in contrast to warfarin which has a half-life of 40 hours). The NOAC half-lives can be significantly prolonged in patients with renal impairment and doses may accumulate. • Dabigatran should be avoided if creatinine clearance <30mL/min. Rivaroxaban should be avoided if creatinine clearance <15mL/min and should be used with caution if creatinine clearance 15-29mL/min. Apixaban is not recommended if creatinine clearance <15mL/min, and a low dose of 2.5mg twice daily is recommended in patients with creatinine clearance 15-29mL/min, or with a serum creatinine ≥133micromole/L associated with age ≥80 years or bodyweight ≤60kg, or in patients with at least two of the following characteristics: age ≥80 years, body weight≤60 kg, or serum creatinine ≥133micromole/L. • Extreme caution is advised when prescribing a NOAC to a patient with any degree of renal impairment (particularly if eGFR <50). The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients who are acutely unwell can deteriorate very quickly. • In clinical trials, more patients stopped taking dabigatran and rivaroxaban than warfarin because of side effects. Dabigatran (both doses) caused more GI symptoms than warfarin, e.g. dyspepsia, whereas rivaroxaban caused more nose bleeds and haematuria than warfarin. • Problems can arise if unplanned surgery or procedures are needed;   ○ Apixaban: stop at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding, or at least 24 hours prior to the procedure if there is a low risk of bleeding. If surgery or invasive procedures ***Continued on next page***

Table 3a continued

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.

- Rivaroxaban: stop at least 24 hours prior to surgery or invasive procedure. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
- Dabigatran: the manufacturer gives the following discontinuation rules for invasive or surgical procedures:

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50 - <80	~ 15	2-3 days before	1-2 days before
≥ 30 - <50	~ 18	4 days before	2-3 days before (> 48 hours)

If an acute intervention is required, dabigatran should be temporarily discontinued and the procedure should be delayed if possible until at least 12 hours after the last dose—if surgery cannot be delayed the risk of bleeding may be increased, and this risk of bleeding should be weighed against the urgency of the intervention.

- No clearly defined mechanism by which to determine if the NOACs are working effectively in individual patients (because the INR cannot be tested), therefore making compliance difficult to monitor.
- Rivaroxaban and apixaban cannot be dialysed.
- Dabigatran and apixaban must be taken twice daily, so there is potential for lower compliance.
- Dabigatran cannot be crushed or administered by nasogastric tube; there is no data on whether or not apixaban is suitable for crushing or administration via nasogastric tube (though it is not a pro-drug like dabigatran).
- Dabigatran and warfarin are not suitable for monitored dosage systems; there is no data on whether or not apixaban is suitable for a monitored dosage system (though it is not a pro-drug like dabigatran).
- No data on rivaroxaban or apixaban in cardioversion.
- Rivaroxaban should not be prescribed for patients with hepatic disease associated with coagulopathy and clinically significant bleeding risk, including cirrhotic patients with Child Pugh B and C. Dabigatran should be avoided in liver disease, hepatic impairment expected to have any impact on survival, or elevated liver enzymes >2 times the upper limit of normal. However, any anticoagulant should be used with caution if coagulopathy is evident. Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Apixaban is not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment, and in patients with elevated liver enzymes (ALT/AST >2 x upper limit of normal) or total bilirubin ≥1.5 x upper limit of normal.
- The NOACs are more expensive than warfarin. Dabigatran costs ~£802/year, rivaroxaban ~£766/year, and apixaban ~£802/year; warfarin costs ~£380/year. Costs may vary in different settings because of negotiated procurement discounts. The cost of INR monitoring in Suffolk is covered by a block contract.
- Widespread use will cause very significant cost pressures on the Suffolk healthcare system, particularly since the warfarin monitoring service will need to be maintained for the foreseeable future.

Advantages
• The NOACs may be suitable for patients who cannot tolerate warfarin. • The NOACs may be suitable for patients who are compliant with warfarin, and yet are not well controlled (TTR<65%). • No INR monitoring is required for the NOACs, so they may be more convenient for patients who travel regularly for extended periods of time. • The NOACs may be useful for rapid anticoagulation following TIA only in certain high risk patients. • The NOACs have fewer drug and food interactions compared to warfarin. • Dabigatran can be dialysed (however extreme caution is advised when performing this invasive catheter procedure on an anticoagulated patient). • Dabigatran standard dose (150mg twice daily) is statistically significantly more effective in preventing stroke, particularly haemorrhagic stroke, in people with AF with a moderate/ high risk of stroke, compared to warfarin. The number needed to treat to prevent one systemic embolism or stroke per year is 172. • Apixaban is statistically significantly more effective in preventing stroke and systemic embolism compared to warfarin. The number needed to treat for one year to prevent one stroke or systemic embolism is 304. • Rivaroxaban is suitable for monitored dosage systems (MDS). • Rivaroxaban can be crushed. • Overall reduced risk of intracranial haemorrhage with the NOACs. • Dabigatran low dose (110mg twice a day) was associated with a reduced risk of major bleeding (NNT 154 over 1 year) compared with warfarin, though no difference was found between dabigatran standard dose (150mg twice a day) and warfarin in this respect. • Apixaban was associated with a reduced risk of major bleeding compared to warfarin. • In clinical trials, fewer patients stopped taking apixaban than warfarin because of side effects.

Table 3b: Comparison of dabigatran, rivaroxaban, apixaban and warfarin

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Safety data	New drug with a lack of long term safety data. Warnings by the regulatory bodies continue to be issued.	New drug with a lack of long term safety data. Warnings by the regulatory bodies continue to be issued.	New drug (black triangle), with a lack of long term safety data. Warnings by the regulatory bodies continue to be issued.	Drug has been in use for many years; long-term safety data available.
Antidote	No specific antidote.	No specific antidote.	No specific antidote.	Specific antidote.
Risk of bleeding through injury	Urgent medical attention is needed if the patient falls or suffers injury, particularly if their head is injured, due to the risk of bleeding. Reversibility of anticoagulation by NOACs is difficult and uncertain.	Urgent medical attention is needed if the patient falls or suffers injury, particularly if their head is injured, due to the risk of bleeding. Reversibility of anticoagulation by NOACs is difficult and uncertain.	Urgent medical attention is needed if the patient falls or suffers injury, particularly if their head is injured, due to the risk of bleeding. Reversibility of anticoagulation by NOACs is difficult and uncertain.	Urgent medical attention is needed if the patient falls or suffers injury, particularly if their head is injured, due to the risk of bleeding. The anticoagulant effects of warfarin can be reversed.
Stroke prevention efficacy	Dabigatran low dose (110mg twice daily) is non-inferior to warfarin at reducing the risk of stroke and systemic embolism in people with AF. Dabigatran standard dose (150mg twice daily) is statistically significantly more effective in preventing stroke, particularly haemorrhagic stroke, in people with AF with a moderate/high risk of stroke, compared to warfarin. The number needed to treat to prevent one systemic embolism or stroke per year is 172.	Rivaroxaban is non-inferior to warfarin at reducing the risk of stroke and systemic embolism in people with AF.	Apixaban is statistically significantly more effective in preventing stroke and systemic embolism compared to warfarin. The number needed to treat for one year to prevent one stroke or systemic embolism is 304.	Warfarin is non-inferior to dabigatran low dose (110mg twice daily) and to rivaroxaban at reducing the risk of stroke and systemic embolism in people with AF.
Risk of MI	The standard dose of dabigatran (150mg twice a day) was associated with a small but significant increased risk of MI. For every 476 people on dabigatran standard dose (150mg twice daily), one additional MI was observed.	Not known to increase the risk of MI compared to warfarin.	Not known to increase the risk of MI compared to warfarin.	Not known to increase the risk of MI compared to dabigatran, rivaroxaban, or apixaban.

