

## Atrial Fibrillation (Non-valvular): prescriber decision support on anticoagulation

### Contents

Assessing patients for anticoagulation in AF	<a href="#">Page 2</a>
Patient factors and anticoagulant choice	<a href="#">Page 3</a>
Checklist for initiation	<a href="#">Page 4</a>
Warfarin monitoring and reviewing	<a href="#">Page 5</a>
DOAC monitoring and reviewing	<a href="#">Page 6</a>
References	<a href="#">Page 8</a>
Appendix 1: Anticoagulation comparison table	<a href="#">Page 9</a>
Appendix 2: Warfarin	<a href="#">Page 13</a>
Appendix 3: Switching anticoagulation therapy (for AF only)	<a href="#">Page 15</a>
Appendix 4: Notes on HAS-BLED	<a href="#">Page 17</a>

#### Scope:

This document is intended as prescriber decision support for prescribing anticoagulants for patients with non-valvular AF. The diagnosis and management of atrial fibrillation is beyond the scope of this document and prescribers are referred to the full [NICE clinical guideline](#) or NICE Pathway.

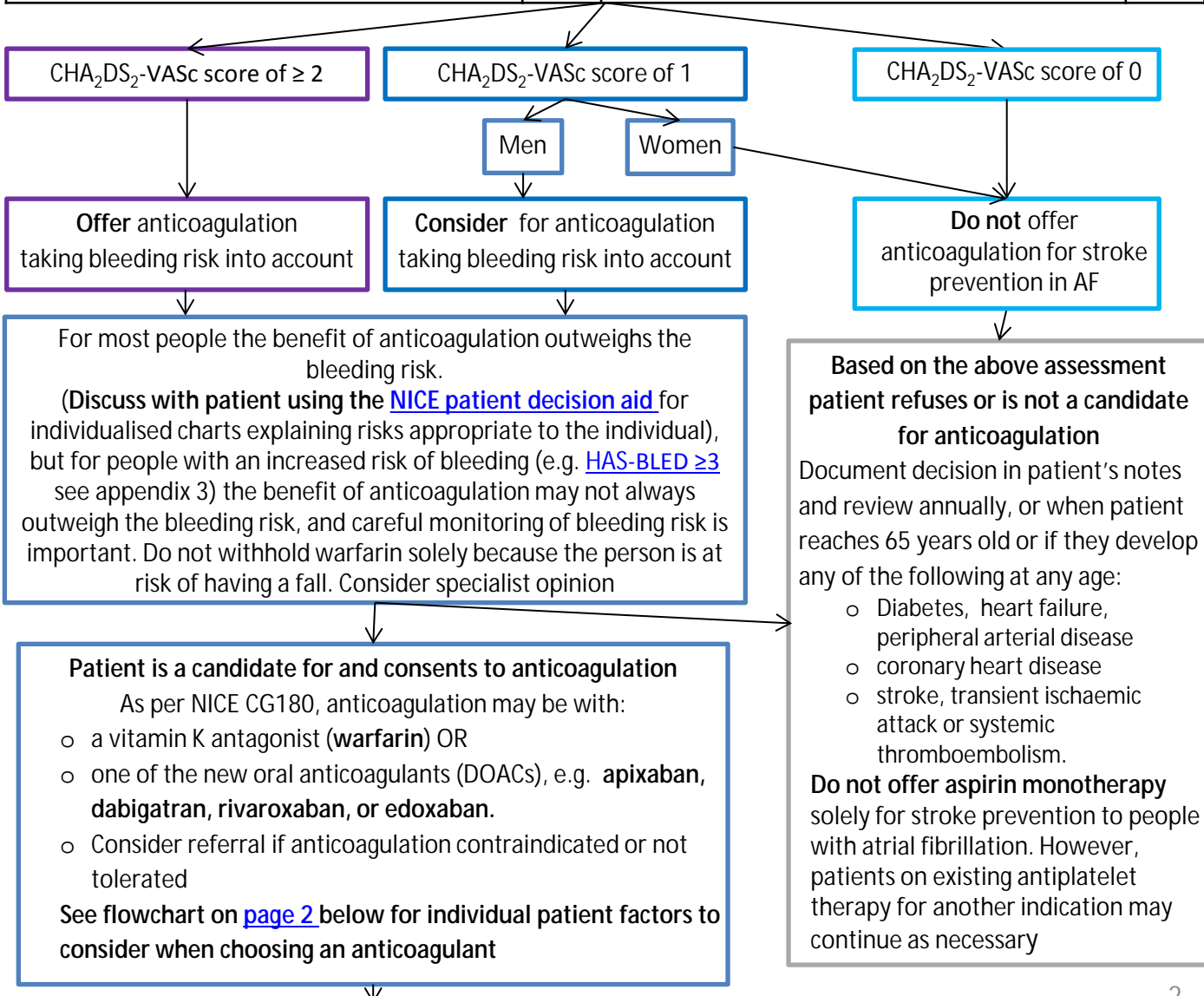
As the decision to take an anticoagulant or not should be a patient level decision supported by information from the prescriber, **this document is intended for use with the [NICE patient decision aid](#)** (which presents information in a patient friendly format including CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores).

