Guidelines for oral anticoagulation of patients with non-valvular atrial fibrillation (AF) to prevent stroke in adults

Contents

1. Atrial Fibrillation Anticoagulant Clinical Decision Aid - Overview and checklist for initiation

1.1. Patient details and risk assessments

Date		**NHS number**		
Patient Name				
DOB		**Age**		
CHA_2DS_2Vasc Score		**ORBIT Score**		**See page 3**
Annual Stroke Risk		**Annual Bleed Risk**		
Modifiable Risk Factors				**See page 4**
Contra-indications to anticoagulation				**See page 4**

1.2. Baseline clinical screening checklist

	U&Es (Creatinine)	Weight* (kg)	FBC	LFTs	Baseline Clotting	BP
Baseline (All patients)						

Recent weight, ideally at time of clinical screening

Creatinine Clearance (CrCl) Using Cockcroft & Gault formula		**See page 10**

1.3. Choice of anticoagulant

non-vitamin K oral anticoagulant (DOAC) [ ] Warfarin [ ] referral [ ]**		**See page 5-6**
****Choice of DOAC**		**See page 7-8**
****Interactions with patient's current medicines**		*Drug interactions with NOACs*
****DOAC Dose**		**See page 9 -10**
****Patient Counselling**		**See appendix 1:** *NOAC counselling checklist*

1.4. Ongoing Monitoring required

DOAC	**U&Es (Creatinine), Weight (kg)*, FBC, LFTs, BP**	**See page 11**
Warfarin		**See page 12**

Recent weight, ideally at time of clinical screening

2. Assessment of stroke and bleeding risks for patients with non-valvular AF

Online calculators are available on GP clinical systems

- CHA2DS2-VASc scoring system for risk of stroke
  Scoring Calculator: https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk
- ORBIT scoring system for risk of bleed (***recommended bleeding risk tool by NICE guidance 196: Atrial fibrillation: diagnosis and management***)
  Scoring Calculator: https://www.mdcalc.com/orbit-bleeding-risk-score-atrial-fibrillation

CHA_2DS_2Vasc Scoring System for AF Stroke Risk[1,2,3]		ORBIT scoring for Bleeding Risk[4]	
Risk Factor	**Score**	**Risk Factor**	**Score**
Congestive heart failure/LV dysfunction	1	Males with haemoglobin <130 g/L or haematocrit <40%. Females with haemoglobin <120 g/L or haematocrit <36%.	2
Hypertension	1		
Age ≥ 75	2	People with a history of bleeding (gastrointestinal or intracranial bleeding, or haemorrhagic stroke)	2
Diabetes mellitus	1	Aged over 74 years	1
Stroke/TIA/systemic arterial embolism	2	estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2	1
Vascular disease (previous MI, peripheral arterial disease, aortic plaque)	1	Treatment with antiplatelets	1
Age 65 -74	1		
Sex (male 0, female 1)	F 1		
Total score *(maximum score 9)*		**Total score** *(maximum score7)*	

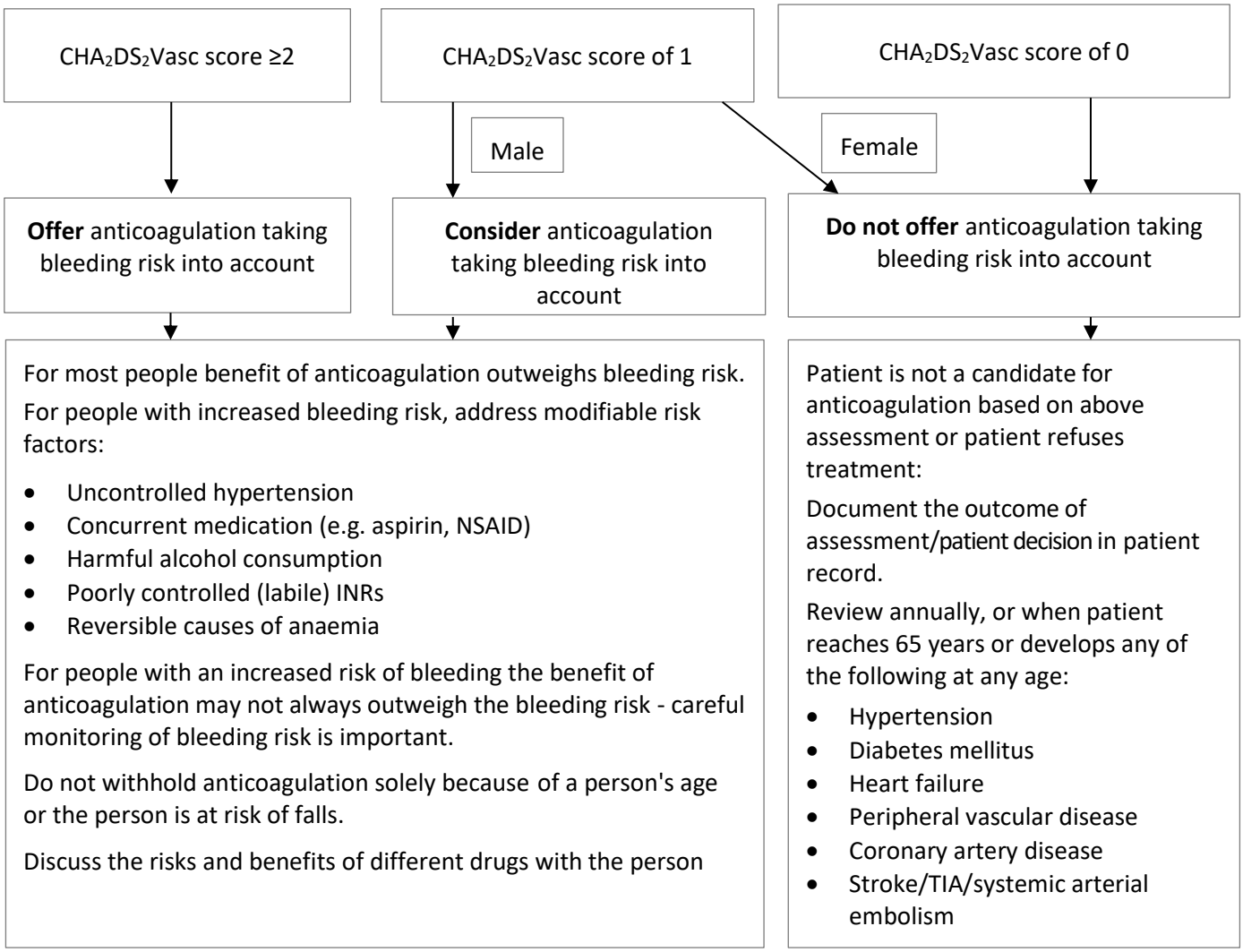
Interpreting CHA_2DS_2Vasc and ORBIT Score

