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

Contents

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 guidance or NICE Pathway.
Some prescribing advice in this guidance, has been locally agreed with specialists from NUH and SFH hospitals and may differ from the advice included by the manufacturers in the summary of product characteristics (SmPC).

Apixaban is the most cost effective DOAC (twice a day dose) and should be used **first line** unless there is a clinical reason for using another DOAC. **Rivaroxaban** is **the second line DOAC** locally (once daily dose).

Assessing patients for anticoagulation in AF

(This guidance applies to patients with non-valvular paroxysmal, persistant 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 CHA_2DS_2-VASc		Assess bleeding risk using ORBIT score (or HAS-BLED where ORBIT is unavailable on clinical systems)		
CHA_2DS_2-VASc Feature	Score	**ORBIT Bleeding Risk Feature**		**Score**
Congestive Heart Failure	1	**Reduced Haemoglobin/ Reduced Haematocrit(HCT)/Anaemia**		2
		Hb <13mg/dL for males	Hb <12 mg/dL for females	
		HCT <40% for males	HCT <36% for females	
		History of anaemia	History of anaemia	
Hypertension	1	Age >74 years		1
Age = >75 years	2	Bleeding history - any history of GI bleeding, intracranial bleeding, or haemorrhagic stroke		2
Age between 65 and 74 years	1	eGFR <60 ml/min/1.73 m2		1
Diabetes mellitus	1	Treatment with antiplatelet agents		1
Stroke / TIA / Thrombo-embolism	2	**ORBIT score Risk** **0-2 = low 3 = medium 4-7 = high**		
Vascular disease (previous MI, peripheral arterial disease or aortic plaque)	1	Address modifiable risks where possible. Offer monitoring and support to modify risk factors for bleeding. Including reversible causes of anaemia, uncontrolled hypertension, poor control of INR, harmful alcohol consumption, concurrent medication e.g. antiplatelets, SSRIs and NSAIDs.		
Female	1			
Score: (maximum score of 9)				

CHA_2DS_2-VASc score of ≥ 2

Offer DOAC* taking bleeding risk into account

CHA_2DS_2-VASc score of 1

Men

Consider for DOAC* taking bleeding risk into account

Women

CHA_2DS_2-VASc score of 0

Do not offer anticoagulation for stroke prevention in AF

For most people the benefit of anticoagulation outweighs the bleeding risk.

(**Discuss with patient using shared decision** explaining risks appropriate to the individual), but for people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important. Do not withhold anticoagulation solely because of a person's age or risk of falls. Consider specialist opinion.

Patient is a candidate for and consents to anticoagulation

As per NICE NG196, first choice anticoagulation is with:

- A direct oral anticoagulant (DOAC) e.g. **1st line apixaban, 2nd line rivaroxaban,** edoxaban or dabigatran**.**
- *If DOAC contraindicated, not tolerated, not suitable offer warfarin.
- Consider referral if anticoagulation contraindicated or not tolerated

See flowchart on page 3 below for individual patient factors to consider when choosing an anticoagulant.

Based on the above assessment patient refuses or is not a candidate for anticoagulation

Document decision in patient's notes and review annually, or when patient reaches 65 years old or if they develop any of the following at any age:

- diabetes, heart failure, peripheral arterial disease
- coronary heart disease
- stroke, transient ischaemic attack or systemic thromboembolism.

Do not offer aspirin monotherapy solely for stroke prevention to people with AF. Review patients on existing antiplatelet therapy and if still considered appropriate for another indication they may continue, as necessary.