## Assessing patients for anticoagulation in AF

(This guidance applies to patients with non-valvular paroxysmal, persistent or permanent AF, atrial flutter or continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm)

**Assess the patient for anticoagulation using the below risk scores**

Assess stroke risk using <a href="#">CHA<sub>2</sub>DS<sub>2</sub>-VASc score</a>		Assess bleeding risk using <a href="#">HAS-BLED score</a>	
Feature	Score	Feature	Score
Congestive Heart Failure	1	Hypertension (uncontrolled SBP >160mmHg)	1
Hypertension	1	Liver disease (Cirrhosis or bilirubin >2x normal with AST/ALT/ALP >3x normal)	1
Age >75 years	2	Renal disease (Dialysis, transplant, or >200 micromol/L)	1
Age between 65 and 74 years	1	Stroke history	1
Diabetes mellitus	1	Bleeding history or predisposition (e.g. anaemia)	1
Stroke / TIA / Thrombo-embolism	2	Labile INRs (i.e. Time in Therapeutic Range < 60%)	1
Vascular disease (previous MI, peripheral arterial disease or aortic plaque)	1	Elderly (e.g. age > 65 years or frail condition)	1
Female	1	Drugs (concomitant antiplatelets, NSAIDs etc) or alcohol abuse (1 point each)	1 or 2
<b>Score: (maximum score of 9)</b>		<b>Score: (maximum score of 9)</b> <b>Address modifiable risks where possible</b>	



## Anticoagulation choice and patient factors

From page 1: Patient is a candidate for and consents to anticoagulation to reduce the risk of stroke

- Discuss the options for anticoagulation with the person and base the choice on:
  - clinical features (see as per flowchart below)
  - patient preferences (see [NICE patient decision aid available here](#))

- **Baseline tests prior to initiation:**

- U+Es (and [Creatinine clearance \(CrCl\)](#) calculated, **DO NOT USE eGFR**)
- FBC
- Clotting
- LFTs
- Weight

If results of these tests are abnormal, investigate as appropriate prior to initiation of anticoagulation

Does the patient have any of the following?

- Significant (moderate or worse) **mitral stenosis** or **prosthetic valves**?
- **Renal disease** [Creatinine clearance](#) <30ml/min? (caution if borderline or at risk of acute kidney injury)
- Remains on concomitant **interacting medicines**? e.g. dronedarone, azole antifungals, HIV protease inhibitors, tacrolimus, ciclosporin, strong CYP3A4 inducers – see *summary table below*
- **Extremes of body weight** (<50kg or >150kg)
- **Poor concordance** anticipated

Yes

**Consider WARFARIN**

(as DOACs either contraindicated, unlicensed or not recommended)

Initiation of warfarin should be as per current pathway

[See initiation checklist below](#)

No

Does the patient have any of the following?

- Known unpredictable **alcohol excess** without established cirrhosis?
- Patient unable to comply with variable dose (e.g. MUST be included in a **compliance aid**)?
- Significant difficulties with INR monitoring and/or accessing anticoagulant clinics that raises safety concerns (*although consider local availability of domiciliary phlebotomy or near patient INR testing e.g. CoaguChek*)?

Yes

**Consider a DOAC**  
(see table 1 below)

(as warfarin either contraindicated, or not recommended)

[See initiation checklist below](#)

No

**Consider warfarin or a DOAC**

(see table 1 below or comparison table for other patient factors)

[See initiation checklist below](#)

### Table 1: Preferred choice of DOAC (based on patient factors)

Where a DOAC is considered appropriate, local consensus is that **apixaban, edoxaban or rivaroxaban may be suitable options for most patients**, although in line with NICE guidance, other DOACs can be considered. The following patient factors may suggest a preferred agent

Renal impairment	<a href="#">NICE CKD 182</a> recommends Apixaban for patients with CrCl 30-50mls/min however other DOACs can be used also if patients have a CrCl above 15mls/min. See <a href="#">appendix 1</a> for more information on dosing.
Increase bleeding risk (HAS-BLED ≥3)	Apixaban
Patient definitely requires compliance aid	Apixaban, Rivaroxaban or Edoxaban (NOT dabigatran)
Swallowing difficulties / enteral feeding tubes	Apixaban, Rivaroxaban (both licensed) or Edoxaban (unlicensed)
Patient with none of the above factors	As per statement above: Apixaban, Rivaroxaban or Edoxaban may be suitable but see <a href="#">appendix 1</a> for other patient factors and interactions