Continued on next page

Table 3b continued

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Risk of GI bleeding	Dabigatran standard dose (150mg twice daily) causes a higher risk of GI bleeding, and at both doses is associated with increased GI side effects, compared to warfarin.	Rivaroxaban causes a higher risk of GI bleeding, and is associated with increased major GI bleeding and increased GI side effects, compared to warfarin.	There was no difference in the frequency of GI bleeds with apixaban compared to warfarin.	Lower risk of GI bleeding and GI side effects compared to dabigatran standard dose (150mg twice daily) and to rivaroxaban.
Half-life	Half-life 12-14 hours (if normal renal function). Risk of treatment failure unless compliance is consistently good. Compliance is critical as protection from stroke will be lost with omission of only one dose, compared to warfarin. May be suitable for patients who are compliant with warfarin treatment, and yet are not well controlled (TTR<65%) The NOAC half-lives can be significantly prolonged in patients with renal impairment and doses may accumulate.	Half-life of rivaroxaban is 5-9 hours in young patients, and 11-13 hours in elderly patients. Risk of treatment failure unless compliance is consistently good. Compliance is critical as protection from stroke will be lost with omission of only one dose, compared to warfarin. May be suitable for patients who are compliant with warfarin treatment, and yet are not well controlled (TTR<65%) The NOAC half-lives can be significantly prolonged in patients with renal impairment and doses may accumulate.	Half-life of apixaban is 12 hours. Risk of treatment failure unless compliance is consistently good. Compliance is critical as protection from stroke will be lost with omission of only one dose, compared to warfarin. May be suitable for patients who are compliant with warfarin treatment, and yet are not well controlled (TTR<65%) The NOAC half-lives can be significantly prolonged in patients with renal impairment and doses may accumulate.	Half-life of warfarin is 40 hours. Less risk of treatment failure if a dose is missed compared to the NOACs.

Continued on next page

Table 3b continued

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Renal impairment	Avoid if creatinine clearance <30mL/min. Extreme caution is advised when prescribing a NOAC to a patient with any degree of renal impairment (particularly if eGFR <50). The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients who are acutely unwell can deteriorate very quickly.	Avoid if creatinine clearance <15mL/min. Use with caution if creatinine clearance 15-29mL/min. Extreme caution is advised when prescribing a NOAC to a patient with any degree of renal impairment (particularly if eGFR <50). The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients who are acutely unwell can deteriorate very quickly.	Apixaban is not recommended if creatinine clearance <15mL/min. A low dose of 2.5mg twice daily is recommended in patients with creatinine clearance 15-29mL/min, or with a serum creatinine ≥133micromole/L associated with age ≥80 years or bodyweight ≤60kg, or in patients with at least two of the following characteristics: age ≥80 years, body weight ≤60kg, or serum creatinine ≥133micromole/L. Extreme caution is advised when prescribing a NOAC to a patient with any degree of renal impairment (particularly if eGFR <50). The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients who are acutely unwell can deteriorate very quickly.	Warfarin is not contra-indicated in renal impairment.
Side-effects	In clinical trials, more patients stopped taking dabigatran than warfarin because of side effects. Dabigatran (both doses) caused more GI symptoms than warfarin, e.g. dyspepsia	In clinical trials, more patients stopped taking rivaroxaban than warfarin because of side effects. Rivaroxaban caused more nose bleeds and haematuria than warfarin.	In clinical trials, fewer patients stopped taking apixaban than warfarin because of side effects.	In clinical trials, fewer patients discontinued warfarin, compared to dabigatran and rivaroxaban, due to side effects.

Continued on next page

Table 3b continued

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Unplanned surgery	Problems can arise if unplanned surgery or procedures are needed. The manufacturer gives advice on discontinuation rules for invasive or surgical procedures (see p.10). If an acute intervention is required, dabigatran should be temporarily discontinued and the procedure should be delayed if possible until at least 12 hours after the last dose—if surgery cannot be delayed the risk of bleeding may be increased, and this risk of bleeding should be weighed against the urgency of the intervention.	Problems can arise if unplanned surgery or procedures are needed. Stop rivaroxaban at least 24 hours prior to intervention. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.	Problems can arise if unplanned surgery or procedures are needed. Stop apixaban at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding, or at least 24 hours prior if there is a low risk of bleeding. 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.	Patients requiring emergency surgery can have the anticoagulant effects of warfarin reversed with dried prothrombin complex and intravenous vitamin K_1.
Monitoring anticoagulant effect	No clearly defined mechanism by which to determine if the NOACs are working effectively in individual patients (because the INR cannot be tested), therefore making compliance difficult to monitor.	No clearly defined mechanism by which to determine if the NOACs are working effectively in individual patients (because the INR cannot be tested), therefore making compliance difficult to monitor.	No clearly defined mechanism by which to determine if the NOACs are working effectively in individual patients (because the INR cannot be tested), therefore making compliance difficult to monitor.	INR can be monitored to ensure patient is within therapeutic range and compliant with treatment.
Dialysis	Can be dialysed (however extreme caution is advised when performing this invasive catheter procedure on an anticoagulated patient).	Cannot be dialysed.	No clinical experience in dialysis therefore not recommended	Cannot be dialysed.
Dosing	Twice daily administration, therefore potentially lower compliance	Once daily administration.	Twice daily administration, therefore potentially lower compliance	Once daily administration.

