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KEY QUESTIONS

Anticoagulation

Cardiovascular specialists **Professor Ahmet Fuat** and **Dr Paul Ferenc** answer key questions on the management of anticoagulation in general practice

Q When might warfarin be the anticoagulant of choice instead of a direct-acting oral anticoagulant (DOAC)?

A In the latest NICE guidelines on atrial fibrillation (AF), DOACs are the preferred choice if anticoagulation is indicated.[1] NICE recommends we offer anticoagulation with a DOAC to adults with non-valvular AF (NVAF) and a CHA2DS2VASc score of 2 or above, and consider anticoagulation with a DOAC in men with AF and a CHA2DS2VASc score of 1, taking into account the risk of bleeding.

There are certain groups in which a vitamin K antagonist (such as warfarin) is still indicated. This includes patients with mechanical heart valves (those with bioprosthetic heart valves do not require anticoagulation unless there are other factors), moderate to severe mitral stenosis (usually due to rheumatic fever) and antiphospholipid syndrome. In addition, as renal clearance accounts for the majority of total DOAC clearance, warfarin is preferred if the creatinine clearance (CrCl) is less than 15ml/min. DOACs are also contraindicated in patients planning pregnancy, or who are pregnant or breastfeeding.

Warfarin is still recommended if the INR target is outside the usual range of 2-3, such as for patients with recurrence of deep vein thrombosis (DVT) or pulmonary embolism (PE) while receiving anticoagulation with an INR greater than 2, and advice should be sought from the specialist team in patients with venous thrombosis at unusual sites, a left ventricular thrombus or more unusual conditions such as non-compaction cardiomyopathy, as there are limited data in these conditions. Patients with active malignancy or on chemotherapy, or on certain medications including some antiepileptics, antiretrovirals and antivirals, should also be discussed with their specialist.

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Q What advice would you give for GPs to manage the transition from warfarin to a DOAC?

A The NICE AF guidelines recommend that all suitable patients on warfarin be considered for a switch to DOAC at review. In England, this is incentivised through the Network Contract DES Investment and Impact Fund (IIF).[2]

The patient should be counselled about the benefits of DOACs, adherence to medication and also the importance of reporting any new medications to the clinician. The DOAC should be available to start once their INR is within the specified range. This varies depending on the particular drug.

The European Heart Rhythm Association (EHRA) provides pragmatic advice on switching from a vitamin K antagonist to any DOAC based on the INR.[3] In summary, the INR should be taken the day the vitamin K antagonist is stopped and depending on the result the DOAC can be started that day, over the next two days or after further INR checks as required (see box 1, right).

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Q What are the key differences between the DOACS?

A There have not been any head-to-head trials comparing the DOACs and NICE recommends using any of the four available. There are, however, variations in dosing and monitoring recommendations according to renal function, age, weight and drug interactions (see box 2, page 28).

Also, there are now commissioning recommendations for clinicians to use edoxaban first line for anticoagulation in NVAF where clinically appropriate. If edoxaban is not appropriate or is contraindicated, clinicians should use rivaroxaban as second preference, then apixaban or dabigatran. There is a procurement deal whereby edoxaban is seen to offer best value to the NHS financially, and rivaroxaban second-best value. In England, the preferential use of edoxaban is also now incentivised through the IIF.[2,4] For patients already prescribed a DOAC, there are likely to be local policies to facilitate review and switching to edoxaban if appropriate. The process poses challenges for practices; it is important to explain to the patient that the evidence shows edoxaban is as effective as the other DOACs. In addition, the once-a-day preparation may differ from their previous regime. Ensure the prescription is available to start edoxaban the day after the last dose of previous DOAC; advise patients to take the evening dose of a twice-daily preparation the day before the change. Note that the IIF pertains to patients with NVAF, not VTE, and there may be situations where an alternative DOAC is used – for example, 15mg rivaroxaban may be used with an antiplatelet following a cardiac event. In acute VTE, edoxaban should only be used after at least five days of parenteral anticoagulant.

Q What monitoring do DOACS require, and how often?

