Guidelines to direct oral anticoagulants

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Direct oral anticoagulants (DOACs) have provided a practical alternative to warfarin sodium and low molecular weight heparin for people requiring anticoagulation. Their advantages include a more predictable clinical effect than warfarin, with no requirement for routine monitoring, regular fixed doses, no food or drink interactions and few drug interactions. Nurses have an important role in ensuring the safe use and administration of medicines. As the use of anticoagulants advances and they are used in a variety of conditions, nurses need to ensure their knowledge of these medicines is up to date to provide safe and informed care. This article provides an overview of the DOACs currently licensed for use in the UK, including their indications, doses, side effects and other considerations.

Until the past few years, warfarin sodium and low molecular weight heparin were the main anticoagulants used in the treatment of venous thromboembolism (VTE) and stroke prevention in non-valvular atrial fibrillation (AF). However, despite their effectiveness, these medicines present practical challenges. Warfarin requires frequent international normalised ratio (INR) monitoring to ensure it remains in the therapeutic range and has various drug, food and drink interactions, while low molecular weight heparin injections can be unpleasant and challenging for some patients to self-administer.

Direct oral anticoagulants (DOACs) have provided a practical alternative to warfarin and low molecular weight heparin for people requiring anticoagulation. Their advantages include a more predictable effect than warfarin, with no requirement for routine monitoring, regular fixed doses, no food or drink

interactions and few drug interactions (Baglin 2013). Four DOACs are currently licensed for use in the UK for a variety of indications: dabigatran etexilate, rivaroxaban, apixaban and edoxaban. The practicality of DOACs over warfarin have made them the first-line treatment for VTE and prevention of stroke in non-valvular AF in most centres across the UK.

None of the DOACs have undergone direct comparison through clinical trials, but the large phase III clinical trials of all four DOACs showed similar efficacy and safety to warfarin, along with the additional advantage of significantly reduced risk of intracranial haemorrhage (Raschi et al 2016). Real-world registry data has largely reflected these clinical trial findings, giving healthcare practitioners reassurance that these medicines offer a safe and practical option for patients requiring anticoagulation (Beyer-Westendorf et al 2013, Agnelli et al 2015, Camm et al 2016, Hecker et al 2016).

Anticoagulants are high-risk medicines with the potential to cause harm, and all staff caring for patients on anticoagulant therapy must have the necessary work competences (National Patient Safety Agency* 2007). This article aims to support nurses to ensure their knowledge is up to date by outlining the properties, dosing, side effects and potential issues associated with DOACs, so that they can provide safe and effective care to patients taking these medicines.

Properties of direct oral anticoagulants

Three of the DOACs – rivaroxaban, apixaban and edoxaban – target and inhibit clotting factor Xa. This is the first clotting factor in the common pathway of the clotting cascade, and its inhibition results in reduction of fibrin formation, a strand-like protein that is an essential component of a blood clot. Similarly, dabigatran inhibits thrombin (factor IIa), another factor in the clotting cascade. This also has the consequence of reducing fibrin production to reduce the risk of clot formation.

The four DOACs share properties such as a fast onset and offset of action compared with warfarin, but they have important differences which may determine agent selection in some patients. For example, dabigatran and apixaban have a twice-daily dosing regimen, while rivaroxaban and edoxaban are once daily. Furthermore, 15mg and 20mg doses of rivaroxaban must be taken with food,

which has been found to increase absorption of 20mg doses by almost 40% (European Medicines Compendium (EMC) 2019). The other three DOACs do not require ingestion with food and, unlike warfarin, none of the DOACs have any interactions with food or alcohol.

Indications for the different direct oral anticoagulants

Table I. Indications for the different direct oral anticoagulants

Indication	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaba
Thromboprophylaxis post-hip and knee replacement	✓	✓	✓	X
Stroke prevention in non-valvular atrial fibrillation	✓	✓	✓	✓
Treatment of venous thromboembolism	✓	✓	✓	✓
Acute coronary syndrome	X	✓	X	X
Coronary artery disease and peripheral artery disease	X	✓	X	X

(Adapted from Czuprynska et al 2017)

Venous thromboembolism

The term VTE describes two interrelated conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). A DVT is a blood clot commonly found in the deep veins of the legs, pelvis and arms, but it can occur in any deep vein. The clot can partially or fully occlude the blood vessel and can lead to the development of a PE if part of the clot breaks away, or if the whole clot moves from the vessel it originated from. When this occurs, the thrombus becomes an embolus, travelling through the right side of the heart and lodging in the pulmonary arteries of the lungs, resulting in a PE.

