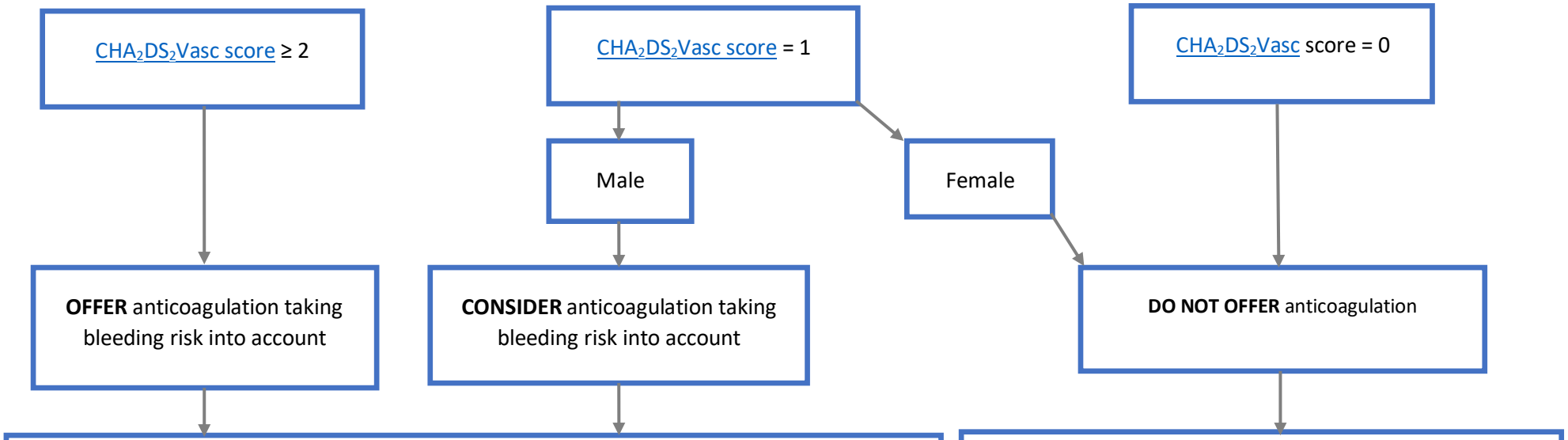
Bath and North East Somerset, Swindon and Wiltshire Clinical Commissioning Group

BSW Formulary

Anticoagulation in non-valvular atrial fibrillation (NVAF): Guidance for prescribers

Flowchart 1. Assessing stroke risk



For most people benefit of anticoagulation outweighs risk.

For people with an increased risk of bleeding (ORBIT ≥ 4) the benefit of anticoagulation may not always outweigh the bleeding risk – careful monitoring of bleeding risk is important

For people with increased bleeding risk address any modifiable risk factors such as: uncontrolled hypertension, concurrent medication (NSAIDs, aspirin), harmful alcohol consumption

Do not withhold anticoagulation solely because the person is at risk of falls

Consider prophylactic PPI for patients at high risk of GI bleeding such as patients with previous history of peptic ulcers, previous gastritis, oesophagitis, reflux, concurrent aspirin, clopidogrel or NSAIDs and patients aged 65 or over.

Move to flowchart 2 for decision making on choice of anticoagulant

Patient is not a candidate for anticoagulation based on above assessment or patient refuses treatment.

Document outcome of assessment or patient decision in patient record.

Review annually or when patient reaches 65 or develops any of the following at any age:

Hypertension
Diabetes mellitus
Heart failure
Peripheral vascular disease
Coronary artery disease
Stroke/TIA/systemic arterial embolism

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Flowchart 2. Decision making on choice of anticoagulant (exclusions) *

Notes

*All patients should be involved in a shared decision-making dialogue about the risks and benefits of anticoagulation. Further decision support tool can be found: https://www.anticoagulation-dst.co.uk

START HERE: Does the patient have a contra-indication to a DOAC? (See below)

- Mechanical heart valve
- Moderate/severe mitral stenosis
- Known hypersensitivity or intolerance to DOACs (Discuss with specialist if needed to review appropriateness in trying alternative DOACs)
- Antiphospholipid syndrome (Refer patient to Haematology)
- Pregnancy/ breast feeding
- Hepatic disease associated with coagulopathy
- Presence of malignant neoplasm at high risk of bleeding or significant risk of major bleeding (discuss with Haematology or Oncology)
- Recent brain or spinal injury
- Recent brain, spinal or ophthalmic surgery
- Known or suspected esophageal varices

Note this list is non exhaustive, please refer to product SmPC for further information

YES

Consider **warfarin** or **LMWH** or **no anticoagulation** (seek specialist advice where needed) (**LMWH** in pregnancy)

NO

Does the patient have an indication for combined antiplatelet therapy such as acute coronary syndrome +/- PCI or history of vascular stenting

YES

Discuss management plan with cardiologist or specialist

NO

Does the patient have hepatic impairment with ALT/AST 2 x ULN or bilirubin ≥ 1.5 ULN?

