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DIRECT ORAL ANTICOAGULANTS: A GUIDE TO APPROPRIATE PRESCRIBING IN ADULTS

- **Direct oral anticoagulants (DOACs) have different dose criteria depending on the specific indication**
- **Dosing errors with DOACs can result in patient harm; under-dosing may increase the risk of embolic events, while over-dosing can result in an increased risk of bleeding**
- **The patient's age, weight, renal function and concomitant medication should be considered when selecting the dose of a DOAC for a specific indication**
- **Clinically significant drug-drug interactions can occur with DOACs**

INTRODUCTION

Direct oral anticoagulants (DOACs), also known as non-vitamin K oral anticoagulants (NOACs), are alternatives to vitamin K anticoagulants (VKAs) such as warfarin. DOACs selectively target thrombin (dabigatran etexilate) or factor Xa (apixaban, edoxaban and rivaroxaban).[1] DOACs have a number of indications and were first authorised in Europe in 2008 for thromboprophylaxis post orthopaedic surgery and for stroke prevention in non-valvular atrial fibrillation (NVAF) in 2011.[2] The use of DOACs has increased globally;[1,3] an Irish study found a rapid increase in the prescribing of DOACs from 2013 to 2017.[4]

While DOACs have a number of advantages over warfarin such as a rapid onset of action, predictable dose-response with fixed doses, less drug and food interactions and a lack of requirement for routine coagulation monitoring,[1,5-7] there are challenges in the prescribing of DOACs and the absolute benefits of DOACs over VKAs are modest.[1] **Dosing errors with DOACs have been reported in clinical practice, resulting in patient harm.**[8-11] The dose of DOAC depends on the **specific indication** and on patient factors including age, weight, renal function and concomitant medication. **It is important to be aware that dose reduction criteria applicable to the management of NVAF may not apply to acute venous thromboembolism (VTE).** The appropriate use of DOACs requires a considered approach to many practical aspects,[5] which will be discussed in this bulletin.

PHARMACOLOGY

The pharmacological properties of the DOACs are summarised in table 1. Apixaban, edoxaban and rivaroxaban are direct factor Xa inhibitors,[12-14] while dabigatran etexilate is a prodrug that is rapidly converted by a serum esterase to dabigatran, which is a direct thrombin inhibitor.[15] All DOACs are substrates of P-glycoprotein (P-gp) and the factor Xa inhibitors (edoxaban to a lesser extent than apixaban and rivaroxaban) are metabolised by cytochrome P450 isoenzymes (CYP).[12-18] **All DOACs are at least partially renally cleared,** therefore there is a potential for drug accumulation in patients with renal impairment.[12-18] **DOACs have a relatively short half-life (approximately 12 hours)** in patients with normal renal function; the half-life may increase in patients with renal impairment.[1]

Table 1: Pharmacological properties of direct oral anticoagulants[1,5,19]

Characteristic	Apixaban	Dabigatran etexilate	Edoxaban	Rivaroxaban
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Bioavailability	50%	6 to 7%	62%	66%*
Time to peak levels	3 to 4 hours	0.5 to 2 hours	1 to 2 hours	2 to 4 hours
Half-life	Approx. 12 hours	12 to 14 hours	10 to 14 hours	9 to 13 hours
Renal clearance %	27%	>80%	50%	33%
Substrate for P-gp	Yes	Yes	Yes	Yes
Metabolism via cytochrome P450 enzymes %	<32%	No	<5%	57%

*P-gp – P-glycoprotein; *applies to the 15mg and 20mg doses given once a day without food; bioavailability 80-100% when these doses are given with food*

INDICATIONS

DOACs are authorised and reimbursed in Ireland for 1) stroke prevention in patients with NVAF and other risk factors, 2) treatment and prevention of recurrence of deep vein thrombosis (DVT) or pulmonary embolus (PE) in adults and 3) thromboprophylaxis post-elective total hip replacement (THR) and total knee replacement (TKR) surgery (excluding edoxaban).[2] **Warfarin remains the OAC of choice for many indications including: mechanical heart valves, valvular AF, antiphospholipid syndrome and in those with severe renal impairment.**[2] Adverse effects associated with DOACs include bleeding (e.g. gastrointestinal (GI), epistaxis, genitourinary, heavy menstrual bleeding), anaemia, dizziness, abnormal liver function tests and abdominal pain.[12-18]