Anticoagulation choice and patient factors

From page 2: 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
  - **Baseline tests prior to initiation:**

❑ **U+Es (and Creatinine clearance (CrCl) calculated, DO NOT USE eGFR)**
❑ **FBC**
❑ **Clotting**
❑ **LFTs**
❑ **Weight**
❑ **Blood pressure**

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?
❑ Confirmed triple positive antiphospholipid syndrome
❑ **Renal disease** Creatinine clearance **<15ml/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** (i.e. body weight <50kg or >150kg)
❑ Poor **concordance** anticipated
❑ Liver disease associated with coagulopathy and clinically relevant bleeding

Yes →

Consider WARFARIN
(as DOACs either contraindicated, unlicensed or not recommended)

Initiation of warfarin should be as per current pathway

See initiation checklist below

❑ Pregnancy and breastfeeding
❑ Active cancer/chemotherapy

→ Refer to specialist advice

No

Offer a DOAC (see table 1 below)
See initiation checklist below

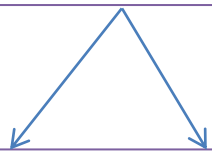
Table 1: Preferred choice of DOAC (based on patient factors)

Where a DOAC is the most appropriate anticoagulant, **apixaban is the most cost effective DOAC (twice a day dose) and should be used first line** for patients with NVAF unless there is a specific clinical reason not to do so. **Rivaroxaban is the second line DOAC locally (once daily dose).** In line with NICE guidance, other DOACs can be considered. The following patient factors may suggest a preferred DOAC.

Renal impairment	Local specialists recommend avoiding DOACs in patients with CrCl<15mL/min due to increased risk of drug accumulation and bleeding. Apixaban has the lowest renal excretion percentage of all the DOACs and may be used at reduced dose (2.5mg BD) with caution if CrCl is <30mL/min and >15mL/min. Dabigatran is contraindicated if CrCL<30ml/min. See appendix 1 for more information of dosing.
High creatinine clearance (>95ml/min)	**Edoxaban** – shows **decreased efficacy** at high creatinine clearance. The local advice is that patients already established on edoxaban and later found to have a CrCl >95ml/min, should have their anticoagulation plan reviewed and switched onto an alternative DOAC. The decision to treat a patient with NVAF and high CrCl with edoxaban ultimately lies with the prescriber after taking into consideration the patient's thromboembolic and bleeding risk.
Increased bleeding risk (Orbit Score ≥4 or HAS-BLED ≥3)	Apixaban
Patients > 75 years old	Local specialists advise caution in using Dabigatran due to concern about increased risk of gastrointestinal bleeding.
Patients >120kg	Use other DOACs (NOT edoxaban) or warfarin if over 150kg.
Patient requires compliance aid	Apixaban, rivaroxaban or edoxaban (NOT dabigatran).
Swallowing difficulties / enteral feeding tubes	Edoxaban, Apixaban or Rivaroxaban. **Poor oral intake or inability to take with food can cause treatment failure with rivaroxaban.**

Checklist and process for initiation of all anticoagulants:

Initiation points
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 (usually comes from the manufacturer)
Recommend the patient to discuss this new medicine with their pharmacist as part of the free new medicines service



DOACs	WARFARIN
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	**Initiation** Warfarin should be initiated as per local pathway (traffic light classification **GREEN**)
Monitoring **For DOACs see monitoring and reviewing section here**	**Monitoring** **For warfarin see monitoring and reviewing section here**
Review **Review** the need for and safety of anticoagulation **at least annually** or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk	

DOACs – monitoring and reviewing

- 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 recommended 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.

Baseline blood tests				
Patient group	**U + Es (Creatinine clearance)**	**Full blood count**	**Coagulation screen**	**Liver function tests**
All	✓	✓	✓	✓
The current national recommendations, once DOAC treatment is started, are to review patients after 1 month, and at least 3 monthly thereafter. Follow up intervals may vary depending on the individual patient's characteristics, comorbidities and co-medications.[27] **Please see below for frequency on blood monitoring during the first year and ongoing**.				
Patient group	**U + Es (Creatinine clearance)**	**Full blood count**	**Coagulation screen**	**Liver function tests**
Creatinine Clearance **> 60ml/min**	Annually*	Annually*	**X** Inappropriate without correct reagent	Annually*
If the person is frail or older than 75 years[28]	6 monthly	6 monthly	**X** Inappropriate without correct reagent	6 monthly
Creatinine Clearance **30-60ml/min****	Minimum 6 monthly**	Minimum 6 monthly**	**X** Inappropriate without correct reagent	Minimum 6 monthly**
Creatinine Clearance **15-30ml/min**	3 monthly***	3 monthly***	**X** Inappropriate without correct reagent	3 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.