## Checklist and process for initiation of all anticoagulants:

Initiation points	Completed by / date:
Inform the patient of indication for the new medicine, dose, frequency, duration of therapy	
Emphasise importance of concordance to therapy especially with shorter acting agents (DOACs)	
Discuss possible undesirable effects	
Inform patient what to do if they miss a dose	
Discuss what to do in the event of injury / bleeding	
Advise patient to inform all healthcare professionals and to discuss OTC medicines with pharmacist (avoid aspirin/NSAIDs)	
Provide patient with an alert card (see <a href="#">formulary</a> or manufacturer)	
Recommend the patient to discuss this new medicine with their pharmacist as part of the free <a href="#">new medicines service</a>	

### **WARFARIN**

#### Initiation

Warfarin should be initiated as per local pathway (traffic light classification **GREEN**)

#### Monitoring

For warfarin see monitoring and reviewing section [here](#)

#### Review

**Review** the need for and quality of anticoagulation **at least annually** or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk

### **DOACs**

#### Initiation

DOACs may be initiated by a primary care prescriber or non-specialist in secondary care (traffic light classification **AMBER 3**). For dose and frequency see individual drug in [appendix 1](#)

South Nottinghamshire and NUH: Patient may be referred to local anticoagulant service for counselling if clinician and patient feel this would be beneficial

#### Monitoring

For DOACs see monitoring and reviewing section [here](#)

#### Review

**Review** the need for and quality of anticoagulation **at least annually** or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk

# Warfarin – monitoring and reviewing

Baseline blood tests				
Patient group	U + Es (Creatinine clearance)	Full blood count	Coagulation screen	Liver function tests
All	✓	✓	✓	✓
Follow up tests				
Patient group	International Normalised Ratio (INR)			
All	<b>As required or as per protocol for self monitoring patients</b>			

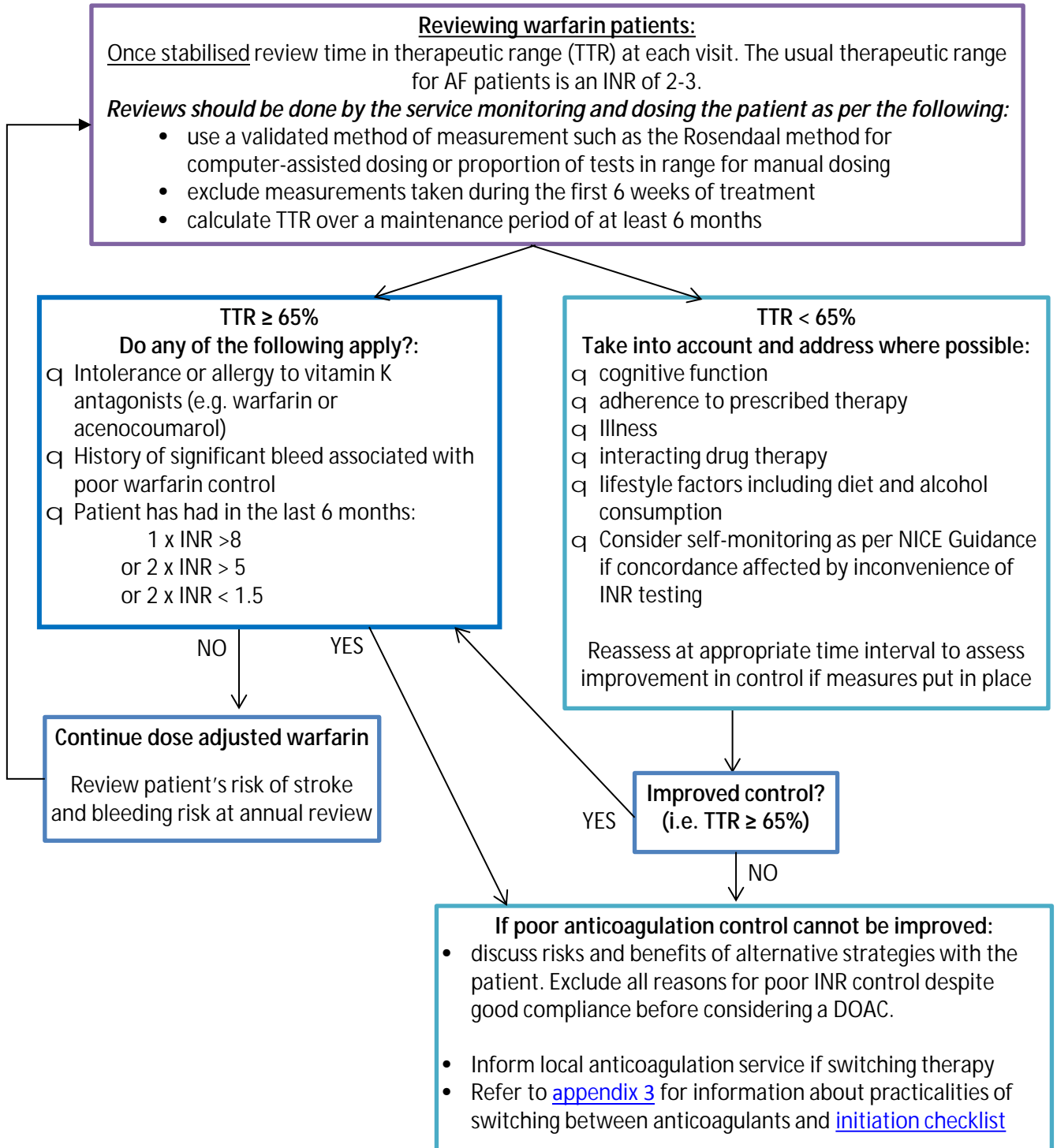
N.B. In addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate

