Coventry & Warwickshire Area Prescribing Committee

Clinical Guideline

Direct Oral Anticoagulation for Non-Valvular Atrial Fibrillation in Adults (aged ≥18 years) Guidance

To be used in conjunction with the relevant Summaries of Product Characteristics (SmPCs) or British National Formulary (BNF) for full prescribing information.

New Diagnosis of NVAF

Assess need/suitability for anticoagulation:
Calculate CHA_2DS_2Vasc stroke risk **and** ORBIT-AF or HAS-BLED bleeding risk.
Do not withhold anticoagulation solely based on age or falls risk

DOACs are first line for anticoagulation in AF.
If there are no specific clinical considerations (see below), use Apixaban as preferred choice.

Contraindications

DOACs should not be used in:

- Risk of major bleeding
- Prosthetic mechanical heart valve
- Moderate to severe mitral stenosis
- Antiphospholipid syndrome
- Renal failure (CrCl < 15ml/min or on RRT)
- Pregnancy/breastfeeding
- Concomitant use of medicines which are contraindicated (SmPCs)
- Uncontrolled severe hypertension (systolic>180)
- Concomitant treatment with any other anticoagulant

Circumstances to seek specialist advice:

- Bioprosthetic (tissue) heart valves/repair (excluding TAVI) – within 3 months post-operative
- Active malignancy and/or on chemotherapy
- Planning a pregnancy
- Patients on triple therapy (dual antiplatelet plus anticoagulant)
- Liver impairment
- Complex drug interactions (e.g., antiepileptics, antiretrovirals)
- Patients who have had major bowel surgery e.g., ileostomy.
- Significant bleeding issues, abnormal clotting screen, low Hb with no identifiable cause, menorrhagia.
- Current or previous serious bleed
- Recent VTE (i.e., within the previous three months)

Undertake baseline investigations for DOAC anticoagulation

These parameters should be documented in notes and discharge/clinic letters

Investigation	Seek specialist advice if:
Weight	Extremes of body weight (<40kg or >120kg)
	Body weight affected by significant fluid overload/ limb amputation/ profound muscle loss, especially if renal function is borderline.
FBC	Platelets <100 $x10^9$ /L Low/ unstable Hb
Baseline clotting	APTT >1.5 x ULN, INR >1.4 n.b. PT/APTT/INR should not be used for monitoring drug effect during DOAC therapy as they are not predictable and do not correlate with circulating levels of drug.
LFTs	ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN Child pugh grade B or C
U+Es	CrCl < 15ml/min

Calculate **Creatinine Clearance** using **actual** body weight.
Care with GP clinical systems which may default to ideal body weight

DO NOT USE eGFR - it can overestimate renal function and increase the risk of bleeding events with DOACs[4]

Informed discussion with patient regarding risks and benefits of anticoagulation.
Shared decision to start DOAC.

Initiate Apixaban or Edoxaban as per criteria below

Preferred option (unless exclusions below apply)	**Prescribe Apixaban 5mg bd**
If at least two of: serum creatinine ≥133 micromol/L, age ≥80, body weight ≤60kg	Reduce dose to Apixaban 2.5mg bd
CrCl 15-29 ml/min	Reduce dose to Apixaban 2.5mg bd

Consider **Edoxaban** in patients:

- where adherence is an issue and once daily dosing is preferred
- on concomitant strong inhibitors of CYP3A4 and P-gp inducers (apixaban not recommended) e.g. azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir)

CrCl 50-95 ml/min, weight >60kg	**Prescribe Edoxaban 60mg daily**
Weight ≤60kg	Reduce dose to Edoxaban 30mg daily
On concomitant regular dronedarone, ciclosporin, erythromycin, ketoconazole	Reduce dose to Edoxaban 30mg daily
CrCl 30-49 ml/min	DO NOT use Edoxaban, heavily renally excreted. Seek specialist advice.
CrCl>95 ml/min	DO NOT use Edoxaban, decreased efficacy at high CrCl. Seek specialist advice.

Complete counselling checklist with patient and record in notes.

Follow up within 3 weeks to check tolerance and adherence.
Community pharmacists are ideally placed to do this as part of the New Medicines Service.

Patients should be reviewed at least annually to include:

- Weight, FBC, LFTs and U+Es.
- Creatinine clearance should be re-calculated, and the drug dosage checked against the SPC for that medication.
- Recalculate bleeding risk and review any modifiable risk factors.
- Adherence to therapy should be checked and any side effects discussed.
- Counselling points from checklist should be reinforced.

More frequent monitoring is needed in the following high-risk groups:

- **6 monthly** review is recommended for frail patients and those aged over 75.[6]
- For patients with impaired renal function or high bleeding risk, review is recommended:
  - Every **6 months** for patients with **CrCl 45-60 ml/min**.
  - Every **3 months** for patients with **CrCl less than 45 ml/min**, **ORBIT ≥4** or **HAS-BLED ≥3**.

