Sussex Oral Anticoagulation Pathway for Stroke Prevention in Atrial Fibrillation (AF)

Offer anticoagulation if CHA_2DS_2VASc ≥2 (**consider** anticoagulation if score=1 in men). Discuss risks and benefits of anticoagulation considering co-morbidities and patient preference.
Perform baseline monitoring: FBC/LFT/U&Es/clotting screen. Check body weight (recorded in last 12 months. Calculate Creatinine Clearance (CrCl).
Assess and modify bleeding risk using HAS-BLED or ORBIT score.
Refer to NICE NG186 (2021) Atrial fibrillation: diagnosis and management for further details.

When to use WARFARIN in AF patients
where DOACs are contraindicated:

- Metallic heart valves.
- Renal impairment (CrCl <15ml/min)
- Antiphospholipid Syndrome
- Moderate or severe mitral stenosis
- Severe liver disease
- Significant drug interactions with DOACs*

or if DOACs are not tolerated, not clinically suitable, or patient preference.

*For ' * ' Refer to the FAQ section below*

DOAC in AF patients:

- Use a direct-acting oral anticoagulant (DOAC) as the preferred agent unless contraindicated. (Refer to warfarin box)
- Check DOAC specific cautions or contraindications. Seek specialist advice if unsure (including active cancer, obesity, bleeding history, CKD, hepatic disease associated with coagulopathy, drug interactions) *

1st line EDOXABAN 60mg once a day

Reduce dose to edoxaban 30mg once a day if one or more of:

- CrCl 15-50ml/min
- Concomitant use of the P-glycoprotein inhibitors dronedarone, erythromycin, ciclosporin, ketoconazole
- Body Weight ≤ 60kg

Use with caution if CrCl >95ml/min*

Other considerations:

- Review antiplatelets, NSAIDs, or concomitant use of drugs that increase bleeding risk. Consider gastroprotection in patients who are at higher risk of bleeding.
- Seek specialist advice if prescribing in the extremely obese patient (i.e., >150 kg).
- In pregnancy & breastfeeding LMWH is the preferred choice of anticoagulation.
- Ensure patient has been counselled, provided with relevant written patient information, and has a DOAC card

DABIGATRAN 150mg twice a day

Reduce to dabigatran 110mg twice a day if:
age ≥ 80 yrs. or taking verapamil
Also consider 110mg twice a day based on individual assessment of bleeding risk & thromboembolic if age 75-80yrs or
CrCl 30-50ml/min

RIVAROXABAN 20mg once daily WITH a meal

Reduce dose to rivaroxaban 15mg once a day WITH a meal if CrCl 15-50ml/min

Preferred DOAC in obesity (wt. >120kg) *

APIXABAN 5MG twice a day

Reduce dose to apixaban 2.5mg twice a day if:

- CrCl 15-29ml/min or
- **If TWO** or more of: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 133 µmol/l

Preferred DOAC if high risk of GI bleed*

Frequently Asked Questions
Direct Acting Oral Anticoagulants for Atrial Fibrillation

Background

Atrial fibrillation (AF) is a major risk factor for stroke and contributes to one in five strokes.

Strokes related to AF are often more severe with higher mortality or greater ongoing disability.

Anticoagulation is a key factor in reducing the risk of stroke in patients with AF

This guidance is only for AF patients:

- with symptomatic or asymptomatic paroxysmal atrial fibrillation (PAF), persistent AF permanent AF and atrial flutter.
- awaiting cardioversion or percutaneous ablation (who on the advice of a cardiologist will require peri-procedural anticoagulation).

The NICE Clinical Guideline (NG 196) for Atrial Fibrillation, updated in June 2021, recommends a direct acting oral anticoagulant (DOAC) as the preferred choice of anticoagulation, and only recommends a vitamin K antagonist (e.g. warfarin) in AF patients for whom DOACs are either contraindicated, not tolerated or not suitable for clinical reasons.

Due to the recently published National DOAC Commissioning Recommendations (January 2022), consideration should be given to the prescription of the most cost-effective DOAC within the local health care economy taking into account the individual patient's co-morbidities.

The following information is intended as a guide to support clinical discussions around prescribing the most **cost-effective DOAC for the patient with AF**. The information should be used in conjunction with the summary of product characteristics for the drug, NICE AF guideline, and NICE Clinical Knowledge Summaries (CKS) - Anticoagulation-Oral.
Specialist advice is available to support prescribing decisions.

In addition, the process of selecting an appropriate anticoagulant should be a shared decision between the patient and the prescriber taking into account the patient's risk of stroke, modified bleeding risk, comorbidities, patient preferences, and cost-effectiveness.