### Reviewing warfarin patients:

Once stabilised review time in therapeutic range (TTR) at each visit. The usual therapeutic range for AF patients is an INR of 2-3.

**Reviews should be done by the service monitoring and dosing the patient as per the following:**

- use a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual dosing
- exclude measurements taken during the first 6 weeks of treatment
- calculate TTR over a maintenance period of at least 6 months



## DOACs – monitoring and reviewing

Baseline blood tests				
Patient group	U + Es (Creatinine clearance)	Full blood count	Coagulation screen	Liver function tests
All	✓	✓	✓	✓
Follow up tests				
Patient group	U + Es (Creatinine clearance)	Full blood count	Coagulation screen	Liver function tests
Creatine Clearance > 60ml/min	Annually ✓	Annually ✓	X Inappropriate without correct reagent	Annually ✓
Creatine Clearance 30-60ml/min	Six Monthly ✓			
* In addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate				

- Clinical trials have demonstrated that the therapeutic anticoagulation effect of DOACs does not require routine monitoring.
- Unlike warfarin, a prothrombin time may not be sensitive to their anticoagulant effect. Likewise an INR **will not** demonstrate the level of anticoagulation.
- As DOACs are predominantly eliminated by the renal route, it is prudent to monitor the renal function of a patient taking a DOAC. The following regimen is broadly in line with NICE guidance on Chronic Kidney Disease and based on consensus clinician opinion. This may recommend more frequent monitoring than that advised in the manufacturer's summary of product characteristics.
- Initial clinical trials only included patients between 50kg and 120kg, but there is increasing evidence that these medications can safely be used up to 150kg<sup>19,20,21,22</sup>

### Local consensus is that:

- **Creatinine clearance** must be used for calculating renal function using the Cockcroft and Gault equation (see below). eGFR is **not** a suitable alternative:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/l)}} \times 1.04 \text{ (female) or } 1.23 \text{ (male)}$$

**NB The clinical systems used in Nottinghamshire in primary care (SystemOne and EMIS) have an inbuilt Cockcroft-Gault based renal function calculator which can be used to dose DOACs. Both systems use ideal body weight (IBW) if actual body weight is greater than 120% IBW. The most up to date values for the patient's actual body weight and height will have to be inserted. These calculators make adjustments for a body mass index that is outside normal ranges and may produce a slightly different result to the equation provided. Controversy exists over which form of weight to use (actual BW, ideal BW, lean BW or adjusted BW).**

- If your built in creatinine clearance calculator does not work, then you can use the [MD+ CALC Creatinine Clearance calculator](#) (it can be downloaded as an app to an apple or android device). Always use the most up to date values and check the default units are correct when entering weight, serum creatinine and height. It would be good practice for the clinician reviewing the patient to document what method was used.
- If you have concerns about dose adjustments for DOACs based on estimating renal function using Cockcroft Gault, please seek advice from your local specialists.

## Criteria for review and discontinuation of DOACs:

Should the individual patient be deemed at a greater risk of developing renal dysfunction, more frequent monitoring may be warranted. The frequency of testing will need to be increased if there is rapid progression, or during intercurrent illness and perioperatively in all patients with CKD.

Side Effect	Action
Haemorrhage	Refer patient immediately to Accident and Emergency (A&E) if serious bleeding occurs eg GI bleeding, epistaxis lasting more than 1 hr
Dyspepsia	Common with dabigatran. Consider a proton pump inhibitor. If persists consider alternative anticoagulant.
Unexplained acute fall in haemoglobin or blood pressure	Refer patient immediately to A&E for investigation
Trauma (especially to the head)	Consider referral to A&E
Excessive bruising	Seek immediate haematologist advice
Any acute illness that MAY affect renal function	Measure U+Es and calculate creatinine clearance. Reduce dose or withhold treatment if required. Consider seeking advice regarding restarting treatment from the local anticoagulation service
Significant reduction in renal function (and see below)	Reduce dose as appropriate according to the medicine's recommended dosing schedule in renal impairment (see above for <a href="#">CrCl calculation</a> ). If renal function continues to worsen discuss with haematologist.
Fall in <a href="#">creatinine clearance</a> to <30ml/min with dabigatran or <15ml/min with rivaroxaban or apixaban	Stop DOAC, assess for bleeding and seek advice as to whether specific assays are indicated / alternative anticoagulation required