A DOACs require monitoring. A baseline FBC and renal and liver function tests should be taken, and repeated at least on an annual basis unless there are any concerns necessitating earlier review.

DOACs require CrCl measurement to determine the correct dose (not interchangeable with eGFR). Often your clinical system will have a template for this – weight and age are also required and these should be checked on an annual basis.

Patients aged under 75 with CrCl greater than 60ml/min should be reviewed at least annually, while a six-monthly review is required if CrCl is 30-60ml/min or the patient is aged over 75 years or frail. A three-monthly review will be required if CrCl is 15-30ml/min. A pragmatic approach to monitoring frequency is to divide the patient's CrCl reading by 10. So a CrCl reading of 50ml/min would indicate five-monthly renal function monitoring.

Bloods should also be undertaken in the case of intercurrent conditions, especially those with the potential to impact on renal or hepatic function.

If there are any concerns, for example about haemoglobin levels or an unexpected change in renal or hepatic function, more frequent testing should be considered.

At each review it is important to ask about bleeding or thromboembolic events, side-effects, adherence (including the alert card), changes in medication (including over-the-counter preparations), reassess the bleeding and stroke risk and review the optimal choice of DOAC and dosing if appropriate. Under-dosing of a DOAC is also a serious concern as it exposes the patient to an increased risk of thromboembolism.

In England, GP practices now have a target under the IIF, which measures the percentage of patients prescribed a DOAC who received a renal function test and a recording of their weight and CrCl, along with a change or confirmation of their medication dose.[2]

Q An advantage of DOACs over warfarin is that they have fewer drug interactions. But when I try to prescribe an NSAID to a patient on a DOAC I receive warnings. How significant is this interaction?

A DOACs are certainly less sensitive than warfarin with regards to drug interactions. However, there are a few important interactions that may require a reduced dose of the DOAC.

CYP3A4 inducers such as rifampicin, carbamazepine and phenytoin should be used with great caution as they reduce DOAC levels. CYP3A4 inhibitors like erythromycin, ketoconazole and verapamil may also affect plasma levels. Edoxaban should be given at a maximum dose of 30mg in patients taking P-glycoprotein inhibitors such as ciclosporin, dronedarone, erythromycin and ketoconazole, as these drugs increase plasma edoxaban. Any dose change should be immediate; don't wait until the current packet runs out.

NSAIDs should be avoided with any anticoagulant as they can cause upper GI bleeding and ulceration, and being on anticoagulation is →

Box 1 Switching from vitamin K antagonist to DOAC

Recommended INR for DOAC initiation varies*.

Pragmatic advice for switching to any DOAC is to check the INR on the day the vitamin K antagonist is stopped, then start DOAC as follows:

INR	INR	INR	INR
<2	**2-2.5**	**2.5-3**	**≥3**
start DOAC that day	start DOAC the next day (ideally), or the same day	start DOAC after 24-48 hours	postpone DOAC and continue daily INR

*Recommended INR for DOAC initiation: apixaban <2; dabigatran <2; edoxaban <2.5; rivaroxaban <3

2 CPD HOURS

Key points

- DOACs are the preferred choice of anticoagulant in NVAF
- Warfarin is still indicated in patients with mechanical heart valves, moderate to severe mitral stenosis, antiphospholipid syndrome, if CrCl <15ml/min and if the INR target is outside the usual range
- When switching from warfarin to a DOAC, the INR should be checked on the day warfarin is stopped and the DOAC started that day, over the next two days, or after further INR checks, depending on the result
- Monitoring of DOACs involves at least annual FBC and renal and liver function tests
- For most patients, the risk of bleeding with anticoagulation is outweighed by the benefits of treatment
- NSAIDs should be avoided with both warfarin and DOACs

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Box 2 Recommended DOAC doses in NVAF

CrCl	≥50ml/min	30-49ml/min	15-29ml/min	<15ml/min
Apixaban	5mg bd*	5mg bd*	2.5mg bd	Not recommended
Dabigatran	150mg bd	150mg bd*	Not recommended	
Edoxaban	60mg od*	30mg od	30mg od	
Rivaroxaban*	20mg od	15mg od	15mg od	