Frequently Asked Questions:

- Why are Sussex Commissioners stating a preferred first choice DOAC for AF patients?
- Is this just for new starters or should I be, where appropriate, switch existing patients to edoxaban?
- I am less familiar with edoxaban – what is the dose for the AF patients?
- What about drug interactions with DOACs?
- Dose reduction for AF patients with renal impairment: all DOACs
- Edoxaban and patients with high creatinine clearance (CrCl> 95 ml/minute)
- DOACs in Obesity and Bariatric surgery
- DOAC for patients who have a recurrent stroke or TIA despite seemingly adequate anticoagulation.
- DOAC in patients at high risk of GI bleeding
- Reversal: there is no licensed reversal agent for edoxaban
- How would I switch a patient from warfarin to a DOAC/edoxaban?
- How would I switch a patient from another DOAC to edoxaban?

Why are Sussex Commissioners stating a preferred first choice DOAC for AF patients?
There are no head-to head clinical trials comparing DOACs with one another in AF and the NICE AF guidelines do not recommend a preferred option. Therefore, all four DOACs are available to prescribers who may then select the most appropriate DOAC for their patients.
As a result of the National DOAC Commissioning Recommendations edoxaban is now the most cost- effective choice. Sussex Commissioners are therefore asking prescribers to consider edoxaban if they feel this is clinically appropriate for their AF patients.

Is this just for new starters or should I be, where appropriate, switch existing patients to edoxaban?
The first step is to consider edoxaban (as a preferred option) in AF patients who are new to a DOAC (this will include patients being switched to a DOAC from warfarin).
Edoxaban can also be considered for existing patients when their DOAC prescription is reviewed (i.e., switching) – taking into account any clinical considerations and the patients' preferences.

I am less familiar with edoxaban – what is the dose for the AF patients?
Table 1: Standard AF doses of DOACs and the criteria for dose reduction

Link to DOAC SPC	edoxaban	rivaroxaban	apixaban	dabigatran
Standard dose	**60mg once a day**	**20mg once a day (with food)**	**5mg twice a day**	**150mg twice a day**
Reduced dose	30mg once a day	15mg once a day (with food)	2.5mg twice a day	110mg twice a day
Criteria for dose reduction	**At least ONE of:** Weight ≤ 60kg CrCl 15-50 ml/min On ciclosporin, dronedarone, erythromycin or ketoconazole	CrCl 15 – 49 ml/min	CrCl 15-29 ml/min **or** **at least TWO of:** Age ≥ 80 years Weight ≤ 60kg SCr ≥ 133 micromol/l	Age ≥ 80 years On Verapamil
Caution	CrCl > 95ml/min (See page 3)			Also consider reduced dose if: Reflux/gastritis Age 75 -80 years CrCl 30-50ml/min 'Bleed risk'
Contraindication	CrCl < 15ml/min	CrCl < 15ml/min	CrCl < 15ml/min	CrCl < 30ml/min

SCr = serum creatinine, CrCl = creatinine clearance

Edoxaban, rivaroxaban and apixaban can be crushed and:
- Mixed with water for administration via an enteral tube.
- Mixed with water or apple puree for patients with swallowing difficulties.

What about drug interactions with DOACs?
Common interactions to consider for **all DOACs** are with antiepileptic agents, HIV antiretrovirals, hepatitis antivirals, antifungals, and chemotherapy agents. Some DOACs require a dose adjustment, some require more frequent monitoring and, in some cases a DOAC should not be prescribed in combination with the interacting medicine(s).

Use of any anticoagulation **in combination with anti- platelet(s)** will increase bleeding risk. However, there will be some patients where combined use is advised – including patients who require 'triple therapy' (anticoagulation + dual antiplatelet therapy) for a defined period. If the plan is unclear refer to specialist for further advice.

With specific reference to AF patients who are prescribed **dronedarone** (secondary care initiation only) the preferred DOAC is either apixaban or edoxaban (30mg once a day – see table 1). Rivaroxaban or dabigatran should not be used.

Please refer to the:
British National Formulary (BNF) and Summary of Product Characteristics (SPC) for specific information.
For HIV medications further information may be found via the Liverpool HIV drug interaction checker.
For patients on chemotherapy (including oral chemotherapy) please liaise with the patient's hospital oncology/haematology team.
If unsure always seek specialist advice.

Renal considerations

Dose reduction for AF patients with renal impairment: all DOACs
For all DOACs there is a 'standard dose' and a 'reduced dose'.
The 'reduced' dose should only be prescribed if the specific criteria are met. Refer to Table 1 for more information.

The dosage will need to be selected based on a **calculation of the creatinine clearance (CrCl).** Do not use estimated glomerular filtration rate (eGFR) which may overestimate renal clearance, especially in elderly patients with low body weight/ body mass index. **Actual body weight** should be used to calculate the CrCl.
MDCal (free online/ app) is a useful tool for CrCl calculations.