Continued on next page

Table 3b continued

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Swallowing difficulties	Cannot be crushed or administered by nasogastric tube.	Can be crushed.	No data on suitability for crushing	Can be crushed. Oral solution available.
Suitability for monitored dosage systems (MDS)	Not suitable.	Suitable.	No data on suitability for MDS.	Not suitable.
Cardio-version	Patients can stay on dabigatran while being cardioverted.	No data in cardioversion.	No data in cardioversion.	Patients can stay on warfarin while being cardioverted.
Drug interactions	Less drug and food interactions than warfarin.	Less drug and food interactions than warfarin.	Less drug and food interactions than warfarin.	Many interactions; consult current SPC.
Hepatic impairment	Should be avoided in liver disease, hepatic impairment expected to have any impact on survival, or elevated liver enzymes >2 times the upper limit of normal. All anticoagulants should be used with caution if coagulopathy is evident.	Should not be prescribed in patients with hepatic disease associated with coagulopathy and clinically significant bleeding risk, including cirrhotic patients with Child Pugh B and C. All anticoagulants should be used with caution if coagulopathy is evident.	Should not be prescribed in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. Use with caution in patients with mild or moderate hepatic impairment and in patients with elevated liver enzymes (ALT/AST >2 x upper limit of normal) or total bilirubin ≥1.5 x upper limit of normal. All anticoagulants should be used with caution if coagulopathy is evident.	Warfarin is not contra-indicated in hepatic impairment. All anticoagulants should be used with caution if coagulopathy is evident.

Continued on next page

Table 3b continued

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Cost	More expensive than warfarin; dabigatran costs approximately £802/year (though costs may vary in different settings because of negotiated procurement discounts). Widespread use will put significant cost pressures on the Suffolk healthcare system, particularly since the warfarin monitoring service will need to be maintained for the foreseeable future.	More expensive than warfarin; rivaroxaban costs approximately £766/year (though costs may vary in different settings because of negotiated procurement discounts). Widespread use will put significant cost pressures on the Suffolk healthcare system, particularly since the warfarin monitoring service will need to be maintained for the foreseeable future.	More expensive than warfarin; apixaban costs approximately £802/year (though costs may vary in different settings because of negotiated procurement discounts). Widespread use will put significant cost pressures on the Suffolk healthcare system, particularly since the warfarin monitoring service will need to be maintained for the foreseeable future.	Warfarin costs approx. £380/year (plus cost of INR monitoring, though in Suffolk this is covered by a block contract).
INR monitoring	No INR monitoring required (may be more convenient for patients who travel regularly for extended periods of time).	No INR monitoring required (may be more convenient for patients who travel regularly for extended periods of time).	No INR monitoring required (may be more convenient for patients who travel regularly for extended periods of time).	INR must be monitored.
Risk of intracranial haemorrhage	Overall reduced risk of intracranial haemorrhage compared to warfarin.	Overall reduced risk of intracranial haemorrhage compared to warfarin.	Overall reduced risk of intracranial haemorrhage compared to warfarin.	The NOACS have an overall reduced risk of intracranial haemorrhage compared to warfarin.
Risk of major bleeding	Dabigatran low dose (110mg twice daily) was associated with a reduced risk of major bleeding (NNT 154 over 1 year) compared with warfarin, though no difference was found between dabigatran standard dose (150mg twice daily) and warfarin in this respect.	There is a similar risk of major bleeding with rivaroxaban compared to warfarin.	Apixaban was associated with a reduced risk of major bleeding compared to warfarin.	Warfarin has a similar risk of major bleeding compared to dabigatran (standard dose) and rivaroxaban.

6. GP responsibilities when:

a) Initiating a NOAC

- NICE criteria to be satisfied (Table 1a, p.3)
- Further strong recommendations to be carefully considered (Table 2a, p.4)
- The following details to be recorded in the patients' notes as a minimum:
  - Which NICE criteria are met
  - Why a NOAC (name and dose) has been selected rather than warfarin

  GPs who are initiating their patient on a NOAC may wish to use the checklist in Appendix 4a (p.26) to record that all relevant details have been considered
- Baseline blood tests to be performed (FBC including clotting screen (platelet count must be >100x10^9/L & stable), U&Es (including eGFR), LFTs)
- Patient to be counselled and issued with the relevant NOAC alert card (Appendix 3, p.22)
- On-going treatment and monitoring to be provided as detailed in (d) below

b) Converting from warfarin to a NOAC

- NICE criteria to be satisfied (Table 1b, p.6)
- Further strong recommendations to be carefully considered (Table 2b, p.7)
- The following details to be recorded in the patients' notes as a minimum:
  - Which NICE criteria are met
  - Why warfarin has been converted to a NOAC (name and dose)

  GPs who are converting their patient from warfarin to a NOAC may wish to use the checklist in Appendix 4b (p.28) to record that all relevant details have been considered
- Blood tests to be performed (FBC including clotting screen (platelet count must be >100x10^9/L & stable), U&Es (including eGFR), LFTs)
- Patient to be counselled and issued with the relevant NOAC alert card (Appendix 3, p.22)
- Conversion to be implemented safely:

  Step 1: Stop warfarin

  Step 2: Wait for 3 days (no anticoagulation during these 3 days)

  Step 3: Check INR. Dabigatran or apixaban can be given as soon as INR<2. Rivaroxaban should be given when INR ≤3
- Anticoagulant services to be informed that warfarin has been stopped.
- On-going treatment and monitoring to be provided as detailed in (d) below

c) Referring patient to a hospital specialist for possible initiation of a NOAC or for conversion from warfarin to a NOAC

The hospital specialist may be from one of the following teams/departments: cardiology, stroke, gastroenterology, nephrology or haematology.

- NICE criteria to be satisfied (Table 1a, p.3 or Table 1b, p.6)
- Further strong recommendations in Table 2a, p.4 (for initiation) or Table 2b, p.7 (for conversion) to be carefully considered
- The relevant checklist in Appendix 4a (p.26) or 4b (p.28) to be completed by the GP and submitted to the hospital specialist. This is to ensure that only appropriate patients are referred to hospital for potential prescribing of a NOAC.