CHA_2DS_2 Vasc	Events per 100 patients/year	
	Stroke/TIA/peripheral emboli	Ischaemic stroke
0	0.3	0.2
1	1.0	0.6
2	3.3	2.5
3	5.3	3.7
4	7.8	5.5
5	11.7	8.4
6	15.9	11.4
7	18.4	13.1

ORBIT Score**	Bleeds per 100 patient-years
0	1.7
1	2.3
2	2.9
3	4.7
4	6.8
5	9.0
6	12.3
7	14.9

**score 0-2: low risk, 3 medium risk, 4-7: high risk

3. Prescriber decision support for anticoagulating patients with non-valvular AF



(Flow diagram adapted from AF (non-valvular): prescriber decision support for anticoagulation, Nottinghamshire Area Prescribing Committee; flow diagram updated March 2022 in line recommendations form NICE CG196)

Contra-indications to anticoagulation[3,5-11]

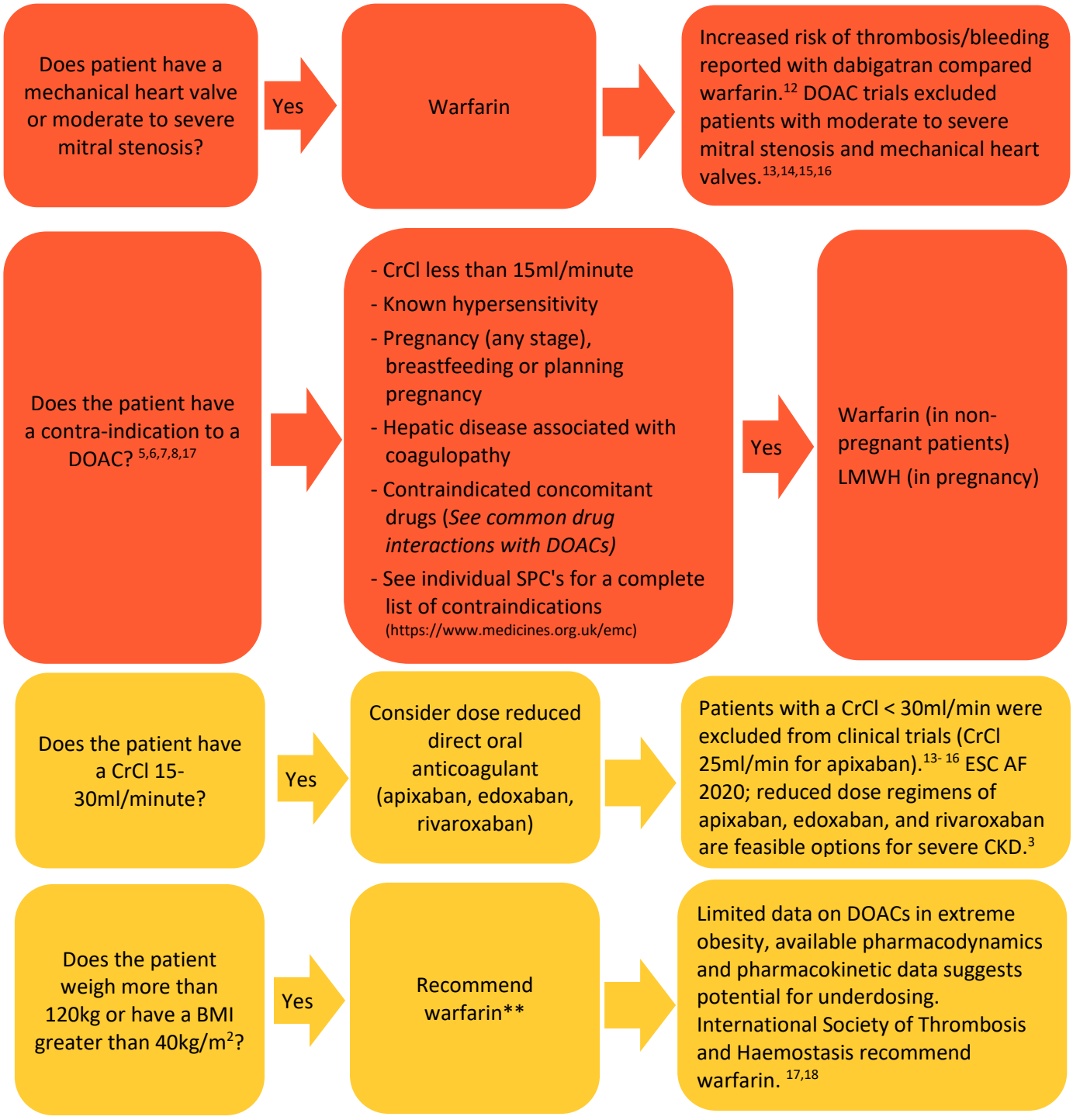
The following list of contraindications are taken from individual Summary of Product Characteristics (SPC's)[5-8], MHRA safety updates 2009[9] and 2013[10], NICE CKS[11] and European Society of Cardiology guidelines for the management of atrial fibrillation 2020[3]. Where needed, discuss the clinical management plan with a specialist if there is a known contra indication to anticoagulation treatment. The list below is not exhaustive; see individual SPCs for additional contraindications for individual anticoagulants (https://www.medicines.org.uk/emc)