National Institute for Health and Care Excellence (NICE) (2020a) guidelines stipulate that VTE events should be treated with at least three months of anticoagulation, although in some cases anticoagulation therapy will be lifelong.

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Non-valvular atrial fibrillation

AF is the most common sustained heart rate and rhythm disorder. Around 25% of people over the age of 40 years will develop AF in their lifetime (Staerk et al 2018). Uncontrolled AF can promote blood stasis within the atria, which increases the risk of thrombus formation. A thrombus can pass into the cerebral and peripheral circulation, leading to thromboembolic complications including ischaemic stroke (Violi et al 2014).

Management of the arrhythmia and effective anticoagulation have an essential role in reducing risk of stroke in non-valvular AF (Floyd and Ferro 2017). The decision to anticoagulate will involve careful consideration of individual risk factors for stroke against bleeding risk factors.

EVIDENCE AND PRACTICE

A nurse's guide to direct oral anticoagulants

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Why you should read this article:

- To understand the properties of the four direct oral anticoagulants (DOACs) currently licensed for use in the UK
- To enhance your knowledge of the indications for each DOAC
- To enable you to recognise the side effects and risk of bleeding associated with each DOAC

Direct oral anticoagulants (DOACs) have provided a practical alternative to warfarin sodium and low molecular weight heparin for people requiring anticoagulation. Their advantages include a more predictable clinical effect than warfarin, with no requirement for routine monitoring, regular fixed doses, no food or drink interactions and few drug interactions. Nurses have an important role in ensuring the safe use and administration of medicines. As the use of

anticoagulants advances and they are used in a variety of conditions, nurses need to ensure their knowledge of these medicines is up to date to provide safe and informed care. This article provides an overview of the DOACs currently licensed for use in the UK, including their indications, doses, side effects and other considerations.

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Conflict of interest

Emma Gee has received speaker honoraria from Bayer, but they have had no input into this article * On 1 April 2016 the statutory patient safety functions previously delivered by NHS England transferred with the national patient safety team to NHS Improvement

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Direct oral anticoagulants (DOACs) have provided a practical alternative to warfarin and low molecular weight heparin for people requiring anticoagulation. Their advantages include a more predictable effect than warfarin, with no requirement for routine monitoring, regular fixed doses, no food or drink interactions and few drug interactions (Baglin 2013). Four DOACs are currently licensed for use in the UK for a variety of indications: dabigatran etexilate, rivaroxaban, apixaban and edoxaban. The practicality of DOACs over warfarin have made them the first-line treatment for VTE and prevention of stroke in non-valvular AF in most centres across the UK.

None of the DOACs have undergone direct comparison through clinical trials, but the large phase III clinical trials of all four DOACs showed similar efficacy and safety to warfarin, along with the additional advantage of significantly reduced risk of intracranial haemorrhage (Raschi et al 2016). Real-world registry data has largely reflected these clinical trial findings, giving healthcare practitioners reassurance that these medicines offer a safe and practical option for patients requiring anticoagulation (Beyer-Westendorf et al 2013, Agnelli et al 2015, Camm et al 2016, Hecker et al 2016).

Anticoagulants are high-risk medicines with the potential to cause harm, and all staff caring for patients on anticoagulant therapy must have the necessary work competences (National Patient Safety Agency* 2007). This article aims to support nurses to ensure their knowledge is up to date by outlining the properties, dosing, side effects and potential issues associated with DOACs, so that they can provide safe and effective care to patients taking these medicines.

Properties of direct oral anticoagulants

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The four DOACs share properties such as a fast onset and offset of action compared with warfarin, but they have important differences which may determine agent selection in some patients. For example, dabigatran and apixaban have a twice-daily dosing regimen, while rivaroxaban and edoxaban are once daily. Furthermore, 15mg and 20mg doses of rivaroxaban must be taken with food, which has been found to increase absorption of 20mg doses by almost 40% (European Medicines Compendium (EMC) 2019). The other three DOACs do not require ingestion with food and, unlike warfarin, none of the DOACs have any interactions with food or alcohol.