## References

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## Appendix 1: Anticoagulant comparison *(For more detailed information, refer to manufacturers Summary of Product Characteristics (SPCs))*

Medicine	Rivaroxaban <sup>2</sup>	Apixaban <sup>3</sup>	Dabigatran <sup>4</sup>	Edoxaban <sup>5</sup>
<b>Presentation</b>	15 and 20mg film coated tablets  <i>NB. 10mg and 2.5mg tablets are not licensed for AF.</i>	2.5 and 5mg film coated tablets	110mg and 150mg hard capsules  <i>NB. 75mg capsules are not licensed for AF.</i>	15, 30 and 60mg film coated tablets
<b>Licensed Indication</b>	All DOACS are licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure (NYHA Class $\geq$ II stated for apixaban and dabigatran), hypertension, age $\geq$ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.  All 4 DOACS have trial evidence of efficacy and safety in use for patients undergoing direct current cardioversions. (Rivaroxaban – X-VERT/ARC; ENSURE-AF-Edoxaban; NCT01593150-Dabigatran; EMANATE-Apixaban).			
<b>Dosing</b> <i>(NB applies to AF indication only)</i>	<b>20 mg ONCE daily</b>  Reduced to 15 mg once daily if CrCl <50ml/min (see below)	<b>5mg TWICE daily</b>  Reduced to 2.5 mg twice daily If at least <i>two</i> of the following:  - age $\geq$ 80 years, - body weight $\leq$ 60 kg, or - serum creatinine $\geq$ 133 micromole/L.	<b>150mg TWICE daily</b>  Reduced to 110mg twice daily if patient is $\geq$ 80 yrs or taking verapamil  Also consider 110mg twice daily if:  - aged between 75-80 years - moderate renal impairment (CrCL 30-50 mL/min) - gastritis, esophagitis or gastroesophageal reflux - increased risk of bleeding	<b>60mg ONCE daily</b>  Reduced to 30mg once daily if  - CrCl 15-50ml/min - low body weight ( $\leq$ 60kg), - concomitant use of potent P-gp inhibitors (eg Dronaderone, Erythromycin, Ketoconazole, Ciclosporin).
<b>Use in renal impairment</b>	Renal function should be assessed prior to DOAC treatment in all patients. Local specialists and ESC Guidelines recommend avoiding DOACs in patients with Creatinine Clearance (CrCL) <30ml/min due to increased risk of drug accumulation. Patients who develop acute renal failure should discontinue DOAC. Creatinine clearance must be calculated (see here for <a href="#">calculator</a> ), eGFR is NOT considered a suitable alternative.			
	CrCl 15-49 ml/min: 15 mg OD (use with caution and see above if CrCl < 30ml/min) CrCl < 15ml/min: Contraindicated	CrCl 15-29ml/min: 2.5mg BD CrCl < 15ml/min: Contraindicated	CrCl < 30ml/min: Contraindicated	CrCl 15-50ml/min: 30mg OD CrCl <15ml/min: Contraindicated
<b>Medicine</b>	<b>Rivaroxaban<sup>2</sup></b>	<b>Apixaban<sup>3</sup></b>	<b>Dabigatran<sup>4</sup></b>	<b>Edoxaban<sup>5</sup></b>

<b>Use in hepatic impairment</b>	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (moderate and severe).	Contraindicated 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 (Child Pugh A or B), but no dose adjustment is required. Caution in patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN as these patients were excluded in clinical trials.	Contraindicated in hepatic impairment or liver disease expected to have any impact on survival  Not recommended in mild-moderate hepatic impairment with liver enzymes >2 ULN.	Contraindicated 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- moderate hepatic impairment with liver enzymes >2 ULN or total bilirubin >1.5ULN.
<b>Administration</b>	The tablet is taken with food	Swallowed with water, with or without food.	Take with or without food. Swallow whole with a glass of water, to facilitate delivery to the stomach.	Take with or without food. Swallow whole with a glass of water, to facilitate delivery to the stomach.
<b>Suitability for patients with swallowing difficulties/ enteral tubes</b>	May be given via gastric tube or crushed and mixed with water or apple puree for patients with swallowing difficulties (licensed route of admin).	Tablets may be crushed and suspended in water, or 5% dextrose in water, or apple juice or mixed with apple puree and immediately administered orally or immediately delivered through a nasogastric tube. Crushed tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours. (licensed route of admin)	Capsules should not be opened- increased risk of bleeding (oral bioavailability may be increased by 75 % when the pellets are removed from the capsule shell)	Tablets may be crushed and administered either in apple puree and taken orally or as a water suspension via a nasogastric tube in patients who are unable to swallow solid oral dose formulations (unlicensed, from personal communication with manufacturer).
<b>Contraindications</b>	All DOACS are contraindicated if: <ul style="list-style-type: none"> <li>• Hypersensitivity to drug or excipients</li> <li>• Active clinically significant bleeding</li> <li>• Risk factors for major bleeding e.g. current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding,</li> </ul>			