Referral to a specialist is appropriate if the patient has complex co-morbidities or if the GP does not feel competent to prescribe a NOAC.

d) Prescribing a NOAC as on-going treatment

- *At least* biannual (3-monthly preferred) clinical review should be carried out to check that each patient continues to meet the prescribing criteria for a NOAC, as detailed in Tables 1a (p.3) and 1b (p.6).
- *At least* annual monitoring of U&Es (including eGFR), FBC, and LFTs is required if the patient's renal function is normal (biannual monitoring preferred); more frequent eGFR monitoring (and also U&Es, FBC, and LFTs) may be required if the renal function is impaired, referring to NICE Clinical Guideline No.73: Chronic Kidney Disease (September 2008), which specifies the frequency of monitoring required (see Table 4 below).
- The NOAC will need to be discontinued and an alternative treatment started if eGFR <40 for dabigatran, <25 for rivaroxaban, or <25 for apixaban. Extreme caution is advised when prescribing a NOAC to a patient with any degree of renal impairment (particularly if eGFR <50). The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients who are acutely unwell can deteriorate very quickly.
- Close clinical surveillance (looking for signs of bleeding or anaemia) is required throughout the treatment period, particularly if body weight <50kg or if patient has renal impairment, due to the risk of accumulation. Stop treatment if severe bleeding occurs.
- Prescribers should also be alert to:
  - The risks associated with using the NOACs in the event of an acute decline in renal function due to an acute co-morbidity (e.g. dehydration, shock, or initiation of nephrotoxic medicines such as NSAIDs, ACE inhibitors, or aminoglycosides). Renal function should be assessed when a decline in renal function is suspected and a full review of treatment should be carried out.
  - The risks associated with changes to concomitant medicines (prescribed/over-the-counter/herbal remedies). A full review of treatment should be carried out.
  - The possibility that patients may be discharged from secondary care on extended thromboprophylaxis (prescribed and supplied by the hospital) to reduce the risk of venous thromboembolism. Oral anticoagulants should not be administered with any other anticoagulant agent. A full review of treatment should be carried out post-discharge.
- Report any adverse events to the MHRA (http://yellowcard.mhra.gov.uk) and adjust or stop treatment as necessary; seek specialist advice when required.

Table 4: Stages of chronic kidney disease and frequency of eGFR monitoring
(from NICE CG No.73: Chronic kidney disease, September 2008)

Stage[a]	GFR (mL/min/1.73m2)	Description
1	≥90	Normal or increased GFR, with other evidence of kidney damage
2	60-89	Slight decrease in GFR, with other evidence of kidney damage
3A	45-59	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30-44	
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure
[a] Use the suffix (p) to denote the presence of proteinuria when staging CKD		

Measurement of eGFR: how often?[a]		
Annually in all at risk groups.		
During intercurrent illness and perioperatively in all patients with CKD.		
Exact frequency should depend on the clinical situation. The frequency of testing may be reduced where eGFR levels remain very stable but will need to be increased if there is rapid progression.		
Stage	**eGFR range (mL/min/1.73m^2)**	**Typical testing frequency**
1 and 2	≥60 + other evidence of kidney disease	12 monthly
3A and 3B	30-59	6 monthly
4	15-29	3 monthly
5	<15	6 weekly
[a]The information in this table is based on GDG concensus and not on evidence		

7. Appendices

Appendix 1

Calculation of $CHADS_2$ or CHA_2DS_2-VASc score for stroke risk assessment

$CHADS_2$

The acronym $CHADS_2$ is derived from individual stroke risk factors. Adding together the points allocated to each risk factor yields the total $CHADS_2$ score.

	Risk factor	Score if present
C	Congestive heart failure	1
H	Hypertension (or treated hypertension)	1
A	Age ≥ 75 years	1
D	Diabetes mellitus	1
S	Previous stroke or TIA	2

Source: Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford AJ. Validation of Clinical Classification Schemes for Predicting Stroke: Results from the National Registry of Atrial Fibrillation. JAMA. 2001; 285: 2864-2870

CHA_2DS_2-VASc

This scoring system is deemed to be better at refining stroke risk than the $CHADS_2$ system. Many patients at low risk according to $CHADS_2$ are not truly low risk and the treatment guidelines are not conclusive for those at intermediate risk.

	Risk factor	Score if present
C	Congestive heart failure	1
H	Hypertension (or treated hypertension)	1
A_2	Age ≥ 75 years	2
D	Diabetes mellitus	1
S_2	Previous stroke, TIA or thromboembolism	2
V	Vascular disease (MI, PAD, aortic plaque)	1
A	Age 65-74 years	1
Sc	Female sex	1

Source: Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. CHEST 2010;137(2):263-72.

Appendix 2
Calculation of HAS-BLED score for bleeding risk assessment

HAS-BLED
The acronym HAS-BLED is derived from the major factors associated with bleeding risk in patients with atrial fibrillation receiving oral anticoagulation. Adding together the points allocated to each risk factor yields the total HAS-BLED score.

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Clinical characteristic	Definition
Hypertension	Systolic BP >160mmHg
Abnormal renal function	Presence of chronic dialysis or renal transplantation or serum creatinine ≥200 micromol/l
Abnormal liver function	Chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.)
Bleeding	Previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc.
Labile INR	Unstable/high INRs or poor time in therapeutic range (e.g. 60%)
Drugs or alcohol (1 point each)	Concomitant use of drugs such as antiplatelet agents, NSAIDs or alcohol abuse
	Maximum 9 points

Source: European Society of Cardiology guidelines for the management of atrial fibrillation.
Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. CHEST 2010; 138 (5):1093–1100

Appendix 3
Patient counselling and alert cards

Patient counselling

Content of NOAC induction counselling
➢ Indication ➢ Risks and benefits of the NOACs, including advantages and disadvantages compared to warfarin ➢ NOAC choice, treatment schedule, and duration ➢ Side-effects ➢ Common interactions including the importance of the patient consulting GP/pharmacist if they are taking/considering taking any new medicines (including the purchase of 'over-the-counter' medicines or herbal remedies); avoid taking concomitant NSAIDs/aspirin ➢ Women should avoid becoming pregnant or breast-feeding during treatment with a NOAC ➢ Advice regarding platelet antagonists (where applicable); concomitant use of these agents increases the risk of major bleeding with dabigatran approximately two-fold ➢ Importance of compliance, particularly with regard to short NOAC half-life ➢ Importance of patient attending at least a biannual clinical review (more frequent reviews may be required if renal function is impaired) ➢ Issue patient with the relevant NOAC alert card (see below) and advise them to show it when being treated by any healthcare professional (e.g. hospital clinicians and dentists) ➢ Patients should seek urgent medical attention if they fall or injure themselves during treatment, particularly if they injure their head, due to the increased risk of bleeding

Alert card - Xarelto®

WHAT SHOULD I KNOW ABOUT XARELTO?

- Xarelto, an anticoagulant, acts to prevent you from suffering dangerous blood clots.
- Xarelto must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, never skip a dose.
- You must not stop taking Xarelto without first talking to your doctor as your risk of blood clots may increase.
- Speak to your health care provider before taking any other medication.
- Inform your health care providers that you are taking Xarelto prior to any surgery or invasive procedure.

Bayer HealthCare

WHEN SHOULD I SEEK ADVICE FROM MY HEALTH CARE PROVIDER?