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Key points

- •Advantages of direct oral anticoagulants (DOACs) over warfarin sodium include a more predictable effect, no requirement for regular monitoring, regular fixed doses, and no interactions with food or drink
- •Four DOACs are currently licensed for use in the UK: dabigatran etexilate, apixaban, rivaroxaban and edoxaban
- •The most common indications for DOAC prescription are treatment of venous thromboembolism and stroke prevention in non-valvular atrial fibrillation
- •The main side effect related to DOACs is bleeding; however, most bleeding will be minor and will not require intervention

Indications for direct oral anticoagulants

Table 1 outlines the indications for the different DOACs. The most common indications for DOAC prescription are treatment of VTE and stroke prevention in non-valvular AF.

Table 1.

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(Adapted from Czuprynska et al 2017)

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National Institute for Health and Care Excellence (NICE) (2020a) guidelines stipulate that VTE events should be treated with at least three months of anticoagulation, although in some cases anticoagulation therapy will be lifelong.

Non-valvular atrial fibrillation

AF is the most common sustained heart rate and rhythm disorder. Around 25% of people over the age of 40 years will develop AF in their lifetime (Staerk et al 2018). Uncontrolled AF can promote blood stasis within the atria, which increases the risk of thrombus formation. A thrombus can pass into the cerebral and peripheral circulation, leading to thromboembolic complications including ischaemic stroke (Violi et al 2014).
Management of the arrhythmia and effective anticoagulation have an essential role in reducing risk of stroke in non-valvular AF (Floyd and Ferro 2017). The decision to anticoagulate will involve careful consideration of individual risk factors for stroke against bleeding risk factors.

Cancer-associated thrombosis

Until the past few years, low molecular weight heparin was the gold standard treatment for patients with thrombosis and active cancer. Clinical trials comparing low molecular weight heparin with edoxaban, rivaroxaban and apixaban for treatment of cancer-associated thrombosis found that these DOACs were favourable in selected patient groups (Raskob et al 2018, Young et al

2018, Agnelli et al 2020), which is now reflected in international guidelines (Khorana et al 2018, Key et al 2020).

Not all patients with cancer-associated thrombosis are suitable for a DOAC. Carrier et al (2018) suggested that treatment decisions should incorporate consideration of individual bleeding risk, type of cancer and possible drug interactions. Risk factors for bleeding include a previous history of bleeding, low platelet count and renal impairment (Carrier et al 2018). DOACs should be avoided in gastrointestinal or genitourinary cancers because they are associated with a higher risk of bleeding than low molecular weight heparin (Khorana et al 2018). Chemotherapy drugs and other concomitant medicines should be checked for interactions with DOACs. Local organisational guidelines and specialist advice should be sought when making clinical decisions about anticoagulation in cancer-associated thrombosis.

Other indications

DOACs first became available in the UK for thromboprophylaxis in hip and knee arthroplasty, with dabigatran, rivaroxaban and apixaban now licensed for this indication. The phase III clinical trials assessed DOACs to be non-inferior to 40mg enoxaparin sodium in preventing VTE after hip and knee arthroplasty, with similar bleeding rates (Eriksson et al 2007a, 2007b, 2008, Kakkar et al 2008, Lassen et al 2008, 2009, 2010a, 2010b, Turpie et al 2009). NICE (2019a) guidelines state that extended thromboprophylaxis must be used in patients undergoing total hip replacement (35 days with DOACs) and elective knee replacement (14 days with DOACs).

Rivaroxaban is licensed for some additional indications, such as acute coronary syndrome (unstable angina and myocardial infarction) and stable coronary or peripheral artery disease. More specifically, rivaroxaban is licensed for use in combination with aspirin plus clopidogrel or aspirin alone for prevention of further atherothrombotic events in people with acute coronary syndrome (NICE 2015). Patients undergoing this therapy should be reassessed within 12 months to determine the treatment duration. The rationale for combining these antiplatelet medicines and anticoagulants is linked to the pathophysiology of arterial clots – atherosclerotic-related clot formation relies on both platelet aggregation and fibrin

production. The phase III clinical trial (Mega et al 2012) found that rivaroxaban was effective at reducing the risk of stroke and myocardial infarction at the expense of an increased risk of bleeding, which has resulted in limited uptake of this treatment regimen.

At the time of writing, the latest indication to be approved is for rivaroxaban in combination with aspirin for prevention of atherothrombotic events in people with coronary or peripheral artery disease or who are at high risk of ischaemic events (NICE 2019b). The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial (Eikelboom et al 2017) found favourable outcomes for patients with coronary and peripheral artery disease when taking 2.5mg rivaroxaban twice daily and 100mg aspirin compared with those taking 100mg aspirin alone.