	<p>recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.</p> <ul style="list-style-type: none"> <li>• Dabigatran is contraindicated and rivaroxaban and apixaban not recommended in patients with prosthetic heart valves</li> <li>• Edoxaban is contraindicated in uncontrolled severe hypertension, during pregnancy and breast feeding. It is not recommended in prosthetic heart valves, moderate to severe mitral stenosis, haemodynamically instable PE, patients requiring thrombolysis or embolectomy for PE or those with active cancer.</li> </ul>			
<b>Drug Interactions-</b> <i>refer to SPC for more information</i>	<p>All DOACs are <b>contraindicated</b> with other <b>anticoagulants</b> and should be used with <b>caution</b> with <b>antiplatelets</b> (e.g. aspirin, clopidogrel, prasugrel, ticagrelor etc) and <b>NSAIDs</b>.</p> <p>Concomitant use with <b>azole antimycotics</b> (e.g. ketoconazole, itraconazole, voriconazole) or <b>HIV protease inhibitors</b> (e.g. ritonavir) is <b>contraindicated with dabigatran</b> and <b>not recommended with rivaroxaban or apixaban</b> due to increased plasma levels and bleeding risk.</p> <p>Concomitant use with <b>rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort</b> is <b>contraindicated with dabigatran</b>, should be <b>avoided with rivaroxaban</b> and used with <b>caution with apixaban</b>.</p>			
	<p><b>Dronedarone</b> should be avoided.</p> <p>Use with <b>posaconazole</b> not recommended.</p> <p><b>Clarithromycin, erythromycin</b> and <b>fluconazole</b> should be used with caution in patients with renal impairment.</p>	<p>Use with <b>posaconazole</b> not recommended.</p>	<p>Contraindicated with <b>ciclosporin</b> and <b>dronedarone</b>.</p> <p>Use with <b>tacrolimus</b> should be avoided.</p> <p>Use with caution with, <b>SSRIs/SNRIs, clarithromycin, amiodarone, posaconazole, quinidine, verapamil</b> (dosage reduction required- see above)</p>	<p>Concomitant use of <b>P-gp inhibitors</b> (<b>ciclosporin, dronedarone, erythromycin or ketoconazole</b>) with <b>edoxaban</b> results in increased concentrations of edoxaban and a reduction to 30mg OD is required. <b>Edoxaban</b> should be used with caution with <b>P-gp inducers</b> (eg <b>phenytoin, carbamazepine, phenobarbital or St. John's Wort</b>).</p>
<b>Food interactions</b>	No specific foods known to interact – see administration section above for advice on taking with or without food			
<b>Common side effects</b>	See Summary of Product characteristics	See Summary of Product characteristics	See Summary of Product characteristics	See Summary of Product characteristics
<b>Major bleed risk compared to warfarin</b>	Similar risk (ROCKET-AF)	Reduced risk (NNT= 104, ARISTOTLE)	Similar risk with 150mg. Reduced risk with 110mg (NNT= 154, RE-LY)	Reduced risk (20% RRR/0.68%ARR; ENGAGE AF-TIMI 48)
<b>Intracranial bleed risk compared to warfarin</b>	Reduced risk (NNT=500, ROCKET-AF)	Reduced risk (NNT=213, ARISTOTLE)	Reduced risk (NNT=228 with 150mg, 197 with 110mg, RE-LY)	Reduced risk (ENGAGE AF-TIMI 48)
<b>Gastrointestinal bleed risk compared to warfarin</b>	Similar risk (ROCKET-AF)	Similar risk (ARISTOTLE)	Increased risk (NNH=205 with 150mg, RE-LY)	Non-significant increased risk with high dose (60mg); Lower risk with low dose (30mg)