When taking an anticoagulant such as Xarelto it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Xarelto if you are at risk of abnormal bleeding, without first discussing this with your doctor.

Tell your health care provider straight away if you have any signs or symptoms of bleeding such as the following:

- unexplained dizziness or weakness
- swelling and discomfort
- sudden, severe headache
- unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding
- menstrual flow or vaginal bleeding that is heavier than normal
- pink or brown urine, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds.

Please read the Patient Information Leaflet for further information on Xarelto and its side effects.

HOW DO I TAKE XARELTO

- To ensure optimal protection, Xarelto must be taken with food.

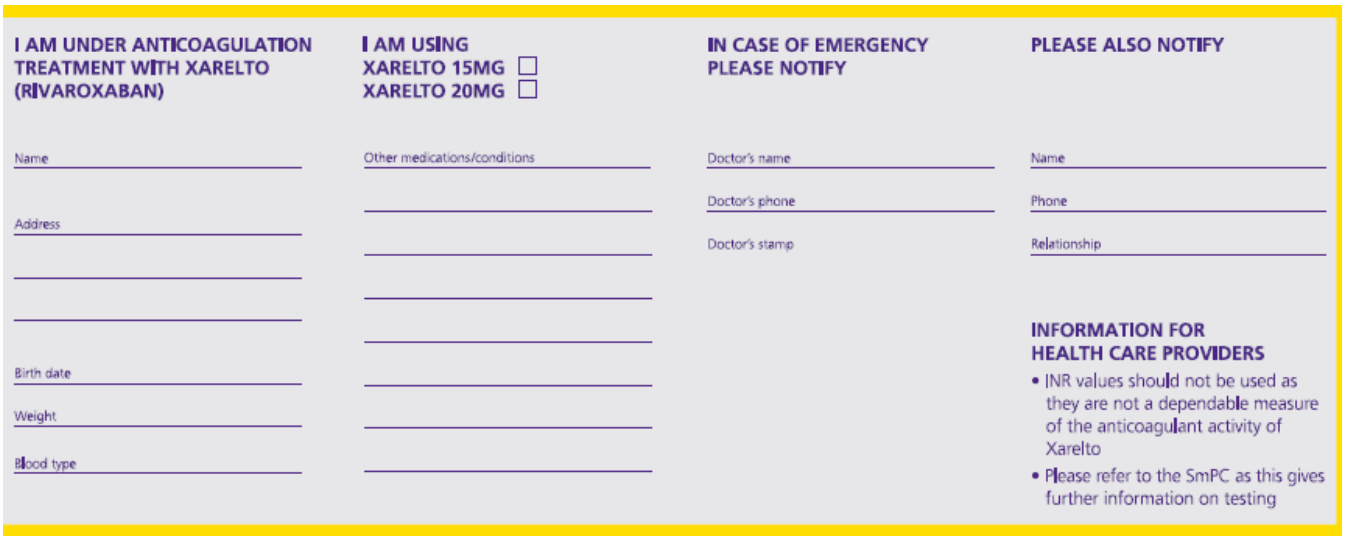
Xarelto rivaroxaban

Date of preparation: May 2012
UK.PH.GM.XAR.2012.223

PATIENT ALERT CARD

Xarelto® 15mg
Xarelto® 20mg

- KEEP THIS CARD WITH YOU AT ALL TIMES
- PRESENT THIS CARD TO EVERY PHYSICIAN OR DENTIST PRIOR TO TREATMENT



I AM UNDER ANTICOAGULATION TREATMENT WITH XARELTO (RIVAROXABAN)

Name _____

Address _____

_____

_____

Birth date _____

Weight _____

Blood type _____

I AM USING
XARELTO 15MG ☐
XARELTO 20MG ☐

Other medications/conditions _____

_____

_____

_____

_____

_____

_____

IN CASE OF EMERGENCY PLEASE NOTIFY

Doctor's name _____

Doctor's phone _____

Doctor's stamp

PLEASE ALSO NOTIFY

Name _____

Phone _____

Relationship _____

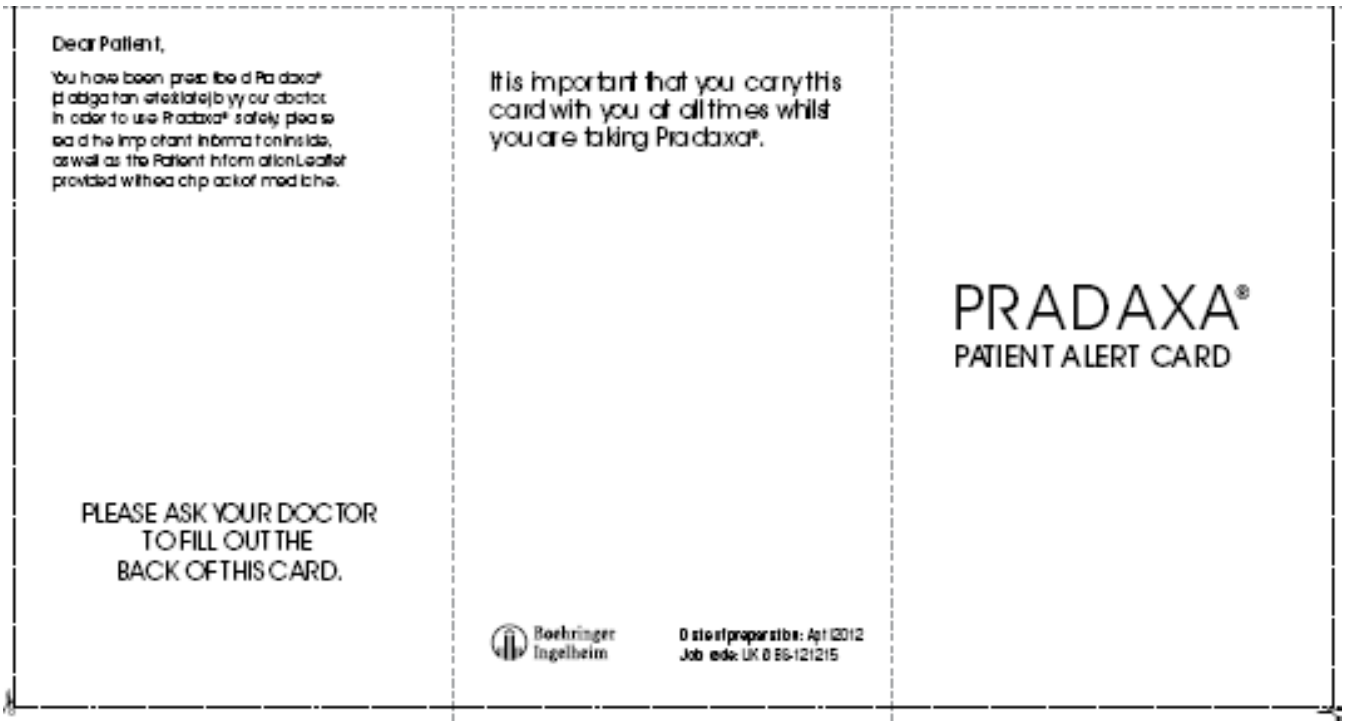
INFORMATION FOR HEALTH CARE PROVIDERS

- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto
- Please refer to the SmPC as this gives further information on testing

