IRISH COLLEGE OF GENERAL PRACTITIONERS
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QUICK REFERENCE GUIDE

Practical use of Direct Oral Anticoagulants (DOACs) in Atrial Fibrillation in General Practice

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Quick Reference Guide

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Practical use of Direct Oral Anticoagulants (DOACs) in atrial fibrillation in general practice

This guide serves as a quick reference on the use of Direct Oral Anticoagulants (DOACs) in atrial fibrillation. It is a summary of the 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation (1). The use of DOACs in other situations such as treatment of DVT/PE or thromboprophylaxis following joint arthroplasty may have different implications for the use of DOACs and the data here should not necessarily be extrapolated to these other indications.

- The HSE application portal for DOAC approval can be accessed here. Online approval is not required for apixaban.
- Keele University has a decision support tool for prescribing of DOACs here.
- A creatinine clearance calculator using the Cockcroft Gault formula is available here
- The American College of Cardiology has a decision support tool which also calculates creatinine clearance here.

The Summary of Product Characteristics for the drugs can be obtained on www.medicines.ie and should be referred to for the most up-to-date information.

Practical start up and follow up for patients on DOACs

Before prescribing a DOAC it is important to consider

1. Indication for anticoagulation
2. Duration of anticoagulation
3. Type and dose of anticoagulation
4. Whether a proton pump inhibitor is needed
5. Baseline haemoglobin, renal and liver function
6. Patient anticoagulation card and education
7. Possible medication interactions
8. Timing of follow-up

A card that can be carried by patients is available at www.DOACforAF.eu.

It should be noted that a DOAC is preferred over warfarin (unless contra-indicated) for stroke prevention in atrial fibrillation by both European and American guidelines. DOACs are contra-indicated in valvular atrial fibrillation. In this context, valvular atrial fibrillation refers to patients with mechanical valves or moderate to severe mitral stenosis. Therefore, patients do not need to await an echocardiogram prior to commencing a DOAC unless a mechanical valve or moderate to severe mitral stenosis is present.

Apixaban is considered the DOAC of choice by the HSE Medicines Management Programme. There is no longer a requirement to make an online application for reimbursement of apixaban. There is still a requirement to apply for reimbursement of all other DOACs (dabigatran, edoxaban and rivaroxaban) via the online application system.

Table 1: Dosing of DOAC in atrial fibrillation

	Standard dose	Reduced dose	Effect of renal function
Apixaban	5mg BD	2.5mg BD (if any two of weight <60kg, creatinine >133umol/l or age >80 years)	Contra indicated if creatine clearance <15ml/min
Dabigatran	150mg BD	110mg BD (consider if >80 years, >75 years with a high bleeding risk, creatinine clearance 30-50ml/min with high bleeding risk or taking verapamil)	Contra indicated if creatine clearance <30ml/min
Edoxaban	60mg OD	30mg OD (if weight <60kg, creatinine clearance <50ml/min, or concomitant therapy with strong P-gp inhibitor)	Contra indicated if creatine clearance <15ml/min reduced effect if creatinine clearance >95ml/min
Rivaroxaban	20mg OD	15mg OD (if creatinine clearance <50ml/min)	Contra indicated if creatinine clearance <15ml/min

All four DOACs are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

Rivaroxaban needs to be taken with food [the area under the curve (AUC) plasma concentration increase by 39% to a very high bioavailability of almost 100%], while there is no food interaction with the other DOACs.

Data have shown that administration in crushed form, e.g. via a nasogastric tube, does not alter the bioavailability for apixaban, rivaroxaban and edoxaban. In contrast, dabigatran capsules must not be opened because opening results in a substantial increase in drug bioavailability (75% increase in bioavailability) and hence cannot be used in blister packs.

Drug interactions

In general, DOAC use is not recommended in combination with drugs that are strong inhibitors of both CYP3A4 and P-gp such as azole-antimycotics (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir).

Conversely, strong inducers of P-gp and/or CYP3A4 (such as carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's Wort) will markedly reduce DOAC plasma levels.

