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REVIEW

Direct oral anticoagulants: the available agents and practical considerations

B Jordaan,[1] **S Louw**[2]

[1] *Department of Pharmacology, University of Pretoria, South Africa*
[2] *Department of Molecular Medicine and Haematology, University of the Witwatersrand and the National Health Laboratory Service, South Africa*
Corresponding author, email: *beatrice.jordaan@up.ac.za*

Thrombosis remains one of the leading causes of death in the world, and South Africa is no exception. In addition, as the population across the globe is ageing, the burden of stroke due to cardiovascular disease and atrial fibrillation (AF) is proliferating exponentially. Infection with HIV, which is prevalent in Africa, contributes significantly to the risk of both venous and arterial thrombosis. Anticoagulation can prevent thrombotic events but careful consideration of the choice of drug is needed to ensure efficacy and safety in the multifaceted anticoagulation drug arena. Although warfarin is still widely used, the direct oral anticoagulants (DOACs) are becoming the agents of choice for acute and chronic anticoagulation. The DOACs are a group of individual drugs, and choice of agent, and even dose, will depend on therapeutic indication, renal and liver function, age, body weight, comorbidities, previous medical history and concomitant medication. In this article the key pharmacological characteristics, indications and contraindications of the available DOACs in South Africa are summarised with the aim to assist with choosing the right anticoagulant, for the right patient, at the right dose, for the right duration.

Keywords: direct oral anticoagulants (DOACs), warfarin, apixaban, dabigatran, rivaroxaban, dosage, body mass index, missed dose, renal function, hepatic function, bleeding, drug reversal

Globally, as well as in South Africa, one of the major cardiovascular diseases is venous thromboembolic disease (VTED) but despite the high burden of VTED, approximately a quarter of at-risk patients remain without prophylaxis.[1] The World Health Organization (WHO) further estimates that, in approximately six years, one in six people in both developing and developed countries will be over the age of 60 years with increased cardiovascular disease (CVD) risks.[2] Furthermore, stroke incidence has more than doubled in low- to middle-income countries in the last four decades, due to aggregating risk factors, including hypertension and AF, both of which are especially prevalent in Africa.[3,4]

For many patients with VTED events and AF, warfarin remains the anticoagulant of choice and healthcare professionals are well versed with the international normalised ratio (INR) for anticoagulation monitoring. Warfarin, however, has numerous drug and food interactions with slow on- and off-set of action and unpredictability of activity.[5-8] These shortcomings in part motivated the development of the direct oral anticoagulants (DOACs). The currently available DOACs in South Africa are apixaban and rivaroxaban (direct factor-Xa inhibitors) and dabigatran (direct factor-IIa [thrombin] inhibitor).[2] The DOACs have more predictable pharmacological properties versus warfarin[5-8] and routine anticoagulation activity monitoring is currently not advocated, although the results of ongoing research are awaited.[9] The quick on- and off-set of actions of the DOACs are further advantages.[5-8]

DOACs mode of action

Apixaban and rivaroxaban prevent thrombin generation and thrombus development by directly inhibiting coagulation factor Xa (FXa). Activation of FX to FXa is pivotal in thrombus formation as FXa, together with factor Va (FVa), converts prothrombin to thrombin. This reaction leads to fibrin clot formation and activation of platelets. One molecule of FXa is able to generate more than 1 000 molecules of thrombin due to amplification in the coagulation cascade. In addition, the FXa activity is increased 300 000-fold when it binds to FVa resulting in an explosive burst of thrombin. Selective inhibitors of FXa, such as apixaban and rivaroxaban, terminate this augmented thrombin burst.[10,11]

Dabigatran is a direct thrombin inhibitor. Thrombin converts fibrinogen to fibrin, which is blood clot. The inhibition of thrombin therefore prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and also inhibits thrombin-induced platelet activation and aggregation.[12]

The indications, dosages and prescription considerations of the DOACs registered in South Africa are provided in Table I.[10-12]

The use of DOACs in elderly patients

The major concerns with DOAC use in elderly patients is renal dysfunction, which necessitates DOAC dose adjustments (Table II), as well as concomitant medications.