				(ENGAGE AF-TIMI 48)
<b>Dyspepsia incidence compared to warfarin</b>	Similar incidence (ROCKET-AF)	No dyspepsia reported (ARISTOTLE)	Increased incidence (NNH=17 with 110mg, 18 with 150mg, RE-LY) Consider co-prescription of a PPI	No dyspepsia reported (ENGAGE AF-TIMI 48)
<b>Medicine</b>	<b>Rivaroxaban<sup>2</sup></b>	<b>Apixaban<sup>3</sup></b>	<b>Dabigatran<sup>4</sup></b>	<b>Edoxaban<sup>5</sup></b>
<b>Suitability for patients with compliance problems</b>	Shorter half-life of DOACs may mean missed doses result in more time without anticoagulation. Difficult to measure compliance.			
	May be put in MCAs (no special storage conditions required)	May be put in MCAs (no special storage conditions required)	Not suitable for use in MCAs (unstable out of original packaging)	May be put in MCAs (no special storage conditions required)
<b>Mechanism of Action</b>	Factor Xa inhibitor		Direct thrombin inhibitor	Factor Xa inhibitor
<b>Extremes of body weight</b>	Initial clinical trials only included patients between 50kg and 120kg, but there is increasing evidence that these medications can safely be used up to 150kg <sup>1,2,3</sup>			
<b>Reversibility (a separate guideline is available in secondary care)</b>	No specific reversal agent. No real evidence or experience on reversal	No specific reversal agent. No real evidence or experience on reversal	Yes (NUH)	No specific reversal agent. No real evidence or experience on reversal.
<b>Pregnancy and breastfeeding- refer to specialist anticoagulation services</b>	Contraindicated in pregnancy and breast feeding	Not recommended during pregnancy.  A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.	Should not be used during pregnancy unless clearly necessary.  Breast-feeding should be discontinued during treatment.	Not recommended during pregnancy.  Breast-feeding should be discontinued during treatment.
<b>Long term safety</b>	Not known (study follow up period 1.9years)	Not known (study follow up period 1.8 years)	Not known (study follow up period 2 years)	Not known (study median follow up period 2.5 years)
<b>Cost (December 2017, may vary according to local procurement discounts)</b>	£655/ year	£692/ year	£619/ year	£637/ year

## Appendix 2: Warfarin *(For more detailed information, refer to manufacturers Summary of Product Characteristics (SPCs))*

Medicine	Warfarin <sup>1</sup>
Presentation	3mg tablets are used in Nottinghamshire <i>(other strengths may be used in other areas)</i>
Licensed Indication	Prophylaxis of systemic embolism in patients with atrial fibrillation.
Dosing <i>(NB applies to AF indication only)</i>	Variable depending on INR (international normalised ratio)
Use in renal impairment	Dose as per INR as in normal renal function <sup>5</sup>
Use in hepatic impairment	Should be avoided in severe hepatic impairment, especially if prothrombin time is already prolonged.
Administration	Take at the same time each day.
Suitability for patients with swallowing difficulties/ enteral tubes	May be crushed and dispersed for enteral tube administration (outside of license) <i>Suspension is not licensed for enteral tube administration.</i>
Contraindications	<ul style="list-style-type: none"> <li>• Hypersensitivity</li> <li>• Haemorrhagic stroke</li> <li>• Clinically significant bleeding</li> <li>• Within 72 hours of major surgery with risk of severe bleeding</li> </ul>
Drug Interactions- <i>refer to SPC for more information</i>	Many- <i>refer to BNF or SPC</i> With INR monitoring warfarin doses can be adjusted to maintain anticoagulation during therapy with many concomitant interacting medicines
Food interactions	INR altered by some food/ drink
Common side effects	See Summary of Product characteristics
Major bleed risk compared to warfarin	NA
Intracranial bleed risk compared to warfarin	NA
Gastrointestinal bleed risk compared to warfarin	NA
Dyspepsia incidence compared to warfarin	NA

<b>Suitability for patients with compliance problems</b>	Some patients may struggle with variability of dosing. INR gives indication of compliance. Generally considered not suitable for multi-compartment compliance aids (MCAs) due to variability of dosing, but may be considered if a mechanism of managing dose changes is assured
<b>Mechanism of Action</b>	Inhibitor of clotting factors II, VII, IX & X
<b>Extremes of body weight</b>	Dose as per INR
<b>Reversibility</b> ( <i>a separate guideline is available in secondary care</i> )	Yes
<b>Pregnancy and breastfeeding-</b> <i>refer to specialist anticoagulation services</i>	Contraindicated in the first and third trimesters of pregnancy and within 48 hours postpartum Warfarin can be used during breast-feeding.
<b>Long term safety</b>	Has been used as an anticoagulant for many years
<b>Cost</b> ( <i>August 2014, may vary according to local procurement discounts</i> )	£240/ year inclusive of monitoring costs (NUH data) Medicine cost alone of 1mg/ml suspension is £1300/ year.