A summary table of common drug interactions is given below. Please refer to the individual Summary of Product Characteristics (SmPC) for full details of drug interactions and dose adjustments before prescribing

Table 2: Summary of interactions with DOAC medications

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Anti-arrhythmic drugs				
Amiodarone	1	1	1	1
Diltiazem		1		
Dronedarone	5	1	2	5
Quinidine	1		1	1
Verapamil	2		1	
Antibiotics				
Clarithromycin/Erythromycin	1	1	2	1
Rifampicin				
Antiviral drugs				
HIV protease inhibitors e.g. ritonavir	5	5	5	5
Antifungal drugs				
Fluconazole				1
Itraconazole, Ketoconazole, Voriconazole,	5	5	2	5
Posaconazole	2	5	2	5
St John's Wort	4	4	4	4
Carbamazepine	4	3	3	4
Levetiracetam	4			4
Phenobarbital	4	3	3	4
Sodium valproate	4	4	4	4
Topiramate		3		3
Other factors				
Age >80	2	1	1	1
Age >75	1	1	1	1
Weight <60	1	1	2	1
Other increased bleeding risk e.g. antiplatelets, NSAIDs, steroid, history of GI bleed, frailty of falling, bleeding predisposition	1	1	1	1

*NSAIDS non-steroidal anti-inflammatory drugs, GI gastrointestinal.
The hatched colour coding indicates no clinical or PK data available, and recommendations are based on the respective NOAC SmPC (where available) or expert opinion.

Numbers are provided to allow ease of reference in black and white printing

Contraindicated due to increased effect	5
Contraindicated due to decreased effect	4
Use with caution due to decreased effect	3
Consider dose adjustment or different DOAC	2
Consider dose adjustment or different DOAC if 2 or more yellow factors present	1

What to check at follow up

- Check for thromboembolic and bleeding events
- Assess adherence
- Check for side effects
- Check for possible drug interactions and over-the-counter medicines
- Assess correct DOAC dosing
- Decide if blood tests required
- Assess modifiable risk factors and manage as appropriate e.g. hypertension

Switching DOAC regimens

It is important to safeguard the continuation of anticoagulant therapy while minimising the risk of bleeding when switching regimens. This is summarised in figure 1.

Because of the slow onset of action of warfarin (half-life 36-48 hours) it may take 5–10 days before the INR is in the therapeutic range, with large individual variations. Therefore, the DOAC and warfarin should be administered concomitantly until the INR is in range. A loading dose is not recommended. As DOACs may have an impact on INR measurements, it is important that the INR (i) is measured just before the next intake of the DOAC during concomitant administration and (ii) is re-measured early after stopping the DOAC (i.e. reflecting solely vitamin K agonist (VKA) therapy to assure adequate anticoagulation). It is also recommended to closely monitor INRs within the first month of warfarin treatment until stable values have been attained (i.e. three consecutive measurements yielded values between 2.0 and 3.0).

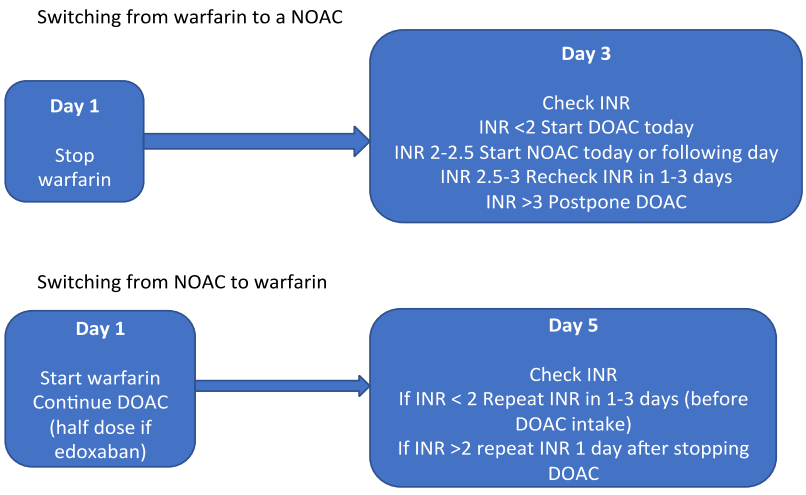

Figure 1: Directions on switching NOAC regimens

Dosing errors

Forgotten dose

The forgotten dose can be taken up until 50% of the dosing interval has lapsed (i.e. 12 hours in once daily dosing and 6 hours in twice daily dosing). After this time the dose should be skipped, and the next dose taken.

Double dose

If a double dose has been taken the patient can omit the next scheduled dose. Overdoses of greater amounts should be referred to hospital for assessment.

Patient unsure if a dose taken

If the patient is unsure if they have already taken a dose and question whether they should take a dose you should advise the following:

1. For those drugs with a twice daily dosing regimen they should just take the next dose as planned
2. For those with a once daily regimen they should take another pill and then continue as planned

Undergoing planned surgical interventions

For those procedures being carried out by another clinician, the decision to continue or stop the anticoagulant and duration of stopping is a matter for the specialist to decide with reference to hospital and international guidelines. This guide seeks to provide information on procedures commonly encountered in the community that may require GP advice e.g. skin surgery.