YES

Consider **warfarin** or discuss with Haematology. Note all DOACs are contra-indicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk

NO

Consider DOAC

Move to flowchart 3 for decision making on choice of DOAC

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Flowchart 3. Anticoagulant treatment options Part A

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Patient assessed as eligible for DOAC (see previous flowchart 1 and 2)

Edoxaban is first line choice of DOAC for NVAF **other than those patients at increased risk of GI bleeding***, **a CrCL of <30ml/min or >95ml/min**, with a **previous intolerance to edoxaban** or **on the advice of a specialist**

CrCL < 15ml/min – DOACs are contraindicated, consider **warfarin**

The licensed doses for all DOACs should be calculated using the Cockcroft Gault method of determining creatinine clearance (CrCl)
(See https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation)
There is a lack of available data on whether using adjusted or ideal body weight when calculating CrCl in patient with extreme weight. Seek specialist for further advice on appropriate dosage.

CrCL >95ml/min – consider alternative DOAC or **warfarin**

Notes

* Risk factors for Gastro-intestinal (GI) bleeding:
- Concurrent use with aspirin, clopidogrel, SSRI/SNRIs or NSAIDs
- Current or history of peptic ulcer, GI hemorrhage or gastritis
(Consider **apixaban**, see **flowchart 4**)

Stomach upset, non-ulcer dyspepsia, indigestion, gastro reflux disease is not part of the exclusion criteria.

** Reduce to 30mg OD if concurrent prescription with strong P-glycoprotein inhibitor and CYP 450 3A4 enzyme i.e., ciclosporin, dronedarone, erythromycin, ketoconazole. Consult BNF for further drug interaction and dosing guidance.

CrCL 15 - 29ml/min → **Apixaban 2.5mg BD**

CrCL 30 - 49 ml/min → **Edoxaban 30mg OD**

CrCL 50 - 95ml/min
- Weight > 60kg → **Edoxaban 60mg OD ****
- Weight ≤ 60kg → **Edoxaban 30mg OD**

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Flowchart 4. Anticoagulant treatment options Part B

Notes

For patients unlikely to comply with BD dosing consider **edoxaban** (if no previous intolerance) or **rivaroxaban** considering risks *vs* benefits.

Andexanet alpha is currently licensed and approved by NICE for the reversal of life-threatening GI bleeding with apixaban and rivaroxaban only.

Consider **warfarin** as another alternative in patients with significant intolerance to edoxaban or multiple DOACs. Discuss with a specialist if needed, Specialist Anticoagulant advice can be obtained from our local hospital:

GWH:

gwh.anticoag.clinic@nhs.net or sarah.bond6@nhs.net

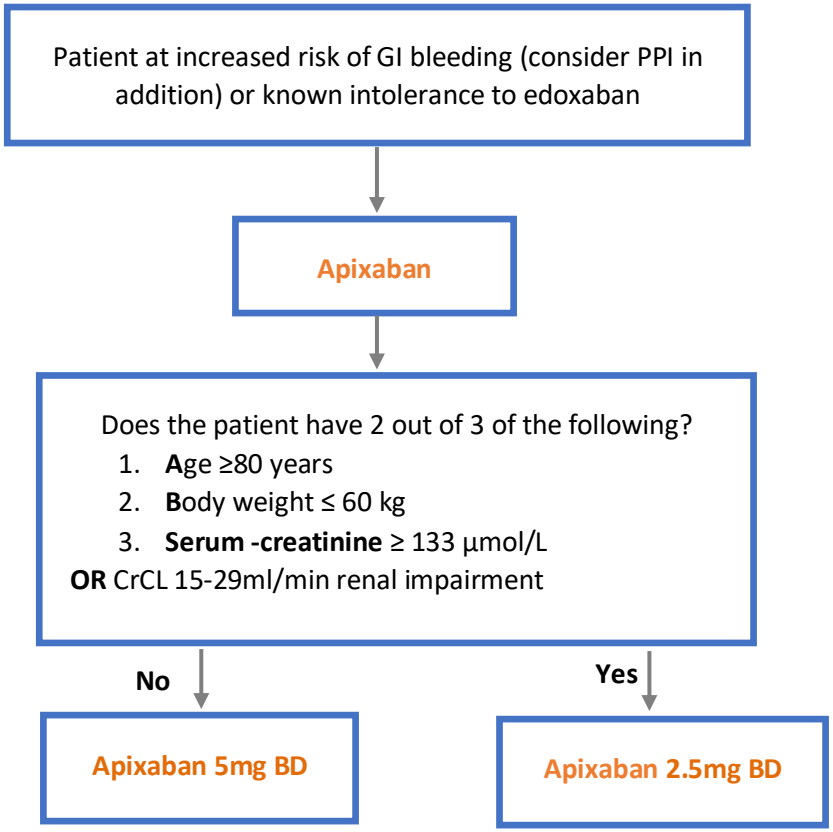
Tel: 01793 604344

RUH:

ruh-tr.AnticoagulationTeam@nhs.net or nathan.hutchinson-jones@nhs.net or via Cinapsis.