Apixaban

No routine dosage adjustment is required in elderly patients on apixaban therapy but in patients with at least two of the following characteristics, the dose should be decreased to

Table I: Indications, dosage and prescription considerations of the direct oral anticoagulants (DOACs) registered in South Africa[10-12]

Drug	Apixaban			Dabigatran		Rivaroxaban		
Registered indications	**Prevention of VTED after elective hip or knee replacement surgery**	**Prevention of SPAF**	**Treatment of DVT and PE and prevention of recurrent DVT and PE**	**Prevention of VTED after elective hip or knee replacement surgery**	**Prevention of SPAF**	**Treatment of DVT and PE and prevention of recurrent DVT and PE**	**Prevention of VTED after elective hip or knee replacement surgery**	**Prevention of SPAF**	**Treatment of DVT and PE and prevention of recurrent DVT and PE**
Dosage	• 2,5 mg twice dly starting 12–24 hrs after surgery • In actively bleeding patient: **delay** therapy	• 5 mg twice dly	• 10 mg twice dly for 7 days after the acute event, then 5 mg twice dly • 2.5 mg twice dly after at least 6 months of treatment for DVT or PE for prevention in patients with ongoing VTED risk	• 110 mg 1–4 hrs after surgery then 220 mg dly • In actively bleeding patient: **delay** therapy • If treatment not started on day of surgery: initiate with 220 mg daily	• 150 mg dly	• 150 mg twice dly after a parenteral anti-coagulant for at least 5 days after the acute event	• 10 mg dly starting 6–10 hrs after surgery • In actively bleeding patient: **delay** therapy	• 20 mg dly	• 15 mg twice dly for 3 weeks after the acute event, then 20 mg dly
Treatment duration	• Hip surgery: 32–38 days • Knee surgery: 10–14 days	• Continue as long as risk for SPAF persists	• 3-6 months • *>6 months for patients with ongoing VTED risk	• Hip surgery: 28 days • Knee surgery: 10 days	• Continue as long as risk for SPAF persists	• 3–6 months • *>6 months for patients with ongoing VTED risk	• Hip surgery: 5 weeks • Knee surgery: 2 weeks	• Continue as long as risk for SPAF persists	• 3- 6 months • *>6 months for patients with ongoing VTED risk
Administration	• Taken with or without food			• Taken with or without food with a full glass of water • Do not open the capsule • Taken with a meal and/or proton pump inhibitor if gastrointestinal symptoms develop			• 10 mg: taken with or without food • 15 and 20 mg: taken with food		
Peak effect	• 1 hr			• 2–3 hrs			• 2–4 hrs		
Effective half-life	• 10–14 hrs			• 12–13 hrs			• 9–13 hrs		

VTED, venous thromboembolic disease; SPAF, stroke and systemic embolism prevention in non-valvular atrial fibrillation; DVT; deep vein thrombosis; dly, daily; hrs, hours; *ongoing treatment duration must be individualised.

2,5 mg twice daily as opposed to 5 mg twice daily:[10]

- age ≥ 80 years
- body weight ≤ 60 kg
- serum creatinine ≥ 1,5 mg/dL (133 µmol/L)

Dabigatran

Dabigatran is 80% renally excreted, and renal impairment is common in the elderly (i.e. > 75 years of age) and therefore kidney function should be assessed prior to therapy initiation and annually thereafter, in this group of patients.[12]

Rivaroxaban

Decreased renal function can result in rivaroxaban accumulation and bleeding and should therefore, be used with caution in patients with renal impairment (CrCl < 50 ml/min).[11]

The use of DOACs at extremes of body mass index (BMI)

According to the registered package inserts of the DOACs, no routine dose adjustment is required based on body weight.[10-12]

According to Stats SA, in 2016 more than 30% of men and more than 60% of women were overweight or obese in South Africa.[13] Obesity is a risk factor for arterial and venous thromboses. Previously, there were concerns regarding sub-therapeutic DOAC levels in patients weighing over 120 kg.[14] New data on DOAC activity in overweight or obese patients published as a meta-analysis of 89 494 patients (45 427 on DOAC and 44 067 on warfarin therapy) indicates that DOACs at standard doses are effective and safe when compared with warfarin in morbidly obese patients.[15] The International Society on Thrombosis and Haemostasis (ISTH) also published recommendations supporting the use of standard dose apixaban and rivaroxaban in patients weighing more than 120 kg.[16] For patients between 120–150 kg, for SPAF or treatment of VTE, the National Health Scotland: Greater Glasgow and Clyde (NHSGGC) Drug and Therapeutics Committee consensus also supports standard dose apixaban. This recommendation is based on phase 4 post-marketing experience, but the

guidance does recommend for individualisation in patients >150 kg.[17]

The use of DOACs in patients with renal impairment

The percentage renal excretion of the DOACs is provided below:[10-12]