** NICE CKS and SPS recommend that if CrCl < 60 mL/min, the frequency of monitoring (in months) can be guided by the CrCl divided by 10. For example, every 3 months if CrCl is 30 mL/minute.

*** PCCS and UKCPA recommend routine surveillance every 6 months in patients over 75 years of age and/or frail and routine surveillance 3 monthly in CrCl 15-30mls/min.

- **Weight should be reviewed annually for any renal function calculations to remain accurate.**
- 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[19,20,21,22]
- The local consensus from our specialists is to use any of the DOACs in patients under 150kg (except edoxaban – not used in patients over 120kg) irrespective of indication for anticoagulation. Rivaroxaban or apixaban can be used in patients above 150kg who have had DVT or PE only (**not for indication of AF**).
- Creatinine clearance **must be used for calculating renal function** using the Cockcroft and Gault equation (see below). eGFR is **not** a suitable alternative:

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

- **For DOAC monitoring, calculate creatinine clearance (CrCl) using the actual body weight from last 12 months (unless recent weight loss/gain). Use adjusted bodyweight if patients > 120kg / BMI > 40. [8]**
- **NB The clinical systems used in Nottinghamshire in primary care (SystmOne and EMIS) have an inbuilt Cockcroft-Gault based renal function calculator which can be used to dose DOACs. The most up to date values for the patient's actual body weight and height will have to be inserted. It should be remembered that all values are estimates of renal function.**

DOACs – Further information on calculating Creatinine Clearance

SystmOne CrCl calculator uses:	EMIS CrCl calculator uses:
From November 2023 the SystmOne renal calculator highlights the dates for when the weight and the creatinine value were last recorded and gives three values for the CrCl using: ideal, actual, and adjusted body weight.	- actual body weight for CrCl calculation for patients taking apixaban, edoxaban or rivaroxaban - and ideal body weight for dabigatran. There is text information added to advise whether actual or IBW has been used each time a calculation is made.

- Alternatively, MD+ Calc Creatinine Clearance Calculator can be used (can be downloaded as an app to an apple or android device), **which gives values for IBW, Adjusted BW and Actual weight.** 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.

Points for discussion during a DOAC review

- Assess adherence to treatment.
- Look for signs of bleeding or anaemia.
- Ask about other adverse effects of DOAC.
- Assess for features of thromboembolic events, such as symptoms of stroke, or breathlessness (which may suggest a pulmonary embolism). See the CKS topics on Stroke and TIA and Pulmonary embolism for more information.
- Ask about the use of other medications, including over-the-counter (OTC) products, to identify possible drug interactions with DOAC.
- Assess and minimize modifiable risk factors for bleeding, such as uncontrolled hypertension, medication predisposing for bleeding (such as aspirin), and excessive alcohol intake.
- Give appropriate information and advice on DOAC treatment.

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 inter-current illness and peri-operatively in all patients with CKD.

Side Effect	Action
Haemorrhage	Refer patient immediately to Accident and Emergency (A&E) if serious bleeding occurs e.g. 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, but CrCl still >30mL/min (and see below)	Reduce dose as appropriate according to the medicine's recommended dosing schedule in renal impairment (see above for CrCl calculation). If renal function continues to worsen discuss with haematologist.
Fall in creatinine clearance to <30mL/min with dabigatran, or <15mL/min with apixaban, rivaroxaban, edoxaban	Stop DOAC, assess for bleeding and seek advice as to whether specific assays are indicated / alternative anticoagulation required. **Note that local specialists recommend avoiding DOACs in patients with Creatinine Clearance CrCL<15ml/min (for dabigatran avoid if CrCL<30mL/min) due to increased risk of accumulation and bleeding.** Apixaban has the lowest renal excretion percentage of all the DOACs and may be used with caution at reduced dose (2.5mg BD) if CrCl is <30mL/min and >15mL/min.

Warfarin – monitoring and reviewing.