SFT:

nicolamcquaid@nhs.net or sft.anticoagulation.service@nhs.net



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Appendix note to accompany the decision algorithm: Switching between anticoagulants in non-valvular atrial fibrillation (NVAF)[1,2]

From / To	Warfarin	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Warfarin	**This advice applies to patients with normal renal function.** In patients with renal impairment, higher than therapeutic plasma concentrations are expected and a longer interval may be required, seek specialist advice. **When switching TO warfarin do a baseline INR before starting warfarin - if baseline already high then discuss with a specialist or anticoagulant clinic for advice.**	Stop – start when INR ≤3.0.	Stop – Start as soon as INR is <2.0	Stop – Start as soon as INR is <2.0	Stop – Start when the INR is ≤ 2.5
Rivaroxaban	Commence warfarin in combination with rivaroxaban. Rivaroxaban should be discontinued when INR is in therapeutic range (normally ≥2). Measure INR prior to each dose of rivaroxaban being administered & 24hrs after rivaroxaban is stopped.		Stop – Start	Stop – Start	Stop – Start
Apixaban	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.	Stop - Start		Stop - Start	Stop - Start
Dabigatran	**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.	Stop - Start	Stop - Start		Stop - Start
Edoxaban	If on 60 mg dose, give 30 mg edoxaban OD plus an appropriate warfarin dose.If on 30 mg dose, give 15 mg edoxaban OD plus an appropriate warfarin dose. Patients should not take a loading dose of warfarin in order to promptly achieve a stable INR between 2 and 3. Once an INR ≥ 2.0 is achieved, Edoxaban should be discontinued. Most patients (85%) should be able to achieve an INR ≥ 2.0 within 14 days of concomitant administration. After 14 days it is recommended that edoxaban is discontinued and the warfarin continued to be titrated to achieve an INR between 2 and 3. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least 3 times just prior to taking the daily dose of edoxaban to minimise the influence of edoxaban on INR measurements. See SPC for further details.	Stop - Start	Stop - Start	Stop - Start	

Stop – Start = Discontinue original and commence new treatment at the time that the next scheduled dose of original drug would be due.

Caution: DOAC's half-life can be increased in a patient with severe impaired renal function, consult specialist advice on switching between anticoagulants.

Ensure patient is counselled on new anticoagulant including indication, side effects, precautions and an **anticoagulation alert card** is given with written information. Refer to community pharmacy for **new medicines service** (NMS).

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- Annually or more frequently if clinical concerns
    - Full blood count
    - Liver function tests
    - Urea and electrolytes
    - Weight and Serum creatinine (for creatinine clearance)

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

Suggested process for safe switching from warfarin to a DOAC[3]

Is a switch to a DOAC appropriate?

A switch from warfarin to a DOAC should **not** be considered for patients:

- With a prosthetic mechanical valve
- With moderate to severe mitral stenosis
- With antiphospholipid antibody syndrome (APLS)
- Who are pregnant, breastfeeding or planning a pregnancy
- Requiring a higher INR than the standard INR range of 2.0 – 3.0
- With severe renal impairment - Creatinine Clearance (CrCl) < 15ml/min
- With active malignancy/ chemotherapy (unless advised by a specialist)
- Prescribed interacting drugs – check SPCs (links below) for full list
    - Some HIV antiretrovirals and hepatitis antivirals - check with HIV drug interactions website at https://www.hiv-druginteractions.org/
    - Some antiepileptics- phenytoin, carbamazepine, phenobarbitone or rifampicin are likely to reduce DOAC levels so should be discussed with an anticoagulation specialist
- On triple therapy (dual antiplatelet therapy plus warfarin) without discussing with an anticoagulant specialist or cardiologist
- When switching to a DOAC, care should be taken to follow the recommendations in the relevant SmPC

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Warfarin to DOAC switch in non-valvular atrial fibrillation

For adults with AF who are already taking a vitamin K antagonist and are stable, continue with their current medication and the option of switching treatment should be discussed at their next routine appointment, where clinically appropriate. Considering the person's time in therapeutic range (TTR), reassess anticoagulation for person whose anticoagulation is poorly controlled, shown by any of the following:

Two INR values >5 or one INR value >8 within the past 6 months
Two INR values <1.5 within the past 6 months, or TTR <65%

Pragmatic approach to stopping warfarin and starting DOAC in relation to the INR SmPCs recommend different INRs at which to initiate DOACs after stopping warfarin. This approach would require repeat INR checks daily until the required INR is achieved.