Edoxaban and patients with high creatinine clearance (CrCl> 95 ml/minute)
A trend towards decreasing efficacy with increasing CrCl was observed for edoxaban (compared to well-managed warfarin) in the ENGAGE- AF trial.
The manufacturers recommend that edoxaban should only be used in patients with AF and CrCl > 95ml/min after a careful evaluation of the individual thromboembolic and bleeding risk.
This is not listed as a caution by the manufacturers of apixaban, dabigatran or rivaroxaban.

DOACs: Obesity and Bariatric surgery

All four DOACs licensed for AF are appropriate for patients with BMI up to 40 kg/m^2 or weight 120 kg. **Rivaroxaban** (or apixaban – less supportive data) is the preferred DOAC for patients with BMI >40 kg/m^2 or weight >120 kg. Please refer to individual product SPC for more information.
The data on the **use of any DOAC in patients >150kg is very limited**.
It is advisable to seek specialist advice from your local Trust Haematologist who will be able to advise on the most appropriate choice of anticoagulation (which may be warfarin).
The Haematologist may recommend measuring peak and /or trough levels of the DOAC and will be able to advise on process and interpretation of results.

Changes in the absorption of DOACs **after bariatric surgery** may result in reduced blood levels. Seek specialist advice prior to initiation or if considering switching between DOACs.

Patients who have a recurrent stroke or TIA despite seemingly adequate anticoagulation.

Although anticoagulation for patients with AF does significantly reduce the risk of stroke or TIA (RRR 67%) the risk remains even in patients who are seemingly appropriately anticoagulated.
Always check patient adherence, appropriate prescription (dose and frequency) of DOAC and recent time in therapeutic range for warfarin when assessing treatment.
Consider prescribing a DOAC with clinical trial evidence for superior efficacy for preventing ischaemic stroke and haemorrhagic stroke (apixaban or dabigatran 150mg twice a day if suitable – see table 1).

Patients at high risk of GI bleeding

Although, compared to warfarin, DOACs reduce the overall risk of bleeding and importantly the rate of intra-cranial haemorrhage they do increase the risk of GI bleeding (compared to warfarin). GI bleeding is rarely fatal but may result in significant (short term) morbidity.
For patients at high risk of GI bleeding consider apixaban BD or dabigatran 110mg BD.
If uncertain seek specialist advice

Reversal: there is no licensed reversal agent for edoxaban

Outcomes of major bleeds with DOACs are no worse than those with warfarin even in the absence of a specific reversal agent. Due to the short half-life of DOACs in many cases withholding the medication and supportive care will be sufficient. Haematology and emergency departments will advise/treat patients with significant bleeding.
Although DOACs have been used now for several years it was not until May 2021 NICE approved andexanet alfa (TA697) (hospital only) as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding – but only if the bleed is in the gastrointestinal tract. Use in the management of ICH is only permitted as part of a research trial.
Edoxaban is not included by NICE as there were insufficient patients in the clinical trial programme who were taking edoxaban.
It is anticipated that in clinical practice andexanet alfa will have a limited role to play.

Idarucizumab for the rapid reversal of dabigatran (hospital only) has been available since 2016.

Switching to a DOAC /edoxaban from warfarin

How would I switch a patient from warfarin to a DOAC/edoxaban?
The patient's **current INR** is needed.
Check baseline bloods: renal function, full blood count and liver function tests (use results from last 3 months if stable).
Check up-to date weight (needed to calculate CrCl)

The manufactures of the DOACs recommend different INRs for the AF patients at which to initiate DOACs **after stopping warfarin**:

- apixaban and dabigatran: Start when INR < 2
- edoxaban: Start when INR < 2.5
- rivaroxaban: Start when INR < 3

This approach may require repeat INR checks daily until the required INR is achieved.

The EHRA guidance (2021) gives more pragmatic guidance on when to start DOACs after stopping warfarin:

- If INR < 2.0 commence DOAC that day
- If INR between 2 and 2.5: commence DOAC the next day
- If INR between 2.5 and 3: withhold warfarin for 24-48 hours and then initiate DOAC

Repeat INR testing will be required for higher INRs as the time for the INR to fall can vary between patients.

Ensure that warfarin is removed from the patient's prescription, that the service providing INR monitoring for the patient is informed that warfarin has been discontinued and that the patient understands that this is ***instead of*** warfarin (not as well as).

How would I switch a patient from another DOAC to edoxaban?
Once you have decided that edoxaban is a clinically appropriate choice for your patient and you have discussed the switch with the patient, select the correct edoxaban dose (table 1) using up-to date weight and renal function to calculate the creatinine clearance.
Discontinue the initial DOAC (apixaban, dabigatran, or rivaroxaban), and start edoxaban when the next dose of the initial DOAC (apixaban, dabigatran, or rivaroxaban) is due.

Ensure that the initial DOAC (apixaban, dabigatran, or rivaroxaban) is removed from the patient's repeat prescription and that the patient understands the dose and frequency of the newly prescribed edoxaban and that is ***instead of*** the previously prescribed DOAC (not as well as).