Alert cards can be ordered free of charge from stores:
Tel: 01473 329 180
Email: brian.day@nsft.nhs.uk

Or they can be printed from this website:
http://www.xarelto-info.co.uk/site-resources/pdfs/Patient_Alert_Card_15and20mg.pdf

Alert card - Pradaxa®



Dear Patient,

You have been prescribed Pradaxa® (dabigatran etexilate) by your doctor. In order to use Pradaxa® safely please read the important information inside, as well as the Patient Information Leaflet provided with each pack of medicine.

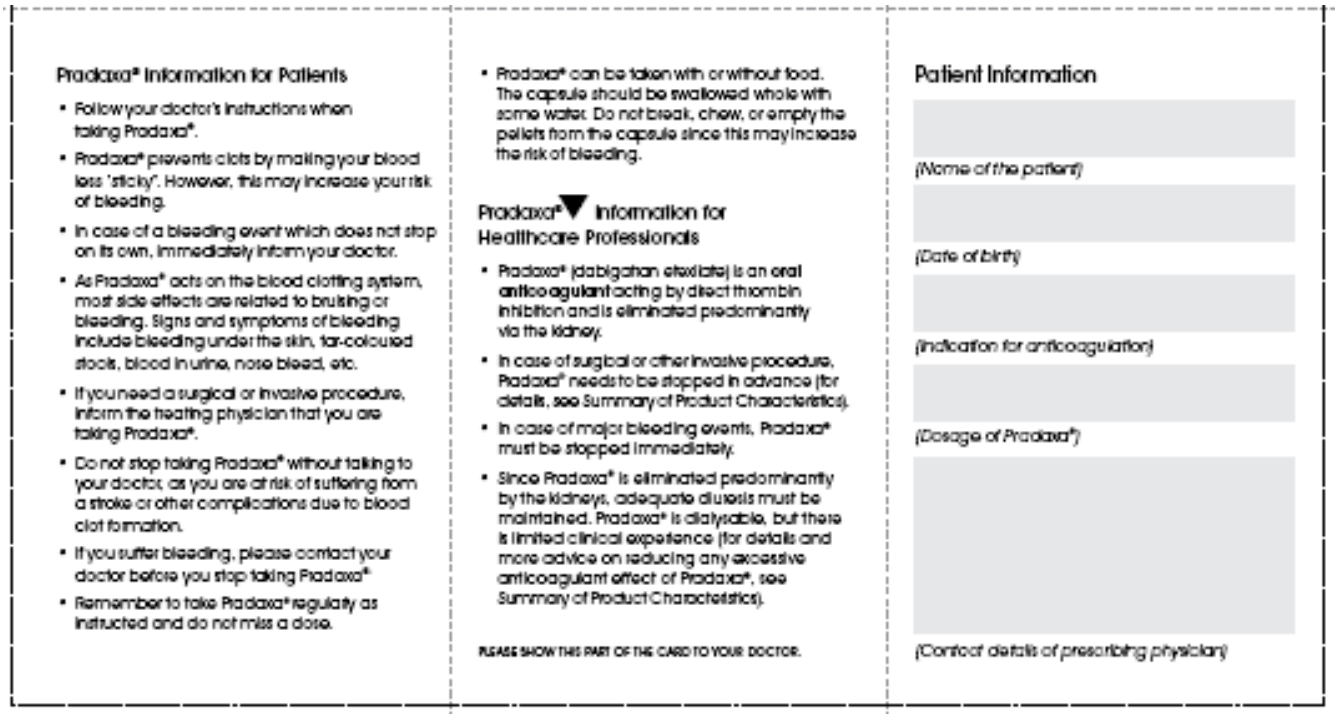
PLEASE ASK YOUR DOCTOR TO FILL OUT THE BACK OF THIS CARD.

It is important that you carry this card with you at all times whilst you are taking Pradaxa®.

Boehringer Ingelheim

Dossier preparation: Apr 2012
Job code: UK 0 86-121215

PRADAXA®
PATIENT ALERT CARD



Pradaxa® Information for Patients

- Follow your doctor's instructions when taking Pradaxa®.
- Pradaxa® prevents clots by making your blood less "sticky". However, this may increase your risk of bleeding.
- In case of a bleeding event which does not stop on its own, immediately inform your doctor.
- As Pradaxa® acts on the blood clotting system, most side effects are related to bruising or bleeding. Signs and symptoms of bleeding include bleeding under the skin, tar-coloured stools, blood in urine, nose bleed, etc.
- If you need a surgical or invasive procedure, inform the treating physician that you are taking Pradaxa®.
- Do not stop taking Pradaxa® without talking to your doctor, as you are at risk of suffering from a stroke or other complications due to blood clot formation.
- If you suffer bleeding, please contact your doctor before you stop taking Pradaxa®.
- Remember to take Pradaxa® regularly as instructed and do not miss a dose.

- Pradaxa® can be taken with or without food. The capsule should be swallowed whole with some water. Do not break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding.

Pradaxa® Information for Healthcare Professionals

- Pradaxa® (dabigatran etexilate) is an **oral anticoagulant** acting by direct thrombin inhibition and is eliminated predominantly via the kidneys.
- In case of surgical or other invasive procedure, Pradaxa® needs to be stopped in advance (for details, see Summary of Product Characteristics).
- In case of major bleeding events, Pradaxa® must be stopped immediately.
- Since Pradaxa® is eliminated predominantly by the kidneys, adequate diuresis must be maintained. Pradaxa® is dialysable, but there is limited clinical experience (for details and more advice on reducing any excessive anticoagulant effect of Pradaxa®, see Summary of Product Characteristics).

PLEASE SHOW THIS PART OF THE CARD TO YOUR DOCTOR.

Patient Information

(Name of the patient)

(Date of birth)

(Indication for anticoagulation)

(Dosage of Pradaxa®)

(Contact details of prescribing physician)

Alert cards can be ordered free of charge from stores:
Tel: 01473 329 180
Email: brian.day@nsft.nhs.uk

Or they can be printed from this website:
http://www.pradaxa.co.uk/downloads/patient-alert-card.pdf

Alert card - Eliquis®

IT IS IMPORTANT YOU CARRY THIS CARD WITH YOU AT ALL TIMES WHILE YOU ARE TAKING ELIQUIS®.