For adults with AF already taking warfarin and are stable, continue with current medication and discuss the option of switching treatment at their next routine appointment, considering contraindication to DOACS and the person's time in therapeutic range. In view of the results from recent FRAIL-AF trial, if an elderly patient (over 75) is already established on warfarin (and their TTR is good), we do not necessarily change them to a DOAC. In addition, if there is a need to change them to a DOAC, consider avoiding Dabigatran due to the risk of catastrophic bleed in the elderly.

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	**As required or as per protocol for self monitoring patients**			

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. It is not unreasonable to monitor FBC, UE and LFT annually in these patients, but this isn't strictly required. FBC monitoring could provide early detection of anaemia (which may indicate underlying bleeding issue) and thrombocytopenia (which will increase the risk of bleeding).

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

TTR ≥ 65%

Do any of the following apply?:

- ❑ Intolerance or allergy to vitamin K antagonists (e.g. warfarin or acenocoumarol)
- ❑ History of significant bleed associated with poor warfarin control
- ❑ Patient has had in the last 6 months:
  1 x INR >8
  or 2 x INR > 5
  or 2 x INR < 1.5

NO

Continue dose adjusted warfarin

Review patient's risk of stroke and bleeding risk at annual review

TTR < 65%

Take into account and address where possible:

- ❑ cognitive function
- ❑ adherence to prescribed therapy
- ❑ illness
- ❑ interacting drug therapy
- ❑ lifestyle factors including diet and alcohol consumption
- ❑ Consider self-monitoring as per NICE Guidance if concordance affected by inconvenience of INR testing

Reassess at appropriate time interval to assess improvement in control if measures put in place

Improved control? (i.e. TTR ≥ 65%)

YES

YES

NO

If poor anticoagulation control cannot be improved:

- discuss risks and benefits of alternative strategies with the patient. Exclude all reasons for poor INR control despite good compliance before considering a DOAC.
- Inform local anticoagulation service if switching therapy
- Refer to Appendix 3 for information about practicalities of switching between anticoagulants and initiation checklist

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

Medicine	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Mechanism of Action	Factor Xa inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Presentation	2.5 and 5mg film coated tablets	110mg and 150mg hard capsules *NB. 75mg capsules are not licensed for AF.*	15, 30 and 60mg film coated tablets	15 and 20mg film coated tablets. *NB. 10mg and 2.5mg tablets are not licensed for AF.*
Licensed Doses *(NB applies to AF indication only)*	**5mg TWICE daily** Reduced to 2.5 mg twice daily if at least *two* of the following: - age ≥ 80 years, - body weight ≤ 60 kg, or - serum creatinine ≥ 133 micromole/L	**150mg TWICE daily** Reduced to 110mg twice daily if patient is: - ≥ 80 years* or taking verapamil; - aged between 75-80 years**; - moderate renal impairment (CrCl 30-50 mL/min); - gastritis, esophagitis or gastro-esophageal reflux; - increased risk of bleeding. **** Local specialists advise caution in using Dabigatran in patients over 75 years old, due to concern about increased risk of gastrointestinal bleeding.***	**60mg ONCE daily** Reduced to 30mg once daily if -CrCl 15-50mL/min -low body weight (≤60kg), concomitant use of potent P-gp inhibitors (e.g. Dronaderone, Erythromycin, Ketoconazole, Ciclosporin).	**20 mg ONCE daily** Reduced to 15 mg once daily if CrCl <50mL/min
Use in renal impairment	• **Renal function should be assessed prior to DOAC treatment in all patients.** • DOACs can be used in patients with renal impairment in line with the SPC of the specific agent (as below). • Patients who develop acute renal failure should discontinue the DOAC and seek specialist advice • Creatinine clearance must be calculated (see here for calculator), eGFR is **NOT** considered **a suitable alternative**.			
Licensed doses in renal impairment	CrCl 15-29mL/min: 2.5mg BD (use with caution) CrCl < 15mL/min: Contraindicated	CrCl < 30mL/min: Contraindicated	CrCl >95ml/min: **DO NOT use** edoxaban, shows decreased efficacy at high creatinine clearance. CrCl 15-50mL/min: 30mg OD CrCl <15mL/min: Contraindicated	CrCl 15-49 mL/min: 15 mg OD CrCl < 15mL/min: Contraindicated
Extremes of body weight	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[1,2,3] The local consensus from our specialists is to use any of the DOACs in patients under 150kg (except edoxaban – not used in patients over 120kg) irrespective of indication for anticoagulation. Rivaroxaban or apixaban can be used in patients above 150kg who have had DVT or PE only (ie **not in context of AF**).			
Use in hepatic impairment	Check spc.	Check spc.	Check spc.	Check spc.