- Clinically significant bleeding
- Recent intracranial haemorrhage
- A significant risk of major bleeding such as:
    - Current or recent upper gastrointestinal ulceration
    - Presence of malignant neoplasm at high risk of bleeding
    - Known or suspected oesophageal varices
    - Recent brain, head or spinal injury/surgery or ophthalmic surgery
    - Arteriovenous malformation, vascular aneurysm or major intraspinal or intracerebral vascular abnormalities
    - Within 72 hours of major surgery
    - Thrombocytopenia platelets $<50 \times 10^9$/L
- Concomitant treatment with any other anticoagulant

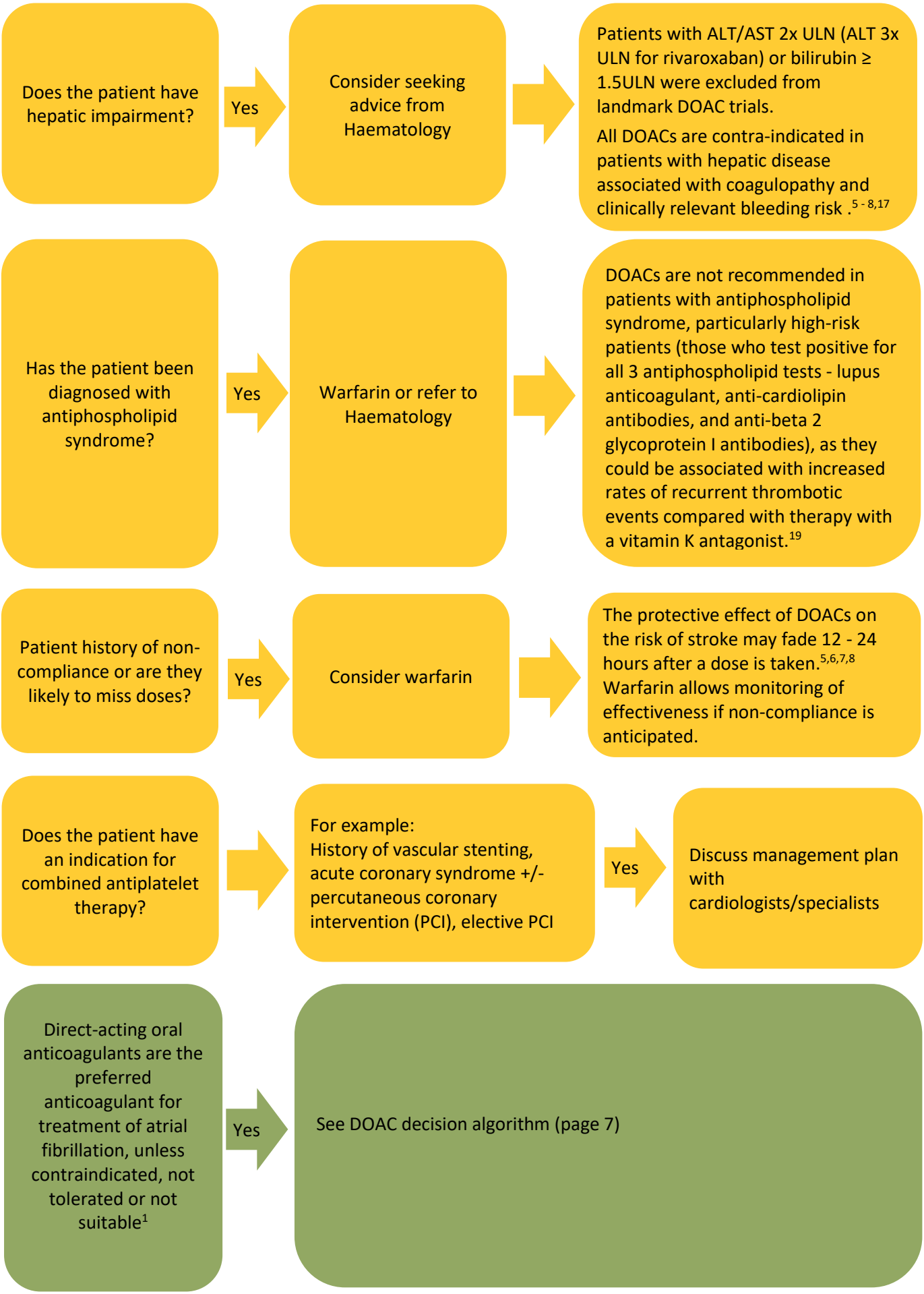
4. Choice of oral anticoagulant based on patient characteristics