SHOW THIS CARD TO YOUR PHARMACIST, DENTIST AND OTHER HEALTHCARE PROFESSIONALS.

Bristol-Myers Squibb Pfizer

Date of preparation: November 2012
CAUK.12NP310
SPAF – 0010a

Patient Information

Name of patient

.....

.....

Date of birth

.....

Please ask your doctor to complete this section.

Indication for anticoagulation

.....

.....

Dosage of Eliquis®

.....

Contact details of prescribing physician

.....

.....

.....

.....

Eliquis® (apixaban)

Patient Alert Card

5 mg and 2.5 mg twice daily

Dear Patient,

You have been prescribed Eliquis® (apixaban) by your doctor. In order to use Eliquis® safely, please read the important information inside, as well as the Patient Information Leaflet provided with each pack of medicine.

Remember to take Eliquis® regularly as instructed and do not miss a dose.

Tell your doctor before you take this medicine if you are at an increased risk of bleeding.

Speak to your healthcare professional before taking any other medication.

Eliquis® Information for PATIENTS

- Your doctor has prescribed Eliquis® to prevent clots
- Remember to take Eliquis® regularly as instructed. If you miss a dose, take it as soon as you remember and continue to follow your dosing schedule
- Do not stop taking Eliquis® without talking to your doctor, as you are at risk of suffering from a stroke or other complications due to blood clot formation
- Eliquis® prevents clots by helping to thin your blood. However, this may increase your risk of bleeding
- Signs and symptoms of bleeding include bruising or bleeding under the skin, tar-coloured stools, blood in urine, nose-bleed, dizziness, tiredness, paleness or weakness, sudden severe headache, coughing up blood or vomiting blood or material that looks like coffee grounds, etc.
- In case of a bleeding event which does not stop on its own, **immediately seek medical attention**
- If you need a surgical or invasive procedure, inform the treating physician that you are taking Eliquis®

Eliquis®▼ Information for HEALTHCARE PROFESSIONALS

- Eliquis® (apixaban) is an oral anticoagulant acting by direct selective inhibition of factor Xa
- Eliquis® may increase the risk of bleeding. In case of major bleeding events, Eliquis® should be stopped immediately
- In case of surgical or other invasive procedure, Eliquis® needs to be stopped in advance (for details, see Summary of Product Characteristics)
- The prothrombin time (PT), INR and activated partial thromboplastin time (aPTT) clotting tests are not recommended to measure the anticoagulation effect of Eliquis®

Alert cards can be ordered free of charge from stores:
Tel: 01473 329 180
Email: brian.day@nsft.nhs.uk

Or they can be printed from this website:
https://eliquis.co.uk/Images/5829_FINAL_Patient%20Alert%20Card_WEB_.pdf

Appendix 4 Checklist 4a
GP referral to hospital specialist for possible initiation of a NOAC

This checklist applies to patients with AF who are not currently prescribed warfarin, i.e.

- Patients newly diagnosed with AF
- Existing AF patients who are not able to take warfarin

Patient name:	DOB:	NHS number:
Referring GP:	Practice:	Contact no:

1. I confirm that this patient meets the NICE criteria for the following NOAC(s):

NICE TA 249 criteria for dabigatran Nonvalvular AF and one or more of the following risk factors: • Previous stroke, TIA or systemic embolism • Left ventricular ejection fraction below 40% • Symptomatic heart failure of New York Heart Association ≥ class 2 • Age 75 years or older • Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension	Please tick if criteria met
NICE TA 256 criteria for rivaroxaban Nonvalvular AF and one or more risk factors such as: • Congestive heart failure • Hypertension • Age 75 years or older • Diabetes mellitus • Prior stroke or TIA	
NICE TA 275 criteria for apixaban Nonvalvular AF and one or more risk factors such as: • Prior stroke or TIA • Age 75 years or older • Hypertension • Diabetes mellitus • Symptomatic heart failure	

2. I am requesting initiation of a NOAC in preference to warfarin because (please tick all that apply):

Warfarin is contraindicated	
Venous access for INR monitoring is not possible	
There are insurmountable difficulties with safe compliance of INR monitoring and dose adjustments, e.g. due to cognitive impairment	
HAS-BLED score ≥3	
Warfarin has been stopped due to intolerance	
Warfarin has been stopped due to poor response	
Warfarin has been stopped due to a significant bleed while taking warfarin	
Patient choice (following an informed discussion of risks and benefits of treatment)	

3. I confirm the following (please delete Y/N as applicable):

Patient has a history of significant peptic ulcer disease	Y/N
Patient has significant ischaemic heart disease	Y/N
Patient has contraindications to dabigatran	Y/N
Patient has contraindications to rivaroxaban	Y/N
Patient has contraindications to apixaban	Y/N
An informed discussion has taken place with the patient about the risks and benefits of NOACs compared to warfarin	Y/N

4. Additional information - Please provide the following:

Details of any complex co-morbidities:			
Recent patient results for: (please attach)	FBC (including clotting screen)	U&Es (including eGFR)	LFTs

CHA_2DS_2-VASc score			
	Risk factor	**Score if present**	**Patient score**
C	Congestive heart failure	1	
H	Hypertension or treated hypertension	1	
A_2	Age ≥ 75 years	2	
D	Diabetes mellitus	1	
S_2	Previous stroke, TIA or thromboembolism	2	
V	Vascular disease (MI, PAD, aortic plaque)	1	
A	Age 65-75 years	1	
Sc	Female sex	1	
		Total	

HAS-BLED score			
	Clinical characteristic	**Score if present**	**Patient score**
H	Hypertension. *Systolic >160mmHg*	1	
A	Abnormal renal and liver function (1 point each). *Presence of chronic dialysis or renal transplantation or serum creatinine ≥200 micromol/l. Chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement*	1 or 2	
S	Stroke	1	
B	Bleeding. *Previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia*	1	
L	Labile INRs. *Unstable/high INRs or poor time in therapeutic range, e.g. 60%*	1	
E	Elderly. *Over 65 years*	1	
D	Drugs or alcohol (1 point each)**.** *Concomitant use of drugs such as antiplatelet agents, NSAIDs or alcohol abuse*	1 or 2	
		Total	

Additional comments:

GP signature……..Date……

Appendix 4 Checklist 4b
GP referral to hospital specialist for possible conversion from warfarin to a NOAC

This checklist applies to patients with AF who are currently prescribed warfarin

Patient name:	DOB:	NHS number:
Referring GP:	Practice:	Contact no:

1. I confirm that this patient meets the NICE criteria for the following NOAC(s):

NICE TA 249 criteria for dabigatran Nonvalvular AF and one or more of the following risk factors: • Previous stroke, TIA or systemic embolism • Left ventricular ejection fraction below 40% • Symptomatic heart failure of New York Heart Association ≥ class 2 • Age 75 years or older • Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension	Please tick if criteria met
NICE TA 256 criteria for rivaroxaban Nonvalvular AF and one or more risk factors such as: • Congestive heart failure • Hypertension • Age 75 years or older • Diabetes mellitus • Prior stroke or TIA	
NICE TA 275 criteria for apixaban Nonvalvular AF and one or more risk factors such as: • Prior stroke or TIA • Age 75 years or older • Hypertension • Diabetes mellitus • Symptomatic heart failure	

2. I am requesting conversion from warfarin to a NOAC because (please tick all that apply):

TTR <65% after 6 months on warfarin (and patient compliant with treatment)	
History of significant bleed while taking warfarin	
History of ischaemic stroke or TIA while taking warfarin (and patient compliant with treatment)	
Concurrent regular use of medicines that continue to cause wide INR fluctuations after a 3 month trial of warfarin, despite increased INR testing and warfarin dose adjustments	
HAS-BLED score ≥3	
Venous access for INR monitoring is becoming unacceptably difficult	
There are insurmountable difficulties with safe compliance of INR monitoring and dose adjustments, e.g. due to cognitive impairment	
Patient choice (following an informed discussion of risks and benefits of treatment)	

3. I confirm the following (please delete Y/N as appropriate):

Patient has a history of significant peptic ulcer disease	Y/N
Patient has significant ischaemic heart disease	Y/N
Patient has contraindications to dabigatran	Y/N
Patient has contraindications to rivaroxaban	Y/N
Patient has contraindications to apixaban	
An informed discussion has taken place with the patient about the risks and benefits of NOACs compared to warfarin	Y/N

4. Additional information - Please provide the following:

Details of any complex co-morbidities:			
Recent patient results for: (please attach)	FBC (including clotting screen)	U&Es (including eGFR)	LFTs

CHA_2DS_2-VASc score			
	Risk factor	**Score if present**	**Patient score**
C	Congestive heart failure	1	
H	Hypertension or treated hypertension	1	
A_2	Age ≥ 75 years	2	
D	Diabetes mellitus	1	
S_2	Previous stroke, TIA or thromboembolism	2	
V	Vascular disease (MI, PAD, aortic plaque)	1	
A	Age 65-75 years	1	
Sc	Female sex	1	
		Total	

HAS-BLED score			
	Clinical characteristic	**Score if present**	**Patient score**
H	Hypertension. *Systolic >160mmHg*	1	
A	Abnormal renal and liver function (1 point each). *Presence of chronic dialysis or renal transplantation or serum creatinine ≥200 micromol/l. Chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement*	1 or 2	
S	Stroke	1	
B	Bleeding. *Previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia*	1	
L	Labile INRs. *Unstable/high INRs or poor time in therapeutic range, e.g. 60%*	1	
E	Elderly. *Over 65 years*	1	
D	Drugs or alcohol (1 point each). *Concomitant use of drugs such as antiplatelet agents, NSAIDs or alcohol abuse*	1 or 2	
		Total	

Additional comments:

GP signature……..Date……

Appendix 5
Further information from the RE-LY, ROCKET AF, and ARISTOTLE clinical trials

Information on dabigatran and rivaroxaban obtained from a document produced by NHS Northamptonshire Prescribing Advisory Group: Implementation of NICE TA 249 and NICE TA 256.

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 trial 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 twice daily) 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 twice daily) 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.

Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor which has the potential advantage over warfarin of not requiring blood monitoring, and, unlike warfarin, has no known food interactions 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 of 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

Apixaban

Apixaban is an oral direct factor Xa inhibitor which has the potential advantage over warfarin of not requiring blood monitoring and having fewer drug interactions.

The ARISTOTLE study was a randomised, double-blind, double-dummy trial which compared apixaban with warfarin in patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was to determine if apixaban was non-inferior to warfarin in reducing the rate of ischaemic or haemorrhagic stroke, or systemic embolism. The primary safety outcome was major bleeding. Secondary objectives were to determine if apixaban was superior to warfarin with respect to the primary outcome and to the rates of major bleeding and death from any cause.

The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P = 0.01 for superiority).
The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001).
The rate of haemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P = 0.42).

Apixaban was thus shown to be superior to warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke, and demonstrated a reduced risk of major bleeding.

There are a number of issues raised by the 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, and limitations in the study methodology. Many of these issues have been considered by NICE.

Guidance aims and choice of NOAC

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

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 (2-3) 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).

- In ARISTOTLE, patients in the warfarin group had an INR in the therapeutic range (2.0 to 3.0) for a median of 66.0% of the time and a mean of 62.2% of the time.

- The average TTR at West Suffolk hospital is 71.95%.

- The average age of the patients in the RE-LY trial was 71, in ROCKET AF was 73, and in ARISTOTLE was 70; 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%). The rate of discontinuation due to side effects was lower in patients treated with apixaban compared to warfarin.

- 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 the NOACs is not known. Studies in human volunteers have shown that Prothrombin Complex Concentrate (PCC) can reverse the laboratory abnormalities caused by rivaroxaban, but not dabigatran. However both drugs are associated with a 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. Recombinant Factor VIIa (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. Administration of activated charcoal may be useful in the management of apixaban overdose, while administration of recombinant factor VIIa may be considered in the event of life-threatening bleeding, though there is no data to support this.

- 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. Apixaban is not recommended in patients undergoing dialysis.

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

- Dabigatran is not suitable for patients with CrCl < 30mL/min and requires regular tests of renal function.

- Rivaroxaban is to be used with caution in patients with CrCl 15 - 29 mL/min.

- Apixaban is not recommended in patients with CrCl <15mL/min and the dose should be reduced 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 the risk of myocardial infarction was seen with apixaban vs warfarin in ARISTOTLE, or rivaroxaban vs warfarin in ROCKET-AF, or in any other studies involving rivaroxaban.

- Long term safety and tolerability of the NOACs is not yet known. Apixaban is a “black triangle” drug.

- 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 (MDS) due to the need for dose adjustments. Dabigatran is unstable after being removed from the blister pack and is therefore also not suitable for putting into an MDS. There is no data on whether or not apixaban is suitable for an MDS. Rivaroxaban may be put into an MDS.

- The effects of non-compliance with the NOACs might be more significant because of their short half-lives compared to warfarin.