Stroke prevention: Randomised controlled trials (RCTs) have shown that DOACs are as effective as warfarin in preventing stroke in patients with NVAF[20-23]; evidence suggests DOACs are associated with a reduced risk of intracerebral haemorrhage.[20-28] DOACs are recommended by many specialists for stroke prevention in patients with NVAF.[1,5,28,29] The HSE Medicines Management Programme (MMP) recommends warfarin as a first-line OAC when the time in the therapeutic range (TTR) is >70%, or apixaban if a DOAC is preferred.[2] **DOACs are contraindicated in patients with mechanical heart valves due to an increased risk of thromboembolic and bleeding events.**[1,8,29]

Prevention of VTE after major orthopaedic surgery: RCTs have found DOACs to be as effective (apixaban and dabigatran) or more effective (rivaroxaban) than heparin for preventing VTE following elective THR/TKR surgery.[30-40] Guidelines recommend DOACs as an option for VTE prophylaxis if the risk of VTE outweighs the risk of bleeding in patients having a THR/TKR.[8,41,42]

Treatment and prevention of recurrent VTE: The management of VTE requires anticoagulation therapy.[43,44] RCTs found DOACs to be non-inferior to VKAs in the management of patients with VTE, with similar or reduced rates of major bleeding.[1,43-50] **Apixaban and rivaroxaban do not require initial parenteral treatment with heparin**, however dabigatran and edoxaban do.[12,13,16-18,20] Guidelines recommend DOACs in preference to VKAs for the treatment of VTE in suitable patients.[1,43,51] The duration of anticoagulation needs to be individualised to the patient, whereby **the risk of recurrent VTE needs to be weighed up against the risk of bleeding.[44]** Treatment with OAC is recommended for at least 3 months;[43,51] extended use is considered for those at risk of recurrent VTE (e.g. those with an unprovoked VTE, recurrent VTE or a persistent risk factor).[43,44,51-53] Depending on the DOAC used, a dose reduction for long term secondary prevention may be indicated following six months of initial therapy.[44,54]. Evidence suggests that DOACs are effective for the treatment of VTE in patients with cancer (an unauthorised indication),[55-58] however there is an increased risk of bleeding especially in patients with cancer of the GI tract.[1,55,56] A DOAC may be considered on specialist advice in individual patients with cancer, such as those with a specific cancer (e.g. excluding GI or urothelial cancer), who are without risk factors for bleeding or potential drug-drug interactions (including chemotherapy) and a stable platelet count of >50 x 10 9/L.[43,44,51,59]

Other indications: Rivaroxaban (2.5 mg) is also authorised (not currently reimbursed) for use in combination with aspirin for the prevention of atherothrombotic events in adults with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events.[14,60] It is also authorised (not reimbursed) for use with aspirin alone or with dual antiplatelet therapy for the prevention of atherothrombotic events after an acute coronary syndrome with elevated cardiac biomarkers.[14,61] Emerging evidence suggests that DOACs may be effective in patients with bioprosthetic valves.[62,63]

Contraindications: All DOACs are contraindicated in patients with hypersensitivity reactions to DOACs, active bleeding or anatomical lesions predisposing to life-threatening bleeding, advanced liver disease with coagulopathy or bleeding and concomitant administration with other anticoagulants (except under specific circumstances); individual DOACs are also contraindicated or not recommended in conditions including advanced renal disease, prosthetic valves and antiphospholipid syndrome, and in pregnancy and breastfeeeding.[15-18] Due to a lack of data, the use of DOACs is not recommended in patients who have had gastric bypass surgery or gastrectomy due to concerns about reduced absorption;[64-66] further studies are needed.

ASPECTS TO CONSIDER WHEN PRESCRIBING A DOAC

The decision to commence a patient on a DOAC should be based on the benefits (prevention of an embolus) versus the risks (e.g. bleeding) for the individual patient.[6] Baseline investigations include a full blood count, renal and hepatic function, which should be assessed prior to commencing a DOAC. A number of factors need to be considered when starting a patient on a DOAC for a specific indication including the dose and duration of the DOAC, renal function, age, weight, risk of bleeding, drug interactions, cost and patient education.