NICE CG 196 places direct-acting oral anticoagulants as the preferred anticoagulant for treatment of atrial fibrillation, unless contraindicated, not tolerated or not suitable. When direct-acting oral anticoagulants are contraindicated, not tolerated or not suitable, a vitamin K antagonist may be offered. Those already taking a vitamin K antagonist and are stable may continue with their current medication and discuss the option of switching treatment at their next routine appointment, taking into account the person's time in therapeutic range[1].

NB: Patients should already have been screened for an absolute contraindication to oral anticoagulation as per guidance on page 4.



**The choice anticoagulant for obese patients over 120kg should be discussed with the patient. If a DOAC appears the best choice for a patient, refer to haematology as anti-Xa level monitoring may be required.

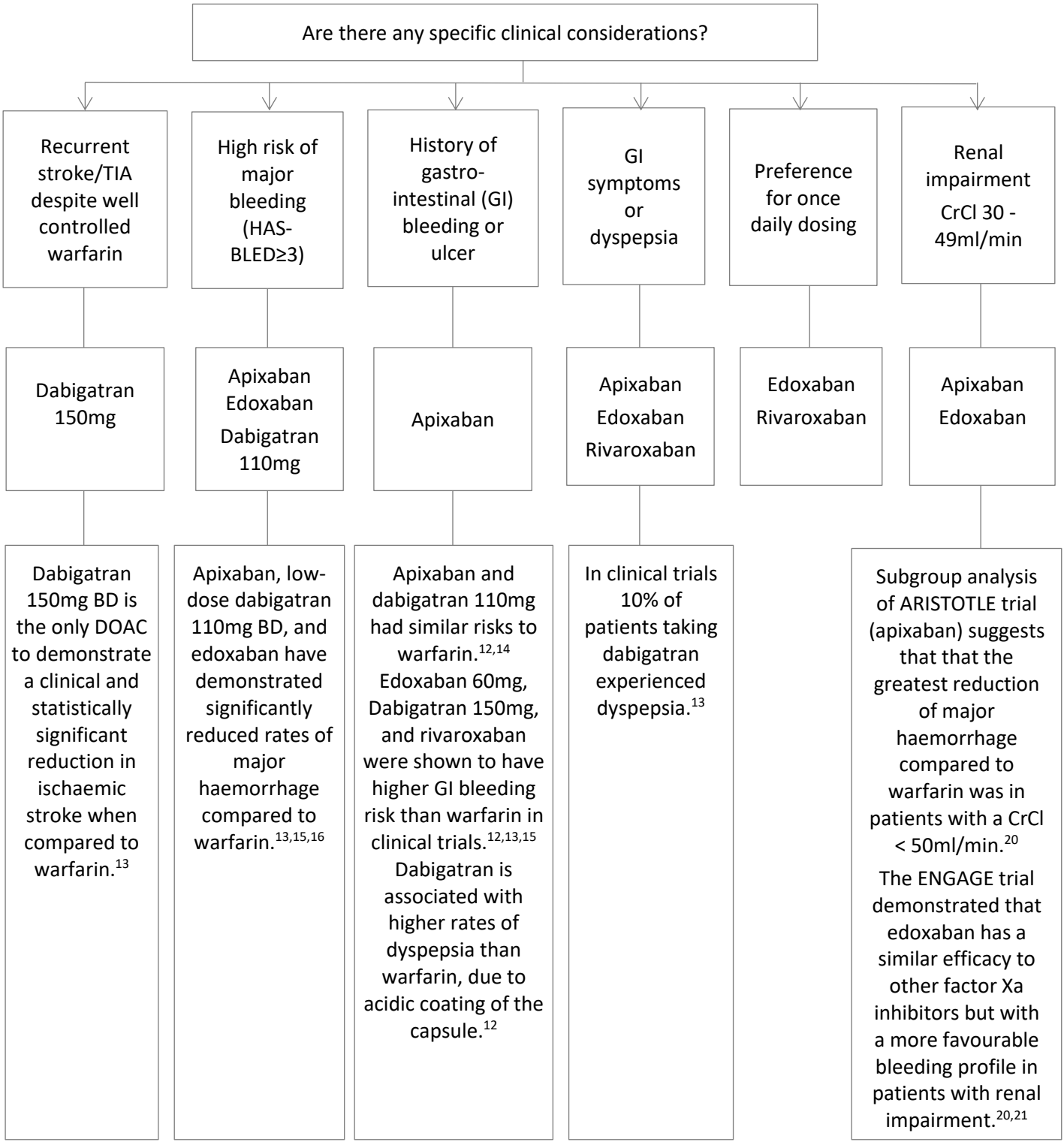

Does the patient have hepatic impairment?
Yes
Consider seeking advice from Haematology
Patients with ALT/AST 2x ULN (ALT 3x ULN for rivaroxaban) or bilirubin ≥ 1.5ULN were excluded from landmark DOAC trials.
All DOACs are contra-indicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk .[5 - 8,17]
Has the patient been diagnosed with antiphospholipid syndrome?
Yes
Warfarin or refer to Haematology
DOACs are not recommended in patients with antiphospholipid syndrome, particularly high-risk patients (those who test positive for all 3 antiphospholipid tests - lupus anticoagulant, anti-cardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies), as they could be associated with increased rates of recurrent thrombotic events compared with therapy with a vitamin K antagonist.[19]
Patient history of non-compliance or are they likely to miss doses?
Yes
Consider warfarin
The protective effect of DOACs on the risk of stroke may fade 12 - 24 hours after a dose is taken.[5,6,7,8] Warfarin allows monitoring of effectiveness if non-compliance is anticipated.
Does the patient have an indication for combined antiplatelet therapy?
For example:
History of vascular stenting, acute coronary syndrome +/- percutaneous coronary intervention (PCI), elective PCI
Yes
Discuss management plan with cardiologists/specialists
Direct-acting oral anticoagulants are the preferred anticoagulant for treatment of atrial fibrillation, unless contraindicated, not tolerated or not suitable[1]
Yes
See DOAC decision algorithm (page 7)

5. Choice of DOAC based on patient characteristics

NB: There have been no head-to-head trials between DOACs. The guidance below is based on indirect comparisons. Dosing advice can be found on page 9.

If there are no specific clinical consideration or patient specific characteristics determining a DOAC choice, use the DOAC of lowest acquisition cost.

For Hertfordshire and West Essex ICS this is apixaban (generic)



6. Choice of DOAC based on patient logistical considerations