Procedures with minor bleeding risk are defined by the European Heart Rhythm Association (ERHA) as

- Dental interventions
    - Extraction of 1-3 teeth
    - Periodontal surgery
    - Incision of abscess
- Implant positioning
- Cataract or glaucoma intervention
- Endoscopy without biopsy of resection
- Superficial surgery (e.g. abscess incision, small dermatological excisions)

For these procedures it is recommended not to interrupt oral anticoagulation where bleeding is easily controlled. In general, these procedures can be performed 12–24 hours after the last DOAC intake. It may be practical to have the intervention scheduled 18–24 hours after the last DOAC intake and then restart 6 hours later (skipping one dose of dabigatran or apixaban or no dose of edoxaban or rivaroxaban). The patient may only leave the ambulatory practice/outpatient clinic/hospital if any periinterventional bleeding has completely stopped.

Further details on higher risk procedures and timing of stopping in those with chronic kidney disease are available in ERHA guidelines but these are a matter for the team performing these procedures. The level of risk associated with specific procedures are summarised in Table 3.

Table 3: Interventions with a low and high risk of bleeding

Interventions with low bleeding risk (i.e. infrequent or with low clinical impact)
• Endoscopy with biopsy • Prostate or bladder biopsy • Electrophysiological study or catheter ablation (except complex procedures) • Non-coronary angiography (for coronary angiography and ACS) • Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with high bleeding risk (i.e. frequent and/or with high impact)
• Complex endoscopy (e.g. polypectomy, Endoscopic Retrograde Cholangiopancreatography ERCP with sphincterotomy) • Spinal or epidural anaesthesia; lumbar diagnostic puncture • Thoracic surgery • Abdominal surgery • Major orthopaedic surgery • Liver biopsy • Transurethral prostate resection • Kidney biopsy • Extracorporeal shockwave lithotripsy (ESWL)
Interventions with high bleeding risk AND increased thromboembolic risk
• Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

Use of antiplatelet drugs with DOACs

The use of antiplatelet drugs in combination with DOACs is a matter for the treating specialist and, in general, patients on an indication for antiplatelet therapy requiring simultaneous DOAC treatment should be reviewed by the relevant specialist. Combination antithrombotic therapy increases the risk of fatal and non-fatal bleeding. In a Danish registry of patients with atrial fibrillation (n=82 854; mean follow-up over three years) the annual incidence of bleeding was less than 4% for aspirin or warfarin monotherapy, but rose to 15.7% for triple therapy comprising aspirin, clopidogrel and warfarin. The gastrointestinal tract is the most common site for bleeding, followed by upper airways.

However, it is recognised that in some cases GPs may have a patient who has been on an antiplatelet for many years and now requires a DOAC for atrial fibrillation. The challenge is to weigh the risks and benefits of continuing with antiplatelet therapy over stopping due to increased bleeding risk. Current guidelines state that anticoagulation only without additional antiplatelet agents is considered sufficient for most AF patients with stable coronary artery disease (that is more than one year post an event or percutaneous coronary intervention). It is particularly important to determine the reason for antiplatelet therapy because it is not indicated for primary prevention e.g. in diabetes or hypertension without evidence of atherosclerotic disease. Some patients at high risk of ischaemic events may be considered for dual therapy with an antiplatelet and DOAC.

DOACs in ischaemic heart disease

It is noted that a recent study (2) has shown better cardiovascular outcomes but more major bleeding events when using a combination of aspirin 100mg OD and **low dose** rivaroxaban (2.5mg BD) in patients with atherosclerosis not on anticoagulation (i.e. in sinus rhythm). However, these data cannot be extrapolated to full dose anticoagulation.

Management of bleeding

For mild bleeding determine last DOAC intake and if any possibility of double dosing, delay or discontinue the next dose and consider any medications that may be contributing to bleeding e.g. non-steroidal anti-inflammatory drugs or antiplatelet agents. Also consider if worsening renal function may be contributing to bleeding tendency due to increased plasma drug concentrations. For all other bleeding, refer to hospital for assessment. In case of recurrent minor bleeding events without causal therapeutic options (e.g. cautery in epistaxis), an alternative DOAC with a potentially different bleeding profile could be considered. Patients with anaemia on a DOAC still require investigation for a possible cause of anaemia.

Reversal agents

There is no role for reversal agents in general practice.

There are now specific reversal agents for DOACs which may be used in hospital for severe life-threatening bleeding only. Idarucizumab is a humanised anti-dabigatran monoclonal antibody fragment that can be used for emergency reversal of the anticoagulant effect of dabigatran. Factor Xa inhibitors include apixaban, edoxaban and rivaroxaban. Andexanet alfa is a recombinant protein that acts as a decoy for the direct oral fXa inhibitors. Evidence is limited for these agents at present (3).

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