DOAC dosing

Each DOAC has different dose recommendations depending on the specific indication and has different dose reduction criteria for individual patients;[5-7] **the Summary of Product Characteristics (SmPC) (available on www.hpra.ie and www.medicines.ie) which contains all prescribing information should be consulted when prescribing for an individual patient**. The following factors need to be considered when choosing the appropriate dose of a DOAC: **the indication for the DOAC, patient's age, weight, renal function, concomitant medications and risk of bleeding.[12-18,67] It is important to be aware that dose reduction advice for individual agents may pertain to NVAF and not to acute VTE.** Under-dosing may increase the risk of embolic events while over-dosing can result in an increased risk of bleeding.[6] **Risk factors for dosing errors include older age, renal impairment, concomitant medications and use in patients with a higher risk of bleeding.[9,10]** Of note, apixaban and rivaroxaban were among the most commonly reported antithrombotics to be involved in medication incidents (including dosing errors) in Irish hospitals between 2017-2018.[68]

Administration

Dabigatran comes as a capsule formulation **and should remain in the original container.[15,16] The capsule must not be opened or crushed as this may result in an increased bioavailability (up to 75%) and a subsequent increased risk of bleeding.[5,15,16]** The dabigatran capsule must be swallowed whole with a glass of water.[15,16]Apixaban, rivaroxaban and edoxaban may be crushed and mixed with fluid and/or administered via nasogastric tubes if required.[5,12-18] **Rivaroxaban 15mg and 20mg must be taken with food;[18]** thromboembolic events have been reported when rivaroxaban is taken on an empty stomach.[8]

Renal impairment

All DOACs are excreted by the kidneys and dose adjustments may be required for some indications in those with renal impairment,[5,6] therefore **renal function must be measured prior to selecting the dose of any DOAC**. **Renal function should be assessed by calculating the estimated creatinine clearance (CrCl) using the Cockcroft-Gault method** (see figure 1).[5,6] The current consensus is that renal function should be assessed at least annually for

those on long-term DOACs, with more frequent monitoring for those in clinical situations where renal function may decline and in patients with impaired renal function at baseline.[5,6] The European Heart Rhythm Association recommends that if the CrCl is ≤60mL/min, the frequency of monitoring (in months) can be guided by the CrCl divided by 10.[5] For example, if the CrCl is 30mL/min, the renal function and dose should be reassessed every 3 months.[6] **The risk of developing renal impairment increases with age, therefore the monitoring of renal function over time is important in those on DOACs long-term** (e.g. patients with NVAF or on extended preventive therapy for VTE).[6] Note that the recommendations for dose reduction in renal impairment for individual DOACs may differ depending on the specific indication (e.g. in severe renal impairment, the dose of apixaban should be reduced in patients with NVAF, but NOT for patients with VTE); refer to the specific SmPC for the individual DOAC.[12]

Figure 1: Cockcroft and Gault formula for calculation of estimated creatinine clearance[5,69]

$$\text{Estimated creatinine clearance in mL/minute} = \frac{(140 - \text{Age}) \times \text{Weight*} \times \text{Constant}}{\text{Serum creatinine}}$$

Age in years; weight in kilograms; serum creatinine in micromole/litre; constant = 1.23 for men, 1.04 for women

*actual body weight was used in the DOAC clinical trials

In general, **use of dabigatran is contraindicated in patients with CrCl <30mL/min, and use of apixaban, edoxaban and rivaroxaban is not recommended in those with CrCl <15mL/min.**[5,12-18] An observational study of patients on DOACs with NVAF in routine clinical practice found that 43% of patients did not have appropriate dose reduction according to renal function (associated with higher risk of major bleeding) and 13% had inappropriate dose reduction with normal renal function (associated with higher risk of stroke).[70] A possible decreased efficacy of edoxaban 60mg daily compared with warfarin was observed in patients with AF with a CrCl >95mL/min;[5,13] edoxaban for NVAF should only be used in those with a high CrCl after careful evaluation of the individual thromboembolic and bleeding risk.[5,8,13]