Medicine	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Administration	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.	**The tablet is taken with food. Poor oral intake or inability to take with food can cause treatment failure with rivaroxaban.**
Food interactions	No specific foods known to interact – see administration section above for advice on taking with or without food. **Poor oral intake or inability to take with food can cause treatment failure with rivaroxaban.**			
Suitability for patients with swallowing difficulties/ enteral tubes	Tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally - suspension stable for up to 4 hours. Alternatively, tablets can be crushed and suspended in 60mL of water or G5W and delivered immediately through a nasogastric tube. (Licenced route of administration)	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).	For patients who are unable to swallow whole tablets, tablets may be crushed and mixed with water or apple puree and immediately administered orally. Alternatively, tablets may be crushed and suspended in a small amount of water and immediately delivered through a gastric tube after which it should be flushed with water. (Licenced route of administration) Crushed tablets are stable in water and apple puree for up to 4 hours.	Granules for oral suspension are licensed for nasogastric and PEG tubes. Not suitable for administration via enteral feeding tubes terminating beyond the stomach (i.e. in the duodenum or jejunum) due to decreased absorption when given in this manner and thus not appropriate for NJ / PEJ / PEGJ tubes. For patients who are unable to swallow whole tablets, tablets may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed film-coated tablets, the dose should be immediately followed by food. The crushed tablet may also be given through gastric tubes.
Suitability for patients with compliance problems	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)	Not suitable for use in MCAs (unstable out of original packaging)	May be put in MCAs (no special storage conditions required)	May be put in MCAs (no special storage conditions required)
Reversibility *(a separate guideline is available in secondary care)*	Yes. Approved as per NICE TA 697 for life-threatening or uncontrolled bleeding only if the bleed is in the gastrointestinal tract. There is an ongoing clinical trial for intracranial haemorrhage for eligible patients at SFH. See formulary.	Yes	No specific reversal agent. No real evidence or experience on reversal.	Yes. Approved as per NICE TA 697 for life-threatening or uncontrolled bleeding only if the bleed is in the gastrointestinal tract. There is an ongoing clinical trial for intracranial haemorrhage for eligible patients at SFH. See formulary.

Medicine		Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Contraindications		• Hypersensitivity to drug or excipients. • Active clinically significant bleeding. • Risk factors for major bleeding e.g. current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, 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. • In patients with prosthetic heart valves. • In uncontrolled severe hypertension, during pregnancy and breast feeding. • 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.			
Drug Interactions - refer to SPC for more information		• Dabigatran and edoxaban are substrates for P-glycoprotein (P-gp) • Apixaban and rivaroxaban are metabolised by cytochrome P450 enzyme CYP3A4 and are substrates for P-gp. The table below outlines main DOAC drug interactions (drugs in bold font recommend not be used with DOACs – except those marked with * can be used with edoxaban): **N.B. This is not an exhaustive list and if in doubt check for interactions using BNF, SmPC or online interaction checker**			
Class	**Medicine**				
Strong P-gp inhibitors (also CYP3A4 inhibitors)	***Ciclosporin** ***Dronaderone** **Itraconazole** ***Ketoconazole** **Posaconazole** **Tacrolimus** **Voriconazole** **Imatinib** **Crizotinib** **Vandetanib** **Sunitinib** **Abiraterone**	Strong recommendation not to use	Combination contraindicated.	Reduce dose to 30mg daily if on ciclosporin, dronaderone, erythromycin or ketoconazole. Recommend not use with others listed.	Strong recommendation not to use
Other strong P-gp inhibitors (also CYP3A4 inhibitors)	Amiodarone Clarithromycin Quinidine Verapamil	Caution.	Caution. If on verapamil give 110mg twice daily.	Caution.	Caution.
HIV Protease inhibitors (P-gp inhibitors and	**Ritonavir** **Telaprevir** **Lopinavir**	Strong recommendation not to use.	Concomitant use not recommended.	Not recommended to use.	Strong recommendation not to use.