Doses of direct oral anticoagulants

While DOACs are given at fixed doses, the dose is dependent on the indication they have been prescribed for. Treatment for acute VTE with apixaban and rivaroxaban requires an initial regimen of a higher dose that is stepped down to a maintenance dose. Edoxaban and dabigatran require a five-day period of low molecular weight heparin before DOAC initiation. Standard dosing of DOACs for stroke prevention in non-valvular AF follows a fixed-dose regimen.

Appropriate DOAC dosing is crucial to avoid over-anticoagulation or under-anticoagulation. Because of the dose variations between agents and for different clinical indications, DOAC dosing has the potential to lead to medication errors if not carefully managed.

Dose adjustment criteria

The standard DOAC dosages are not suitable for all patients, and individual differences such as weight, age, baseline bloods, co-morbidities, concomitant medicines and drug interactions should be accounted for when selecting a patient's optimal dose. Each DOAC has a reduced dose with distinct criteria, and it is recommended that healthcare practitioners consult the British National

Formulary (Joint Formulary Committee 2020) or EMC (2019, 2020a, 2020b, 2020c) for guidance. If the guidance is not clear, experience and clinical judgement should be used (Czuprynska et al 2017).

All four DOACs are renally eliminated to varying degrees, dabigatran being the most renally cleared at 80%, edoxaban at 50%, rivaroxaban at 35% and apixaban the least at 27% (Steffel et al 2018). A decline in renal function is associated with potential drug accumulation and associated increased bleeding risk (Lutz et al 2017). Renal function should be calculated using creatinine clearance (Cockroft-Gault formula) for all patients before initiation, with use prohibited in patients with a creatinine clearance of below 15mL per minute, or 30mL per minute for dabigatran. Additionally, the hepatic elimination rates vary between each of the DOACs. Impaired liver function may lead to increased risk of bleeding for patients who are taking DOACs and therefore should not be used in moderate or severe liver dysfunction (Burnett et al 2016).

Side effects and risk of bleeding

The main side effect related to DOACs is bleeding. Other common side effects of DOACs include dizziness, headache, nausea, rash, pruritis, hypotension, increased liver function tests and dyspepsia with dabigatran (EMC 2019, 2020a, 2020b, 2020c).

The use of DOACs increases the risk of bleeding and can cause serious bleeds that are potentially fatal. Bleeding rates in the DOAC clinical trials were comparable, or lower, with DOACs than with alternative anticoagulants such as warfarin and low molecular weight heparin (Connolly et al 2009, Schulman et al

Some patient groups are at higher risk of bleeding than others, with risk factors including: advanced age; history of bleeding or anaemia; active cancer; previous stroke; chronic renal or liver disease; hypertension; acute or chronic illness; suboptimal anticoagulation control; alcohol intake; and certain concomitant medicines (Pisters et al 2010, Konstantinides et al 2020).

Most bleeding will be minor – for example epistaxis (nosebleeds) or gingival (gum) bleeding – and will not require intervention. Around 1-4% of people taking DOACs will experience major bleeding (Hellenbart et al 2017). This can occur at any site, but commonly includes gastrointestinal, genitourinary and intracranial

bleeding. In the event of bleeding in patients taking DOACs, local guidelines should be followed. Where possible, the timing of the last DOAC dose administered should be established and further anticoagulation should be withheld (Burnett et al 2016).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) increase bleeding risk and should be avoided with all DOACs. The indication for concomitant antiplatelet therapy should be reviewed when initiating DOACs. If dual antiplatelet therapy in AF is necessary, the European Society of Cardiology (Valgimigli et al 2018) guidelines recommend that the lowest effective tested DOAC dose for stroke prevention should be applied.

Information and shared decision-making

Before initiating DOACs, the benefits and risks should be discussed with the patient, and they should be provided with written information leaflets and a patient alert card. Verbal and written information should include the DOAC action, indication, expected duration of treatment, and how and when to take it. The patient should also be provided with information regarding bleeding risk and, importantly, what actions to take in the event of abnormal bleeding or bruising or sustained injuries.

The nuances of individual DOACs should be discussed with the patient, for example the need to eat with rivaroxaban to ensure optimal absorption. Providing effective support is crucial in optimising patient safety and adherence to these medicines, and must be tailored to meet the needs of individual patients. Shared decision-making enables patients to actively participate in their care and treatment, so should frame all discussions (Barratt 2018, Pearce 2019).