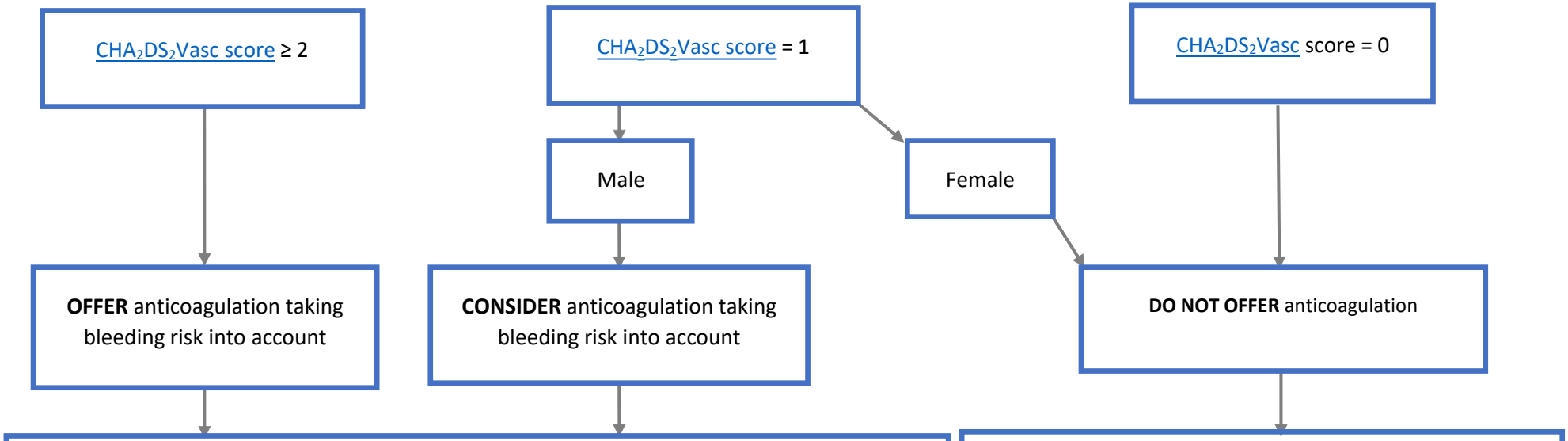
BSW Formulary

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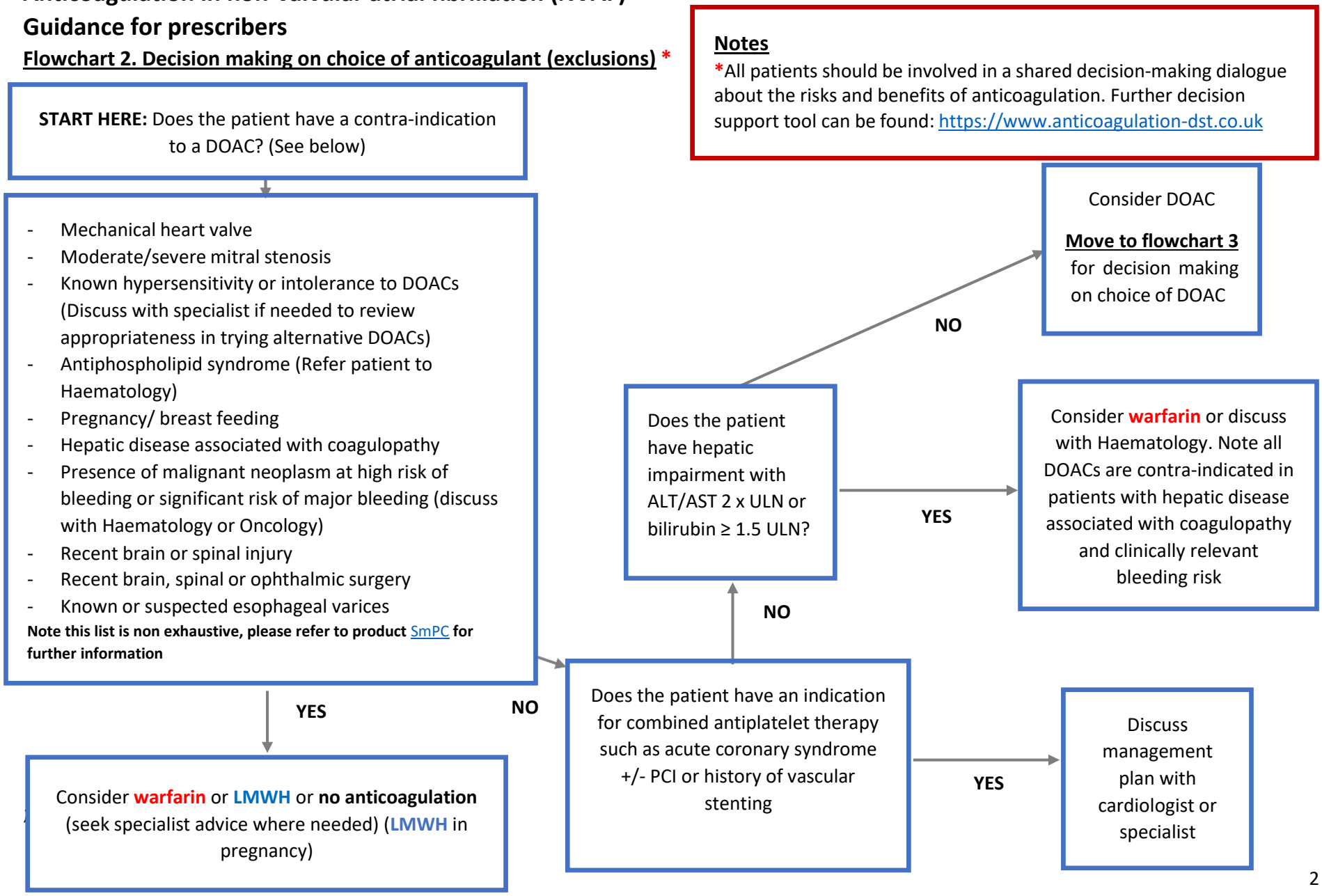
Flowchart 2. Decision making on choice of anticoagulant (exclusions) *



