DIRECT ORAL ANTICOAGULANTS

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Until recently, Warfarin, a Vitamin K antagonist was the only available oral anticoagulant. Its narrow therapeutic index and multiple drug and diet interactions affected its safety, compliance and efficacy. Because of these limitations, the direct oral anticoagulants (DOACs) have recently emerged as a viable alternative to Warfarin.
They enjoy advantages over Warfarin in that they are stable, have shorter half-lives, are without many drug and food interactions, and do not require monitoring. They are however not without disadvantages.

ADVANTAGES	DISADVANTAGES
No monitoring required	No reliable monitoring currently
Less drug interactions	No specific antidotes
No known food interactions	Costly
Short half-life – no bridging required	More gastrointestinal bleeding
Convenient oral daily or twice daily dosing	Contra-indicated in severe renal failure
Less overall bleeding	
Less intracranial bleeding	

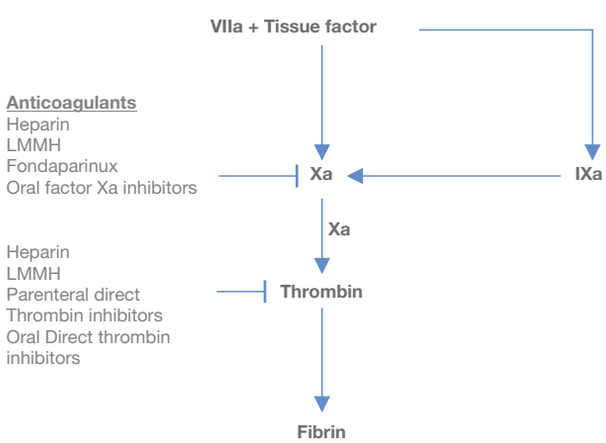
The DOACs can be classified into two broad categories, viz. the Direct Thrombin Inhibitors and the Factor Xa inhibitors. Currently available DOACs in SA include Dabigatran (Pradaxa) and Rivaroxaban (Xarelto). Apixaban and Edoxaban are also available internationally.

Clinical trials have shown the DOACs to be at least as effective as Warfarin and at least as safe in terms of bleeding risks.

They are currently registered in South Africa for the use in patients for:

- Prevention of stroke in non-valvular atrial fibrillation (Xarelto & Pradaxa)
- Prevention of thrombosis in patients undergoing orthopaedic surgery (total hip and knee replacement) (Xarelto & Pradaxa)
- Treatment of acute thrombosis (DVT & PE) (Xarelto only)

Mechanisms of action of anticoagulants



CLINICALLY IMPORTANT PROPERTIES	DABIGATRAN	RIVAROXABAN	APIXABAN
CLINICAL INDICATION AND DOSES			
Atrial fibrillation (indefinite duration)	150 mg or 110 mg twice daily	20 mg daily*	5 mg twice daily†
Acute VTE (3 to 6 months)	150 mg twice daily	20 mg daily, 15 mg twice daily for initial 21d	5 mg twice daily, 10 mg twice daily for initial 7d
VTE prevention after knee or hip replacement surgery (14 or 30 days, respectively)	110 mg (initial dose) then 220 mg daily	10 mg daily	5 mg twice daily, 10 mg twice daily for initial 7d

KEY PHARMACOLOGIC PROPERTIES			
Mechanism of action	Direct factor IIa (thrombin) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Renal clearance	80%	33% (active drug)	25%
HALF - LIFE			
Normal renal function (eGFR > 80 mL/min)	11 h	9 h	9 h
Mild renal impairment (eGFR 50-80 mL/min)	14 h	9 h	9 h
Moderate renal impairment (eGFR 30-49 mL/min)	15 - 17 h	10 - 15 h	10 - 14 h
Onset of action (after oral intake)	1 - 3 h	1 - 3 h	1 - 3 h
KEY PRACTICAL PROPERTIES			
Food or alcohol interactions	None	None	None
Drug interactions	Amiodarone, quinidine, azole antifungals (eg, ketoconazole), rifampin, ritanovir	Azole antifungals (eg, ketoconazole), ritanovir, rifampin, clarithromycin, anticonvulsants (eg, phenytoin, carbamazepine)	Azole antifungals (eg, ketoconazole), ritanovir, rifampin, clarithromycin, anticonvulsants (eg, phenytoin, carbamazepine)
Antidote	None to date	None to date	None to date
Laboratory measurement of anticoagulant effect‡	aPTT or TT, dilute TT (direct thrombin inhibitor assay)	PT or INR (reagent specific), anti–factor Xa assay	PT or INR (minimal effect), anti–factor Xa assay

The choice of which DOAC to use needs to be individualised. Factors such as indication, age, renal function and bleeding risk should all be considered. Below is a table with a suggested approach to commencing DOACs.

Suggested DOACs according to patient characteristics

PATIENT CHARACTERISTIC	SUGGESTED DOAC REGIMEN	COMMENT
Patients with AF at high risk of stroke (eg, CHADS2 score ≥ 3) or with previous stroke	Dabigatran, 150 mg twice daily	This dose of dabigatran conferred the greatest risk reduction in stroke compared with warfarin
	Rivaroxaban, 20 mg daily	More patients with previous stroke were studied with rivaroxaban
Patients with AF at high risk of bleeding	Apixaban, 5 mg twice daily	This dose of apixaban conferred a decreased risk of major bleeding compared with warfarin
	Dabigatran, 110 mg twice daily	This dose of dabigatran conferred a decreased risk of major bleeding compared with warfarin
Patients with dyspepsia or other gastrointestinal complaints	Apixaban or rivaroxaban	These drugs have been associated with less dyspepsia than dabigatran
Patients with AF and anticipated medication compliance problems	Rivaroxaban, 20 mg daily	Once-daily dosing might allow better compliance when there is long-term need for medication
Elderly (≥ 80 y.o), patients with impaired renal function (e.g. eGFR < 50 mL/min)	Apixaban, 2.5 mg twice daily	Apixaban was associated with a reduced the risk of bleeding in patients with impaired renal function

Conclusion

The perfect anticoagulant still remains elusive; however, the advent of the direct oral anticoagulants represents an improvement, and provides more options for the prevention and treatment of patients with thrombosis. The choice of which DOACs to use should be individualised according to indication, age, renal function and specific bleeding risks all receiving consideration. Notwithstanding the benefits of these drugs, their cost remains one of the major hurdles in their routine use.

References

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