### Appendix 3: Switching anticoagulant therapy for non-valvular AF patients only

(Nb that this information applies to non-valvular AF indication only- see SPCs for alternative indications)

	Rivaroxaban <sup>2</sup>	Apixaban <sup>3</sup>	Dabigatran <sup>4</sup>	Edoxaban <sup>5</sup>
<b>Warfarin to DOAC</b>	Stop warfarin and initiate rivaroxaban when INR is $\leq 3.0$ .	Stop warfarin and initiate apixaban when INR is $\leq 2.0$ .	Stop warfarin and initiate dabigatran when INR is $\leq 2.0$ .	Discontinue warfarin and start edoxaban when the INR is $\leq 2.5$
<b>Oral to parenteral anticoagulant*</b>	Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken.	Give the first dose of parenteral anticoagulant at the time the next apixaban dose would be taken.	Wait 12 hours after the last dose of dabigatran before switching to a parenteral anticoagulant	Discontinue edoxaban and start the parenteral anticoagulant at the time of the next dose of edoxaban
<b>Parenteral anticoagulants to oral anticoagulant**</b>	LMWH: Start rivaroxaban 0 to 2 hours before the time of the next scheduled dose  UFH: Start rivaroxaban at the time of discontinuation of UFH	Give the first dose of apixaban at the time the next parenteral anticoagulant dose is due.		LMWH: Discontinue LMWH and start edoxaban at the time of the next scheduled administration of LMWH  UFH: Discontinue the infusion and start edoxaban 4 hours later
<b>DOAC to Warfarin</b>	<b>Discuss with local anticoagulation service before switching depending on local pathway for warfarin initiation and monitoring (below information is a guide if prescriber is responsible for coumarin monitoring)</b>			
	Give warfarin and rivaroxaban concurrently until the INR is $\geq 2.0$ .  Initiate warfarin at standard dose for 2 days and then dose as per INR. INRs should be taken at least 24hrs after the previous dose of rivaroxaban (immediately before the ) next dose.  INRs may be falsely elevated during rivaroxaban therapy, but once rivaroxaban is discontinued, may be done reliably at least 24 hours after the last dose	Give warfarin and apixaban concurrently until the INR is $\geq 2.0$ .  Initiate warfarin at standard dose for 2 days and then dose as per INR. Obtain an INR prior to the next scheduled dose of apixaban.  INRs should be taken immediately before the next DOAC dose as all Xa inhibitors can variably prolong the PT.	Adjust the starting time of warfarin based on CrCL as follows: • CrCL $\geq 50$ mL/min, start warfarin 3 days before discontinuing dabigatran • CrCL $\geq 30-49$ mL/min, start warfarin 2 days before discontinuing dabigatran  INRs may be falsely elevated until dabigatran has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.	<u>Oral option:</u> For patients taking: • 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. • 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly.  INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. INRs should be taken immediately before the next DOAC dose as all Xa inhibitors can variably prolong the



				<p>PT.</p> <p>Once a stable INR <math>\geq 2.0</math> is achieved, edoxaban should be discontinued and the warfarin continued</p> <p><u>Parenteral option:</u></p> <p>Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR <math>\geq 2.0</math> is achieved the parenteral anticoagulant should be discontinued and the warfarin continued</p>
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Key: LMWH = low molecular weight heparin (e.g. enoxaparin), UFH = unfractionated heparin

\*For Warfarin parenteral anticoagulant can be started immediately.

\*\*Warfarin can be given concomitantly with parenteral anticoagulant. Concomitant therapy may be required until therapeutic level achieved or as per local policy.

## Appendix 4: Notes on HAS-BLED score

Assess bleeding risk using <a href="#">HAS-BLED score</a>	
Feature	Score
Hypertension (uncontrolled SBP >160mmHg)	1
Liver disease (Cirrhosis or bilirubin >2x normal with AST/ALT/ALP >3x normal)	1
Renal disease (Dialysis, transplant, or >200 micromol/L)	1
Stroke history	1
Bleeding history or predisposition (e.g. anaemia)	1
Labile INRs (i.e. Time in Therapeutic Range < 60%)	1
Elderly (e.g. age > 65 years or frail condition)	1
Drugs (concomitant antiplatelets, NSAIDs etc) or alcohol abuse (1 point each)	1 or 2
<b>Score: (maximum score of 9)</b> <b>Address modifiable risks where possible</b>	

The HAS-BLED score estimates the 1-year risk for major bleeding (intracranial, hospitalization, haemoglobin decrease > 2 g/L, and/or transfusion) <sup>1</sup>

“HAS-BLED should not be used on its own to exclude patients from oral anticoagulant therapy; it allows the clinician to identify bleeding risk factors and to correct those that are modifiable, i.e. by controlling blood pressure, removing concomitant antiplatelet or nonsteroidal anti-inflammatory drugs, and counseling the patient about reducing alcohol intake (if excessive). Thus, bleeding risk assessment with HAS-BLED should not be used as an excuse not to prescribe oral anticoagulant, but rather to highlight those patients in whom caution with such treatment and regular review is warranted”. <sup>2</sup>

A HAS-BLED score of ≥3 indicates that caution is warranted when prescribing oral anticoagulation and regular review is recommended. <sup>1</sup>

HAS-BLED score total points	Major Bleeding Risk (% per annum)	Risk description
0	1.13	Low
1	1.02	Moderate
2	1.88	
A HAS-BLED score of ≥3 indicates that caution is warranted when prescribing oral anticoagulation and regular review is recommended.		
3	3.74	High
4	8.70	
5 to 9	Insufficient data	

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