Are there any specific logistical considerations?

Need for a monitored dosage system?	→	**Apixaban, edoxaban**, and **rivaroxaban** can be put in monitored dosage systems.	**Dabigatran** capsules should be stored in the original package in order to protect from moisture.[5]
Swallowing difficulties or administration of medicines via enteral tube?	→	**Apixaban** and **rivaroxaban** are licensed to be crushed, dispersed in water and administered via gastric tubes.[6,7] **Edoxaban** tablets can be crushed and administered either via a nasogastric tube or orally mixed in apple puree in patients who are unable to swallow solid oral dose formulations (unlicensed).[22]	**Dabigatran** capsules should not be opened as this leads to increased bioavalibility and potentially increased bleeding.[5]

7. DOAC dosing for stroke risk reduction in non-valvular AF

- NB: The dose guidance below is specific to the use of DOAC therapy for stroke risk reduction in AF. Dosing recommendations for deep vein thrombosis, pulmonary embolism, acute coronary syndrome or post-hip/knee replacement can be found in the individual Summary of Product Characteristics via https://www.medicines.org.uk/emc
- Always check the latest Summary of Product Characteristics https://www.medicines.org.uk/emc for dosage adjustments (e.g. in liver impairment) and drug interactions before prescribing.
- See **page 10** for calculating **creatinine clearance using the Cockcroft-Gault equation for DOAC dose calculation**
- In general, as there is insufficent evidence for efficacy at lower doses for some agents, doses of DOACs should not be reduced unless a dose reduction is clinically indicated as outlined in the table below.

Dabigatran[5]	**Rivaroxaban**[6]	**Apixaban**[7] **FIRST LINE DOAC OF CHOICE**	**Edoxaban**[8]
Standard dose: **150mg TWICE daily**	Standard dose: **20mg ONCE daily**	Standard dose: **5 mg TWICE daily**	Standard dose: **60mg ONCE daily** **(See note below *)**

Reduce dose to:
 	
110mg TWICE daily
 	
If 1 or more of the following risk factors:
• age ≥ 80yrs
• taking verapamil
 	
Or consider reducing based on an individual assessment of the thromboembolic and bleeding risk if the following:
 	
• age 75-80yrs
• CrCl 30-50ml/min
• patients with gastritis, oesophagitis or gastroesophageal reflux
• patients at increased risk of bleeding
	Reduce dose to**:**
	
	15mg ONCE daily
	
	If the following risk factor:
	• CrCl 15 - 49 ml/min
		Reduce dose to:
		
		2.5 mg TWICE daily
		
		If 2 or more of the following risk factors:
		• age ≥ 80 yrs
		• weight ≤ 60kg
		• serum creatinine ≥ 133 micromol/L
		Or
		• CrCl 15 - 29ml/min
			Reduce dose to:
			
			30mg ONCE daily
			
			If 1 or more of the following risk factors:
			• CrCl 15 - 50ml/min
			• weight ≤ 60kg
			• concomitant use of P-gp inhibitors:
			  ○ ciclosporin
			  ○ dronedarone
			  ○ erythromycin
			  ○ ketoconazole