Weight

In general, there is limited data available on the use of DOACs in patients at extremes of body weight (BW) (e.g. <50kg and >120 kg), as these patients were underrepresented in clinical trials.[1,5] **Low BW (<50kg) may increase exposure to a DOAC, with an increased risk of bleeding and higher mortality.**[5,71-73] Low BW may also be associated with other risk factors such as increased age, frailty, cancer and renal impairment, therefore caution is needed when these patients are being anticoagulated.[5] Some resources recommend that DOACs should be avoided or used with caution in those <50kg;[15,16,72-75] there are dose reduction criteria for underweight patients (<60kg) prescribed apixaban and edoxaban.[12,13]

There are concerns that DOAC underdosing could occur in patients with morbid obesity (BW >120kg or a body mass index [BMI] of >40 kg/m^2).[1,5,76,77] Guidelines recommend that standard doses of DOACs are used in patients with a BW of ≤120kg or a BMI ≤40 kg/m^2, and suggest that alternative OACs should be considered for patients with a BW >120kg or BMI of >40 kg/m^2.[76,78]

Risk of bleeding

It is important to consider that all OACs including DOACs are associated with an increased risk of bleeding. There is evidence to suggest that DOACs (excluding apixaban) have a higher risk of GI bleeding compared to warfarin.[21-22,79-83] Factors associated with an increased risk of bleeding include older age, low body weight ≤60kg, impaired renal function, concomitant medications (e.g. antiplatelets, non-steroidal anti-inflammatory drugs [NSAIDs], selective serotonin re-uptake inhibitors [SSRIs] and systemic steroids), history of GI bleeding, recent surgery, frailty or falls risk, anaemia and thrombocytopenia.[5] In some patients proton pump inhibitors may be considered to reduce the risk of GI bleeding, especially in those with a history of GI bleeding or ulcer and in patients requiring concomitant use of dual antiplatelet therapy.[5] **Use of a score such as HAS-BLED may be useful for an estimation of bleeding risk and to address any modifiable risk factors for bleeding.**[6]

Drug interactions

DOACs are associated with less drug interactions than VKAs, however clinically significant drug interactions can occur. The SmPC of the individual DOAC should be reviewed for patients who are prescribed potentially interacting medicines.

Pharmacokinetic interactions: **As all DOACs are substrates for the efflux transporter P-gp**,[1,2,5,52] drugs that induce or inhibit P-gp may affect DOAC plasma concentration, resulting in an increased risk of thrombosis or bleeding respectively.[2,54] **Factor Xa inhibitors, in particular apixaban and rivaroxaban are substrates for CYP3A4**, therefore drug interactions may occur when these drugs are co-administered with CYP3A4 inducers or inhibitors.[1,2,5,54] To reduce the risk of bleeding with concurrent CYP3A4/P-gp inhibitors, DOACs may require dose adjustment (e.g. dabigatran, edoxaban) or the interacting drugs should be avoided altogether.[84] Other factors such as the indication for the DOAC, the patient's age, weight and renal function which can also impact on a clinically relevant drug interaction occurring must be considered.[5]

Pharmacodynamic (PD) interactions: Patients on DOACs are at risk of potential PD drug interactions when prescribed other medications that can also increase the risk of bleeding (e.g. NSAIDs, systemic steroids, antiplatelets and SSRIs).[2,5,12-18,85] DOACs are contraindicated with other anticoagulants (except in specific circumstances e.g. switching from DOAC to VKA).[14-18]

Patient education

Patient education on use of a DOAC is important to reduce the risk of medication errors. **The patient should be educated on the importance of strict adherence to the dosing regimen**, how to manage missed doses and how to recognise the signs and minimise the risk of bleeding (e.g. the avoidance of potentially interacting drugs including over-the-counter medicines and excessive alcohol).[5,8,86] Evidence suggests adherence to DOACs ranges from 38 to 99% (depends on the healthcare setting and definition of adherence).[5] **A recent study of patients with NVAF found that discontinuation of OACs (including DOACs) led to a 2 to 3-fold higher risk of ischaemic stroke than those who continued OACs.**[87] Use of DOACs may be challenging in patients who are unable to take their medication as prescribed.[88] Methods to improve adherence include education (e.g. leaflets, instructions at initiation of DOAC therapy and at every prescription renewal, patient anticoagulation cards), medication boxes (not suitable for dabigatran), smartphone applications and once daily regimens where authorised.[5] **Patients should be informed of the importance of not missing doses, as missing one or two doses of a DOAC may leave the patient inadequately anticoagulated.**[88] The forgotten dose may 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 forgotten dose should be skipped, and the next dose taken.[12-18,29] This advice may vary for specific indications (e.g. prevention of VTE following orthopaedic surgery).[15]