Notes re: antiplatelets

Combination antiplatelet and anticoagulant therapy significantly increases the risk of bleeding. If patients are on antiplatelet therapy, indication and duration should be reviewed when anticoagulation is initiated and annually thereafter. Gastroprotection should be considered.[6]

Patients on a single antiplatelet post-MI who have not had a cardiovascular event in the past 12 months can usually have antiplatelet therapy stopped;[6] however for more complex patients or other indications (e.g., polycythaemia) it is best to seek advice from a specialist team before altering treatment.

If antiplatelet treatment is for a recent stroke caused by AF it can be stopped once anticoagulation is started[6].

Do not offer aspirin monotherapy solely for stroke prevention to people with AF. The evidence for effective stroke prevention with aspirin in AF is weak, with potential for harm. The risk of major bleeding or intracranial haemorrhage (ICH) with aspirin is not significantly different to that of DOAC, especially in the elderly.

Patient Counselling Checklist

Explain purpose of anticoagulation with DOAC: Avoidance of embolic stroke/peripheral embolisation secondary to AF.	
Inform the patient how to take the medication: • dose and frequency. • duration of therapy (lifelong for NVAF). • swallow tablets whole • if rivaroxaban is prescribed, ensure it is taken with food.	
Emphasise the importance of adherence and what to do if doses are missed: • Edoxaban and rivaroxaban can be taken within 12 hours of missed dose, otherwise omit the missed dose. • Apixaban and dabigatran can be taken within 6 hours of missed dose, otherwise omit the missed dose.	
Explain serious side effects and what to do if they occur: • seek urgent medical attention if patient develops **severe bleeding**, e.g., blood in faeces (dark tarry stools), vomit (coffee ground) or sputum, vaginal bleeding (other than regular period), nose bleeds, bloody urine, severe and spontaneous bruises or new indigestion type symptoms. • 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. • New or persistent **headaches**.	
Explain to patient to inform other health care professionals that they are taking a DOAC if prescribed new medications or if surgery/invasive procedures (including dental extractions) are being planned. The DOAC may need to be stopped before the surgery/procedure.	
Explain 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 (including OTC ibuprofen); consider NSAID gel as alternative for musculoskeletal pain if appropriate.	
Advise patient to seek advice if planning to become pregnant or breastfeed.	
Storage: edoxaban, rivaroxaban or apixaban are suitable for monitored dosage systems. Dabigatran is hygroscopic outside of the original packaging and should only be taken out of the blister pack immediately prior to taking it orally.	
Referral to Community Pharmacy New Medicines Service (NMS) – suitable for patients prescribed anticoagulants for the first time.	
Monitoring and review: advise patient frequency of review of treatment and blood tests: • annually if CrCl >60ml/min • 6 monthly if 45-60 ml/min or age >75 • 3 monthly if CrCl<45 or high bleeding risk.	
Provide patient with an alert card and advise them to carry it with them: • Printable version from ESCardio available here • Manufacturers will provide a card in the packaging with the medication. • NHS information book and alert card available from PCSE/NHS Forms.	

Contact information for anticoagulation specialist nurses

UHCW: 02476 965533

Hospital of St Cross: 01788 663131

George Eliot Hospital: 024 7686 5508

Warwick Hospital: 01926 495 321, EXT: 4493

References:

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Please note, these pathways have been developed for the treatment of adult patients in Coventry and Warwickshire, and this guidance does not override the individual responsibility of healthcare professionals to make decisions in consultation with the patient/carer, individual to their circumstances.

Appendix 1: Assessment of Stroke Risk Using the CHA2DS2-VASC score

Use **CHA_2DS_2Vasc** score to assess stroke risk in people with[1]:

- Symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
- Atrial flutter
- A continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm

Assessment of Stroke Risk for Patients with NVAF

Use CHA_2DS_2Vasc to assess stroke risk https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk		
	CHA_2DS_2-VASc	**Score**
C	**C**ongestive heart failure or left ventricular dysfunction	1
H	**H**ypertension	1
A	**A**ge ≥ 75 years	2
D	**D**iabetes	1
S	**S**troke or TIA	2
V as c	**V**as**c**ular disease (previous MI, peripheral arterial disease, aortic plaque)	1
A	**A**ge 65 -74 years	1
S	**S**ex category female	1
	Total score	

NICE Guidance[1] recommends:

- Offer anticoagulation if **CHA_2DS_2-VASc ≥ 2** (men and women) taking bleeding risk into account.
- Consider anticoagulation if **CHA_2DS_2-VASc =1 (men)**
- Do not withhold anticoagulation therapy solely because of the person's age or their risk of having a fall.