**** A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance (CrCl > 95ml/min) after a careful evaluation of the individual thromboembolic and bleeding risk.[8]***

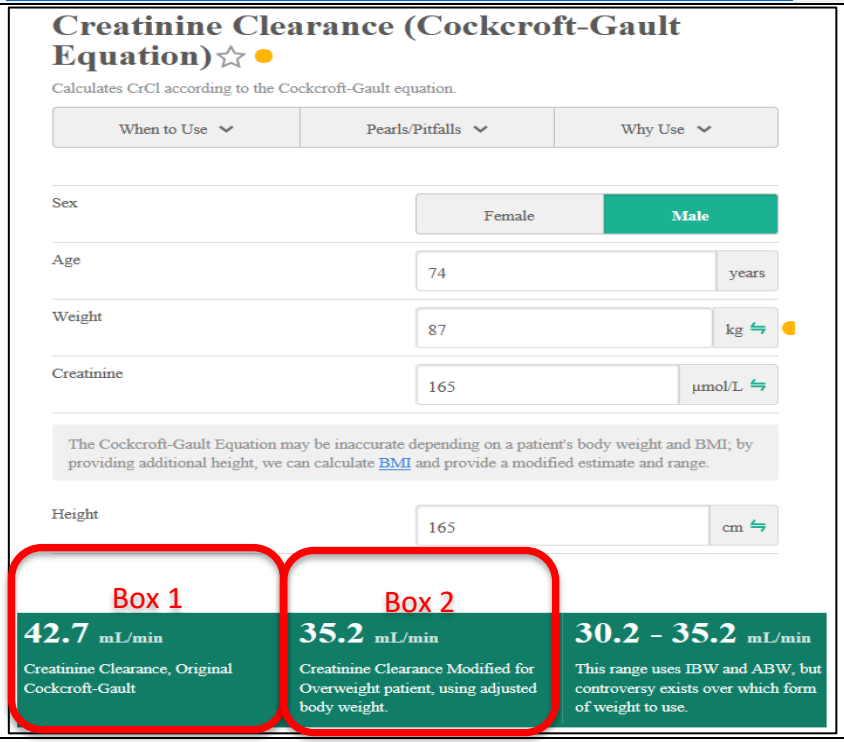
In patients with CrCl > 95ml/min, rivaroxaban has shown numerically, but not statistically significant higher rates of stroke or systemic embolism per 100 patient years compared to warfarin[23] There have been no peer-reviewed phase 3 sub analyses of the efficacy or safety of apixaban or dabigatran compared with warfarin in patients with a CrCl > 95ml/min.[20]

Calculating renal function – Cockroft and Gault formula

The Cockcroft-Gault equation is recommended by the manufacturers of all DOACs for calculating creatinine clearance (CrCl) when prescribing these agents.[5-8] eGFR should not be used, as data suggest it may lead to inappropriate dosing in up to 50% of patients.[24]

Cockcroft-Gault Equation for calculating Creatinine Clearance (CrCl)
CrCl (ml/minute) = $\frac{(140\text{-age}) \times \text{weight}^*}{\text{Serum Creatinine (micromol/L)}}$ x 1.23 (male) or x 1.04 (female)

When calculating CrCl follow the guidance below:

Is Patient:	**What weight should I use?**	**The MD+CALC on line calculator can be used to calculate patients CrCl** https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation	**Which values to use on dose calculator:**	**What about patients on the cusp of a dose change?**
Underweight, normal weight or overweight (BMI <30 kg/m²)	***Actual body weight (kg)***		**Box 1:** Will calculate a CrCl based on patients actual body weight	**Where a patients CrCl places them on the cusp of a dose change it may be particularly important to consider other risk factors such as stroke, bleeding risk, co-morbidities and drug interactions before making a decision.**
Obese or morbidly obese (BMI ≥ 30 kg/m²)	***Adjusted body weight (ABW)(kg)**** **Adjusted body weight = Ideal body weight + 0.4 x (actual body weight – ideal body weight)*		**Box 2:** Will calculate a CrCl based on patients adjusted body weight (ABW)	

***Weight:** The clinical trials of DOACs used actual body weight when estimating CrCl for patients. However the number of patients with obesity within the DOAC trials were small, in addition it is recognised that there are inaccuracies in estimating CrCl using the Cockcroft-Gault equation at extremes of body weight. Therefore for obese or morbidly obese (BMI ≥ 30 kg/m²) patients estimate the CrCl range using adjusted body weight (ABW). This applies an adjustment of 40% of the patient's excess weight over their ideal body weight (IBW). IBW for men = 50 kg + 2.3 kg for each inch over 5 feet and for women IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

8. DOAC monitoring and follow-up

All patients on long-term anticoagulants require a general review at least once a year: [1,11,17]

- Assessment of Stroke and Bleeding Risk
    - Recalculate CHA_2DS_2-VASc and bleeding risk score to confirm if risk/benefit remains unchanged
    - Enquire about the presence of bleeding (Nuisance or Impacting on QOL)
    - Identify and minimise any modifiable risk factors
    - Confirm anticoagulation is still appropriate
- Assess adherence
    - Re-educate on importance of strict intake schedule
    - Identify any side effects, especially those that may be impacting on compliance
- Co-medications
    - Review other medications (inclusive of OTC and herbal medication) for drug interactions
    - See common drug Interactions with DOACs (*Drug interactions with NOACs*)
- Blood sampling and weight
    - Frequency of follow-up blood tests and weight