***Special considerations**

- Apixaban: dose is 2.5mg bd if two or more of: age ≥80; weight ≤60kg; creatinine >133µmol/ml
- Dabigatran: dose is 110mg bd if: age ≥80, or on verapamil. Consider 110mg bd if: age 75-80; CrCl 30-49ml/min; gastro-oesophageal reflux disease; increased bleeding risk
- Edoxaban: dose is 30mg od if weight ≤60kg, or if patient on ciclosporin, dronedarone, erythromycin or ketoconazole
- Rivaroxaban: to be taken with food

likely to increase the severity of any bleeding. All the DOAC manufacturers suggest avoiding concomitant use. NSAIDs can also cause renal issues, which are important with DOACs. If concurrent use is indicated, the patient should be monitored for signs of bleeding or anaemia. Similarly, SSRIs and SNRIs may increase the risk of bleeding when used alongside anticoagulants. Monitor for signs of bleeding and anaemia.

Q When and how should we use the HASBLED or other bleeding risk score?

A The NICE AF guidelines now recommend using the ORBIT score for assessment of bleeding risk rather than HASBLED.[1] However, clinicians should continue to use HASBLED until ORBIT is embedded in GP IT systems. The score should be used to assess and modify the bleeding risk, not to deny oral anticoagulation.

NICE recommends explaining to patients that for most people the benefit of anticoagulation outweighs the bleeding risk, and that careful monitoring of bleeding is important. Nevertheless, GPs should be cautious and review regularly if the bleeding risk is high.[1,3-5] If a decision is made not to anticoagulate, that patient will be at greater risk of stroke with greater healthcare resource needs and costs.[1,6] Often the risk of stroke without oral anticoagulant therapy exceeds the bleeding risk of treatment, even in the elderly, patients with cognitive impairment and those with frequent falls or frailty.

Q How should co-morbidities and pre-existing medication affect our choice of anticoagulant?

A DOACs are mainly renally excreted, so this must be considered when deciding which DOAC to prescribe and the dose (see box 2, above).

There is minimal evidence for DOAC use in end-stage renal disease and this should be discussed with the specialist team. Hepatic disease also requires careful consideration and the EHRA has developed useful guidance on this.[7]

One consideration is that rivaroxaban is taken with food. This does not apply to the other DOACs. Administration in a crushed form does not reduce bioavailability of apixaban, rivaroxaban or edoxaban, but dabigatran capsules should not be opened. This may be important in patients fed by percutaneous endoscopic gastrostomy, or who struggle to swallow.

A high body mass index (BMI) can also steer the choice of anticoagulation. Currently it is felt that all the DOACs are safe and effective up to a BMI of 40, but for BMI over 40 the data are less robust. If BMI is over 50, plasma level measurements or initiation of a vitamin K antagonist may be appropriate.

Dementia and cognitive impairment pose specific problems. Twice-daily dosing can reduce adherence; once-daily dosing, dosettes or reminders may be useful. The concurrent use of antiepileptic drugs can be challenging and we advise a discussion with the patient's neurologist and cardiologist. Frailty and propensity to falling are not contraindications to oral anticoagulation in general, but precautions and assessment and modification of bleeding risk factors are needed.

Q How should we manage the patient who has bleeding – such as rectal bleeding or haematuria – while on an anticoagulant?

A Unexplained bleeding while on anticoagulation requires investigation via the appropriate pathway, and should not simply be attributed to the anticoagulation therapy alone. In mild bleeding, enquire about the DOAC dose and any new medications; consider testing renal function and FBC. Consider delaying or deferring the next dose, and review the choice of drug and dose. Also review any modifiable bleeding risk factors.

Reinstating the DOAC should be an informed and shared decision with the patient. It is good practice to discuss with the patient how bleeding affects their view of the risks and benefits of anticoagulation. As always, ensure the correct dose is being taken. More frequent monitoring may be appropriate. Remember, for most patients the risk of bleeding is outweighed by the stroke prevention anticoagulation offers as often outcomes of a stroke are far more debilitating than a bleed.

Life-threatening bleeds may require the use of idarucizumab for dabigatran, or andexanet alfa for the other DOACs.

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