Interpretation of stroke or thromboembolism/100 years at risk in relation to the CHA_2DS_2-VASC score		
CHA_2DS_2Vasc score	**Percentage risk of**	
	Stroke/TIA/ peripheral emboli	**Ischaemic stroke**
0	0.3	0.2
1	0.9	0.6
2	2.9	2.2
3	4.6	3.2
4	6.7	4.8
5	10.0	7.2
6	13.6	9.7
7	15.7	11.2
8	15.2	10.8
9	17.4	12.2

Appendix 2: Assessment of Bleeding Risk Using ORBIT-AF or HAS-BLED

Assessment of Bleeding Risk for Patients with NVAF

Use ORBIT or HAS-BLED bleeding risk score to assess the risk of bleeding in people who are starting or have started anticoagulation[1]. Although ORBIT is the best tool for this purpose, HAS-BLED may need to be used until ORBIT is embedded in clinical pathways and electronic systems.

Offer modification and monitoring of risk factors:

- Uncontrolled hypertension (defined as systolic BP>160mmHg)
- Poor control of international normalised ratio (INR) in patients on vitamin K antagonists
- Concurrent medication (e.g. antiplatelets, SSRIs, NSAIDs)
- Harmful alcohol consumption
- Reversible causes of anaemia

Falls risk is not a contraindication to anticoagulation. Stroke risk rises with age. A study of patients with annual stroke risk of 5% showed that a patient would have to fall 295 times for the risks of subdural haematoma to outweigh the benefits of anticoagulation with warfarin; for DOACs, this number is likely to be even higher.[6] However, modifiable risk factors should be assessed, and consideration given to referral to a falls prevention service.

ORBIT-AF to assess bleeding risk[1,9]
https://www.mdcalc.com/calc/10227/orbit-bleeding-risk-score-atrial-fibrillation

	Risk Factor	Score
O	**O**lder age: ≥75 years old	1
R	**R**educed haemoglobin/haematocrit: history of anaemia or Hb <130 g/L males; <120 g/L females; Hct: <40% males; <30% females	2
B	**B**leeding history	2
I	**I**nsufficient renal function: eGFR <60 mL/min/1.73 m^2	1
T	**T**reatment with an antiplatelet agent	1
	Total score (maximum score 7 points)	
	ORBIT-AF ≥ 4 is a high risk	

HAS-BLED score to assess bleeding risk[1,7]
https://www.mdcalc.com/calc/807/has-bled-score-major-bleeding-risk

	Risk factor	Score
H	**H**ypertension (systolic BP >160mmHg or uncontrolled)	1
A	**A**bnormal liver function (hepatic derangement with bilirubin >2 x ULN and AST/ALP or ALP > 3 x ULN)	1
	Abnormal renal function (serum creatinine ≥200micromol/L, dialysis, transplant)	1
S	**S**troke history	1
B	**B**leeding tendency (prior major bleeding or predisposition to bleeding, **bleeding diathesis, unexplained anaemia**)	1
L	**L**abile INR (Unstable/high INRs, time in therapeutic range <60%)	1
E	**E**lderly (age > 65 years, frail condition)	1
D	**D**rugs (concomitant use of drugs predisposing to bleeding, e.g., aspirin, clopidogrel, NSAIDs)	1
	Alcohol (≥8 drinks/week, alcohol abuse)	1
	Total score	
	HAS-BLED ≥3 is a high risk	

Interpretation of bleeding risk using the ORBIT-AF score[9]		Bleeding risk category
ORBIT-AF score	**Major bleeds per 100 patient/years**	
0-2	2.4	Low
3	4.7	Medium
4-7	8.1	High

Interpretation of bleeding risk using the HAS-BLED score		
HAS-BLED score	**Bleeds per 100 patient-years**	**Risk group**
0	1.13	Relatively low
1	1.02	
2	1.88	Moderate
3	3.72	High
4	8.70	
5	12.50	

Appendix 3: Calculating Creatinine Clearance

Cockcroft and Gault (C&G) Equation for Calculating CrCl

The C&G formula is the preferred method of estimating renal function when prescribing DOACs[2]. It provides an estimate of CrCl (which is not equivalent to eGFR). eGFR can overestimate renal function and increase the risk of bleeding events with DOACs[3].

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age (years)}) \times \text{weight* (kg)}}{\text{Serum creatinine (micromol/L)}} \times \begin{matrix}1.23 \text{ (male) or} \\ 1.04 \text{ (female)}\end{matrix}$$

For **all** DOACs, it is important that this is calculated using the patient's *actual body weight. In clinical trials, actual body weight was used to calculate CrCl for rivaroxaban, apixaban and edoxaban[4]. For Dabigatran, the manufacturer recommends use of ideal body weight for overweight or obese patients[5].

The online calculator MD+CALC can be used to calculate CrCl: https://www.mdcalc.com/calc/43/creatinine-clearance-cockcroft-gault-equation. Note that the units for weight and serum creatinine on this online calculator must be changed to **kg** and **micromol/L** respectively before performing the calculation. There is no need to enter a height when actual body weight is being used.

GP practice systems (Vision and EMIS) can also be used to calculate creatinine clearance, but prescribers must be aware of potential for errors if in calculator defaults to ideal body weight and the potential for under or overdosing patients. If in doubt, check calculation on MDCalc.