Patient group	U&Es	Weight	CrCl	FBC	LFTs	BP	Clotting
Baseline (All patients)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CrCl > 60ml/min	Annually	Annually	Annually	Annually	Annually	Annually	INR will not provide information on intensity of anticoagulation effect. INR results for patient on DOACs do not correlate with clinical effect.
Any of the following: Age ≥ 75 years, frail, CrCl 30 - 60ml/min	6 monthly	6 monthly	6 monthly	Annually	Annually	Annually	
CrCl < 30ml/min or an expected decline in renal function	3 monthly	3 monthly	3 monthly	Annually	Annually	Annually	
Intercurrent condition that may impact renal or liver function	If needed	If needed	If needed	If needed	If needed	If needed	

Reassess based on the above whether:

- The chosen OAC/DOAC is the best for the patient
- The chosen dose is correct

9. Warfarin monitoring and follow-up

All patients on long term anticoagulants require a general review at least once a year: [1,11,17]

- **Assessment of Stroke and Bleeding Risk**
  - Recalculate CHA_2DS_2-VASc and bleeding risk score to confirm if risk/benefit remains unchanged
  - Enquire about the presence of bleeding (Nuisance or Impacting on QOL)
  - Identify and minimise any modifiable risk factors
  - Confirm anticoagulation is still appropriate
- **Where suitable, discuss option to switch to a direct-acting oral anticoagulant**
- **Assessing anticoagulation control with warfarin**

  Calculate the person's time in therapeutic range (TTR) at each visit. When calculating TTR:
  - Use a validated measurement method
  - Exclude measurements taken during the first 6 weeks of treatment
  - Calculate TTR over a maintenance period of at least 6 months
- Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:
  - INR values higher than 5 OR 1 INR value higher than 8 within the past 6 months
  - INR values less than 1.5 within the past 6 months
  - TTR less than 65%
- When reassessing, take into account and if possible, address the factors that may contribute to poor control:
  - Patient education
  - Cognitive function
  - Adherence to prescribed therapy
  - Illness
  - Interacting drugs
  - Lifestyle factors including diet and alcohol
  - Inconvenient/inappropriate monitoring arrangements – confirm suitability and consider self-monitoring and self-management arrangements, consider domiciliary monitoring arrangements for those patients with reduced mobility.
- For all patients deemed to have failed on warfarin therapy, establish relevant anticoagulant treatment history. Confirm evidence to support proposed reason for treatment failure, for example:
  - Failed monitoring arrangements – did the patient attend an anticoagulant monitoring service?
  - Labile INR – did the patient achieve a therapeutic INR?
  - Bleeding complications – was the bleed major/ minor? Confirm INR at time of bleed.
  - Drug interactions – any change to concurrent therapy should be considered.
  - Serious ADR – was this documented in patient's records?
  - Severe alopecia – was the patient offered alternative VKA agents?
- If poor INR control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss this with the patient.

10. Communication across secondary/primary care interface - Information to be transferred to GPs

Letters to GPs from secondary care, when anticoagulation has been initiated in secondary care, to include all of the following information:

- Baseline assessment results: CHA_2DS_2-VASc score, ORBIT score, renal function as CrCl, haemoglobin, platelets.
- Discussion with patient/carer:
    - Likelihood of stroke in the individual patient in next year
    - Likelihood of benefit with OAC (NB: It is important that patients/carer understand that there is never 100% certainty that treated patients will not have a stroke).
    - Likelihood of major bleeding in next year
    - Implications of OAC on major bleeding
    - Choice of OAC. (See clinical decision aid)
- Information to be given to patient:
    - Anticoagulant alert card
    - Information for monitoring bleeds
    - Patient leaflet on oral anticoagulants

Appendix 1: DOAC patient counselling checklist

The following should be discussed with all patients started on oral anticoagulation and should be documented in the patient record.

Patient information given[5-8, 17]	√
Explain purpose.	
Dose and frequency.	
Timing of doses. Ensure that rivaroxaban is taken with food.[3]	
Duration of treatment.	
Importance of compliance and what to do if doses are missed – see patient information leaflet	
Explain serious side effects • Bleeding - Seek urgent medical attention if patient develops severe bleeding, e.g. blood in faeces, vomit or sputum, vaginal bleeding. • Advise to seek urgent medical attention if they fall or injure themselves during treatment, especially if they hit their head, due to the increased risk of bleeding. • Unusual headaches.	
Need to inform medical staff that they are taking DOAC if prescribed new medications or surgery /or if invasive procedures (including dental extractions) being planned. Bleeding risk if DOAC started immediately post op.	
Possible interactions with other drugs including herbal remedies - advise patient to read patient information leaflet and discuss with pharmacist or doctor before taking any over the counter remedies.	
Avoid aspirin or NSAIDs (unless clinically indicated)	
Advise patient to seek advice if planning to become pregnant or breastfeed	
Referral to Community Pharmacy New Medicines Service (NMS) – suitable for patients prescribed anticoagulants for the first time	
Monitoring and review: review of treatment and blood tests at least once a year but may be more frequent for some patients **(see monitoring requirements)**	
Alert card and patient information given	