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NHS
Bath and North East Somerset, Swindon and Wiltshire
Integrated Care Board

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Flowchart 3. Anticoagulant treatment options

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

For new initiation: **Apixaban** is first line choice of DOAC for NVAF **other than those patients with a previous intolerance to apixaban** or **on the advice of a specialist**

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)
Seek advice from your local Anticoagulant Specialist in the event of any uncertainty regarding which dose is best to use.

CrCl <15ml/min DOACs are contraindicated consider warfarin

Does the patient have 2 out of 3 of the following?

1. **A**ge ≥80 years
2. **B**ody weight ≤ 60 kg
3. **Serum -creatinine** ≥ 133 µmol/L

OR CrCL 15-29ml/min renal impairment

Yes → **Apixaban2.5mg BD**

No → **Apixaban 5mg BD**

Notes

Drug Interaction:
The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir)
ConsultBNF for further drug interaction and dosing guidance.

Missed dose:
If a dose of apixaban is not taken at the scheduled time, the dose should be taken as soon as possible if within 6 hours of missed dose and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

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

Discuss with a specialist if needed, Specialist Anticoagulantadvice can be obtained from our local hospital:

GWH: gwh.anticoag.clinic@nhs.net or sarah.bond6@nhs.netTel: 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 DOAC prescribing in non-valvular atrial fibrillation (NVAF)

DOAC Prescribing Dosing Table for Non-Valvular AF (NVAF)

DOAC	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Dosing in Non-valvular AF	Prescribe Apixaban 5mg twice daily Reduce dose to 2.5mg twice daily if at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromol/l or if exclusive criteria of CrCl 15 - 29 ml/min.	Prescribe Edoxaban 60mg once daily Reduce dose to 30mg once daily if: Body weight <61kg, or CrCl< 50ml/min, or co-prescribed with ciclosporin, dronedarone, erythromycin or ketoconazole.	Prescribe Rivaroxaban 20mg once daily Reduce dose to 15mg once daily if CrCl< 50mL/min in NVAF patients only.	Prescribe Dabigatran 150mg twice daily if aged <75 years, CrCl> 50mL/min, low risk ofbleeding (weight <50kg with close clinical surveillance) Reduce dose to 110mg twice daily if aged > 80 years or prescribed verapamil. Consider 110mg twice daily based on individual assessment of thrombotic risk and the risk of bleeding in patients aged between 75 and 80years or with CrCl <50mL/min or with increased risk of bleeding (including gastritis, oesophagitis, gastro-oesophageal reflux).
Contraindicated / Not recommended	CrCl <15ml/min	CrCl <15ml/min	CrCl <15ml/min	CrCl <30ml/min
Cautions **See also individual SPCs**		CrCl >95ml/min	CrCl <30ml/min. Take with or after food (15mg and 20mg doses).	Do not use in a standard medication compliance aids (MCA)
Interactions **Check BNF:** www.bnf.org **SPC:** www.medicines.org.uk	Ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir - not recommended (See SPC for full details) Rifampicin, phenytoin, carbamazepine, phenobarbital, St.John's Wort – use with caution.	Rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort – use with caution Ciclosporin, dronedarone, erythromycin, ketoconazole – reduce dose as above. (See BNF and SPC for edoxaban for further information)	Ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, dronedarone – not recommended (See SPC for full details) Rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort – Should be avoided.	Ketoconazole, ciclosporin, itraconazole, tacrolimus, dronedarone - contraindicated (See SPC for full details) Rifampicin, St John's Wort, carbamazepine, phenytoin –should be avoided. Amiodarone, quinidine, ticagrelor, posaconazole – use with caution. Verapamil (use reduced dose). Antidepressants: SSRIs and SNRIs- increased bleeding risk

Reference: Table adapted from PCPA Guidance on Prescribing Anticoagulation in NVAF

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Switch between anticoagulant for Non-Valvular AF (NVAF)

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).

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	

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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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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]

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 warfarin to DOACtherapy 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 or prevention	
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, otherwise omit themissed dose • **Edoxaban and rivaroxaban** can be taken within 12 hours of missed dose, otherwise omit themissed 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 ifnon-compliant	
Common and serious side-effects and who/when to refer: symptoms ofbleeding/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 aspossible if pregnant/considering pregnancy. Avoid in breastfeeding	
Storage: dabigatran must be kept in original packaging – moisture sensitive. All other DOACare 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)	

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

DOAC Agent Counselled: ……..……

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