The European Heart Rhythm Association practical guide gives pragmatic guidance on when to start DOACs after stopping warfarin:[4]
• If INR less than 2: commence DOAC that day
• If INR between 2 and 2.5: commence DOAC the next day (ideally) or the same day
• If INR between 2.5 and 3: withhold warfarin for 24-48 hours and then initiate DOAC

Suggested checklist for safe switching from warfarin to a DOAC[3]
1. Check clinical system for recent U&Es, LFTs and FBC
2. At next INR visit – check INR, record weight, take bloods if not already available or are unstable
3. Calculate creatinine clearance (CrCl)
4. Prescribe DOAC at appropriate dose and advise patient to obtain supplies
5. Advise patient when to stop warfarin in relation to starting DOAC
6. Provide written instructions and involve family members/carers where possible to minimise the risk of patients taking both warfarin and the DOAC concurrently. Particular care should be taken where patients are using medication compliance aids to minimise the risk of incorrect dosing
7. Provide an up-to-date Anticoagulant Alert card
8. Inform community nursing teams if they have been monitoring INR or administering warfarin

References

1. Medicines Management NHS Wiltshire CCG. January 2018 update. Adapted with permission from Gloucester Hospitals NHS Foundation Trust
2. Summary of Product Characteristics (SmPC) - (Emc)." Eliquis 5 Mg Tablets, Lixiana 60mg Tablets, Pradaxa 150 Mg Capsules, Xarelto 20mg Tablets, *Medicines.org.uk*, 2019, www.medicines.org.uk/emc. Accessed 14 Apr. 2022.
3. Williams, Helen. *Guidance for the Safe Switching of Warfarin to Direct Oral Anticoagulants (DOACs) for Patients with Non-Valvular AF and Venous Thromboembolism (DVT / PE) during the Coronavirus Pandemic*. Royal College of General Practitioners, 2020. Accessed 14 Apr. 2022.
4. European Society of Cardiology. "Novel Oral Anticoagulants for Atrial Fibrillation." *Escardio.org*, 2018, www.escardio.org/Guidelines/Recommended-Reading/Heart-Rhythm/Novel-Oral-Anticoagulants-for-Atrial-Fibrillation. Accessed 14 Apr. 2022

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DOAC Counselling Checklist[3]

Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®), Rivaroxaban (Xarelto®)

DOAC Agent Counselled: ……

Counselling points	Sign
Explanation of an anticoagulant (increases clotting time and reduces risk of clot formation) **and explanation of indication for therapy** (AF and stroke risk reduction/DVT/PE)	
Differences between DOAC and warfarin *(if applicable for patients converting from warfarinto DOAC therapy or offering choice of anticoagulation agent)* • No routine INR monitoring • Fixed dosing • No dietary restrictions and alcohol intake permitted (within national guidelines) • Fewer drug interactions	
Name of drug: generic & brand name	
Explanation of dose: strength & frequency	
Duration of therapy: lifelong for AF or explain course length for DVT / PE treatment orprevention	
To take with food (dabigatran and rivaroxaban). Not required for apixaban or edoxaban	
Missed doses: • **Apixaban and dabigatran can** be taken within 6 hours of missed dose, otherwiseomit the missed dose • **Edoxaban and rivaroxaban** can be taken within 12 hours of missed dose, otherwiseomit the missed dose	
Extra doses taken: obtain advice immediately from pharmacist/GP/NHS Direct (111)	
Importance of adherence: short half-life and associated risk of stroke and/or thrombosis if non-compliant	
Common and serious side-effects and who/when to refer: symptoms of bleeding/unexplained bruising. Avoidance of contact sports. • Single/self-terminating bleeding episode – routine appointment with GP/pharmacist • Prolonged/recurrent/severe bleeding/head injury – A&E Major bleeds managed/reversed by supportive measures, Prothrombin ComplexConcentrate (PCC), and availability of antidote	
Drug interactions and concomitant medication: avoid NSAID's. Always check with a pharmacist regarding OTC/herbal/complimentary medicines	
Inform all healthcare professionals of DOAC therapy: GP, nurse, dentist, pharmacist i.e. prior to surgery	
Pregnancy and breastfeeding: potential risk to fetus – obtain medical advice as soon as possible if pregnant/considering pregnancy. Avoid in breastfeeding	
Storage: dabigatran must be kept in original packaging – moisture sensitive. All other DOAC are suitable for standard medication compliance aids/ dosette boxes if required	
Follow-up appointments, blood tests, and repeat prescriptions: where and when	
Issue relevant patient information AF booklet/leaflet and anticoagulant patient alert card	
Give patient opportunity to ask questions and encourage follow up with community pharmacist (NMS – New Medicine Service)	

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