Appendix 2: Switching between oral anticoagulants for non-valvular atrial fibrillation

Consult the Summary of Product Characteristics for each individual anticoagulant for further information.[5-8,11,17]

Switching from	Switching to Warfarin	Dabigatran (Pradaxa)	Edoxaban (Lixiana)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Low Molecular Weight heparin (LMWH)
Warfarin		Discontinue warfarin and start dabigatran: When INR is ≤ 2	Discontinue warfarin and start edoxaban: When INR is ≤ 2.5	Discontinue warfarin and start rivaroxaban: When INR is ≤ 3	Discontinue warfarin and start apixaban: When INR is ≤ 2	Initiate prophylactic or treatment dose LMWH once INR below 2
	INR values may be falsely elevated after the intake of DOACs					
Apixaban (Eliquis)	Commence warfarin in combination with apixaban. Apixaban should be continued for 2 days, after which point INR should be measured prior to each dose of apixaban. Apixaban should be discontinued when INR is ≥ 2.0.	Discontinue apixaban and commence dabigatran at the time that the next dose of apixaban would be due.	Discontinue apixaban and commence edoxaban at the time that the next dose of apixaban would be due.	Discontinue apixaban and commence rivaroxaban at the time that the next dose of apixaban would be due.		Discontinue apixaban and commence LMWH at the time that the next dose of apixaban would be due.
Dabigatran (Pradaxa)	Conversion protocol depends on renal function: For CrCl ≥ 50ml/minute, commence warfarin 3 days prior to discontinuing dabigatran. For CrCl 30-50ml/minute, commence warfarin 2 days prior to discontinuing dabigatran. NB: dabigatran can increase INR. INR measurements should be interpreted cautiously until dabigatran has been stopped for 2 days.		Discontinue dabigatran and commence edoxaban at the time that the next dose of dabigatran would be due.	Discontinue dabigatran and commence rivaroxaban at the time that the next dose of dabigatran would be due.	Discontinue dabigatran and commence apixaban at the time that the next dose of dabigatran would be due.	Discontinue dabigatran and commence LMWH 12-hours after the last dose of dabigatran was administered.
Edoxaban (Lixiana)	Patients on 60 mg dose of edoxaban; administer edoxaban at a dose of 30 mg once daily together with warfarin. Patients 30 mg dose of edoxaban; administer edoxaban at a dose of 15 mg once daily together with warfarin. Measure the INR just prior to the daily dose of edoxaban, continue edoxaban until the INR is ≥ 2.0.	Discontinue edoxaban and commence dabigatran at the time that the next dose of edoxaban would be due.		Discontinue edoxaban and commence rivaroxaban at the time that the next dose of edoxaban would be due.	Discontinue edoxaban and commence apixaban at the time that the next dose of edoxaban would be due.	Discontinue edoxban and commence LMWH at the time that the next dose of edoxaban would be due.
Rivaroxaban (Xarelto)	Commence warfarin in combination with rivaroxaban. Rivaroxaban should be discontinued when INR is in therapeutic range. Measure INR prior to each dose of rivaroxaban being administered.	Discontinue rivaroxaban and commence dabigatran at the time that the next dose of rivaroxaban would be due.	Discontinue rivaroxaban and commence edoxaban at the time that the next dose of rivaroxaban would be due.		Discontinue rivaroxaban and commence apixaban at the time that the next dose of rivaroxaban would be due.	Discontinue rivaroxaban and commence LMWH at the time that the next dose of rivaroxaban would be due.

Switching from	Switching to Warfarin	Dabigatran (Pradaxa)	Edoxaban (Lixiana)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Low Molecular Weight heparin (LMWH)
Low Molecular Weight Heparin (LMWH)	Commence warfarin in combination with LMWH, and monitor INR. Discontinue LMWH once INR in therapeutic range for 2 consecutive days.	Discontinue LMWH and commence dabigatran 0-2 hours before the time that the next dose of LMWH would be due.	Discontinue LMWH and commence edoxaban at the time that the next dose of LMWH would be due.	Discontinue LMWH and commence rivaroxaban 0-2 hours before the time that the next dose of LMWH would be due.	Discontinue LMWH and commence apixaban at the time that the next scheduled dose of LMWH would be due.	

Acknowledgments

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Guidelines adapted for local implementation across Hertfordshire from The East of England Priorities Advisory Committee, Atrial fibrillation anticoagulant clinical decision aid v3.1.

Prescriber Decision Support for Anticoagulating Patients with non-valvular AF Flow diagram adapted from AF (non-valvular): prescriber decision support for anticoagulation, Nottinghamshire Area Prescribing Committee.

Calculating Renal Function – Cockcroft & Gault (C&G) Formula. Section adapted from South London Calculating Creatinine Clearance for DOACs (July 2017).

Version

Version	2.1 Hertfordshire and West Essex guidelines for oral anticoagulation
Title	**Guidelines for oral anticoagulation of patients with non-valvular atrial fibrillation (AF) to prevent stroke in adults**
Developed by	HWE ICB Pharmacy and Medicines Optimisation Team
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