- Apixaban: 25%
- Dabigatran: 80%
- Rivaroxaban: 66%

According to the South African medicine, registration the use of dabigatran in patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min) is contraindicated.[12] Rivaroxaban should be used with caution in patients with severe renal impairment (CrCl 15–30 mL/min).[11]

However, various guidelines and reviews have recently been published with regards to DOAC dose adjustment in patients with renal dysfunction.[18.23] The recent guidelines from the American Heart Association (AHA) regarding DOAC dosing according to renal function is detailed in Table II.[24]

The use of DOACs in patients with hepatic impairment

Since hepatic breakdown of drugs has an effect on the duration of drug activity, hepatic function is of importance especially in the prescription of anticoagulant drugs such as DOACs (Table III).

DOACs drug-drug interactions[24]

Care should be taken if patients on DOAC treatment are treated concomitantly with drugs such as antiplatelet agents (e.g. Aspirin) and nonsteroidal anti-inflammatories (NSAIDs).

In addition, apixaban and rivaroxaban should be administered with caution in patients receiving concomitant strong inhibitors of both Cytochrome 3A4 and P-glycoprotein, such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole and posaconazole), antiretrovirals (ARVs) for infection with human immunodeficiency virus (HIV) such as protease inhibitors (e.g. ritonavir), and additional drugs, including rifampicin, phenytoin, carbamazepine, phenobarbitone and St. John's Wort (*Hypericumperforatum*) as the anticoagulant action of these DOACs can be increased with these concomitant drugs.[10]

Dabigatran is not metabolised by the cytochrome P450 system, therefore, related interactions with, e.g. atorvastatin, diclofenac, rifampicin, carbamazepine or St. John's Wort are not expected with dabigatran.[12]

DOACs missed dose[10-12]

If a dose is missed, the prescribed DOAC should be taken when patient remembers the omission and continue with the once or twice daily intake the next day. The dose should, however, not be doubled within the same day (24 hours) to make up for a missed dose.

For dabigatran, a missed dose may still be taken up to six hours prior to the next scheduled dose. From six hours onward prior to the next scheduled dose, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses.[12]

DOACs bleeding and reversal agents[10-12]

Idarucizumab, a specific reversal for dabigatran, is available in South Africa.[12] No specific reversal agents for apixaban and rivaroxaban is currently available in South Africa.[10-12] Should active haemorrhage occur, for instance during elective surgery, or invasive procedures that place patients at an increased risk of bleeding, apixaban or rivaroxaban should be delayed or discontinued as appropriate. The following supportive treatments are suggested: local compression (where possible), surgical intervention, fluid replacement and haemodynamic support (blood product or component transfusion). For life-threatening bleeding that cannot be controlled with these measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving apixaban and rivaroxaban.[10-12] Administering activated charcoal can be considered.[7] Dabigatran is dialysable because of its low plasma protein binding.[12]

Table II: American Heart Association (AHA) guidelines on DOAC dosing according to renal function[24]

DOAC	Creatinine clearance (CrCl) (mL/min)				
	> 95 mL/min	51–95 mL/min	31–50 mL/min	15–30 mL/min	< 15 mL/min or on dialysis
Apixaban	5 or 2.5 mg BD	5 or 2.5 mg BD	5 or 2.5 mg BD	5 or 2.5 mg BD	5 or 2.5 mg BD
Dabigatran	150 mg BD	150 mg BD	150 mg BD	75 mg BD	Contraindicated
Rivaroxaban	20 mg OD	20 mg OD	15 mg OD	15 mg OD	15 mg OD

BD: twice daily; OD: once daily

Table III: DOAC therapy in patients with hepatic impairment[24]

Severity of liver failure (Child Pugh Score)	Apixaban	Dabigatran	Rivaroxaban
Mild (A)	No dose adjustment	No dose adjustment	No dose adjustment
Moderate (B)	Use with caution	Use with caution	Avoid use
Severe (C)	Contraindicated	Contraindicated	Contraindicated

Conclusion

Thrombosis, including VTED and stroke, remains a leading cause of death in South Africa. DOACs as a therapeutic class of anticoagulants has become indispensable as substitute for warfarin for both prophylaxis and treatment. Additional trials and real-life post-marketing data will be included in DOAC treatment guidelines to improve patient outcomes.

ORCID

B Jordaan https://orcid.org/0009-0007-4921-4519
S Louw https://orcid.org.0000-0002-4315-1496

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