MONITORING OF A PATIENT PRESCRIBED A DOAC

Patients on DOACs require ongoing monitoring; the lack of routine INR monitoring and less frequent interactions with healthcare professionals may result in an increased risk of adverse outcomes.[2,4,88] Patients commenced on a DOAC should be reviewed after 1 month initially, followed by at least every 6 to 12 months (the follow-up interval depends on factors including age, frailty, renal function, comorbidities).[5] **At each review it is important to ensure that the patient is on the correct dose of DOAC and for the appropriate duration in terms of the indication, and to check/assess the patient's current age, weight, renal function and concomitant medication.**[2,5,8] The patient should be reviewed for adverse effects, and risks (or events) of thromboembolism and bleeding; modifiable risk factors for bleeding should be identified. The patient should be **reminded of the importance of strict adherence to the dosing regimen** and how to minimise the risk of bleeding. Investigations such as haemoglobin, renal and hepatic function should be undertaken at least annually (more frequently if clinically indicated).[2]

OTHER CONSIDERATIONS

Reversal of DOACs: DOACs have short half-lives and, in the case of bleeding, treatment is largely supportive. A specific reversal agent idarucizumab is available for dabigatran in the event of life-threatening bleeding.[1,5] For patients who present with bleeding, identify when the last DOAC was taken, and assess if there is a possibility of double DOAC intake, incorrect dosing, worsening renal function, or if the patient is on any medication that may contribute to bleeding (e.g. NSAIDs, SSRIs).[5,29] For mild bleeding the next DOAC dose should be delayed or discontinued, and patient education should be reinforced.[5,29]

Surgical procedures: Peri-procedural decisions on when to stop a DOAC are usually made by specialists in a hospital setting and depend on the type of surgery and the associated bleeding risk.[5,29] The indication for the DOAC and patient characteristics (e.g. age, renal function, concomitant medication and history of bleeding complications) also need to be considered.[5] In the event of temporary discontinuation peri-operatively, bridging with LMWH is not required for DOACs.[5] In general, for procedures with minimal risk of bleeding (e.g. routine dental work), DOACs can be continued or a single dose withheld on the morning of the procedure.[1]

Switching: It may be necessary to switch patients from warfarin to a DOAC and from DOACs to warfarin. Guidance on switching is specific to each DOAC and may vary by indication; information is available in the SmPC.

SUMMARY OF THE PRACTICAL ASPECTS OF PRESCRIBING DOACs[5,29]

Before prescribing a DOAC consider the following:
• Establish the indication for anticoagulation and the intended duration • Check baseline bloods including haemoglobin, renal and liver function • Choose the optimal anticoagulant and the correct dose for the specific patient (check the Summary of Product Characteristics) • Consider possible drug interactions • Consider the need for a proton pump inhibitor • Provide patient education emphasising the need for adherence to avoid a pro-thrombotic state and how to recognise the signs and minimise the risk of bleeding • Organise follow-up
↓
Follow-up (initially after 1 month) consider the following
• Assess the optimal DOAC and dose for your specific patient • Check for thromboembolic and bleeding events • Assess adherence and reinforce education • Check for side effects • Review medications including over-the-counter medicines; assess for drug interactions • Decide if bloods (haemoglobin, renal and liver function) required: (at least yearly; 6 monthly if ≥75 years; more frequently if creatinine clearance ≤60mL/min; as required if intercurrent condition) • Assess modifiable risk factors for bleeding (e.g. uncontrolled hypertension, medication predisposing to bleeding, excessive alcohol intake)

List of references available on ePublication on www.nmic.ie. Date of publication: February 2021