CYP3A4 inhibitors)	**Darunavir Cobicistat**				
Strong P-gp and CYP3A4 inducers	**Carbamazepine Phenobarbital Phenytoin Primidone Rifampicin St John's Wort Vinblastine Doxorubicin Enzalutamide**	Combination should be avoided.			
Other anticoagulants	E.g. LMWH, warfarin, UFH, fondaparinux	Combination contraindicated except when switching therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter			
Others	Aspirin Clopidogrel NSAID's	Caution. Combination not recommended. A careful risk-benefit assessment should be made prior to initiation if required.			
	Prasugrel Ticagrelor	Combination not recommended.			
	SSRI's and SNRI's	Caution. Monitor for signs of bleeding.			
Pregnancy and breastfeeding - *refer to specialist anticoagulation services.*		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. Edoxaban is contraindicated during breast-feeding. A decision must be made to discontinue breast-feeding or to discontinue/abstain from therapy.	Contraindicated in pregnancy and breast feeding.

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

Medicine	**Warfarin**[1]
Presentation	3mg tablets are used in Nottinghamshire (other strengths may be used in other areas)
Licensed Indication	Prophylaxis of systemic embolism in patients with atrial fibrillation.
Dosing *(NB applies to AF indication only)*	Variable depending on INR (international normalised ratio)
Use in renal impairment	Dose as per INR as in normal renal function[5]
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) *Suspension is not licensed for enteral tube administration.*
Contraindications	• Hypersensitivity • Haemorrhagic stroke • Clinically significant bleeding • Within 72 hours of major surgery with risk of severe bleeding
Drug Interactions- *refer to SPC for more information*	Many- *refer to BNF or SPC* 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
Suitability for patients with compliance problems	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
Mechanism of Action	Inhibitor of clotting factors II, VII, IX & X
Extremes of body weight	Dose as per INR
Reversibility *(a separate guideline is available in secondary care)*	Yes
Pregnancy and breastfeeding- *refer to specialist anticoagulation services*	Contraindicated in the first and third trimesters of pregnancy and within 48 hours postpartum. Warfarin can be used during breast-feeding.

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)

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Warfarin to DOAC	**Inform the patient's anticoagulation clinic if switching away from warfarin.**			
	Stop warfarin and initiate apixaban when INR is ≤ 2.0.	Stop warfarin and initiate dabigatran when INR is ≤ 2.0.	Discontinue warfarin and start edoxaban when the INR is ≤ 2.5	Stop warfarin and initiate rivaroxaban when INR is ≤ 3.0.
Oral to parenteral anticoagulant*	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	Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken.
Parenteral anticoagulants to oral anticoagulant **	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	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
DOAC to Warfarin	**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)**			
	Give warfarin and apixaban concurrently until the INR is ≥ 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 ≥ 50 mL/min, start warfarin 3 days before discontinuing dabigatran • CrCl ≥ 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 PT. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and the warfarin continued. <u>Parenteral option:</u> Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved the parenteral anticoagulant should be discontinued and the warfarin continued.	Give warfarin and rivaroxaban concurrently until the INR is ≥ 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.

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 HAS-BLED score	
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
Score: (maximum score of 9) Address modifiable risks where possible	

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

"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 medicines, 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". [2]

A HAS-BLED score of ≥3 indicates that caution is warranted when prescribing oral anticoagulation and regular review is recommended. [1]

HAS–BLED score total points	Major Bleeding Risk (% per annum)	Risk description
0	1.13	Low
1	1.02	
2	1.88	Moderate
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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