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The Direct Oral Anti-Coagulants

In the management and prevention of thrombotic conditions such as PE, DVT, AF and post-surgery, the current choices for long term oral anticoagulants include warfarin and the direct oral anticoagulants (DOACs).

DOACs promise equivalent benefit to warfarin without the need for constant monitoring, dose alterations or dietary restriction. The three currently on the Australian market are: rivaroxaban (Xarelto® Bayer), dabigatran (Pradaxa® Boehringer Ingelheim), and apixaban (Eliquis® Bristol-Myers Squibb/ Pfizer®).

Efficacy

DOACs are non-inferior to warfarin in the settings of VTE prevention in non-valvular AF and therapy of PE and DVT. Bleeding rates were shown to be equivalent, with intracranial bleeding on warfarin balanced by gastrointestinal bleeding with DOACs.

Pharmacology

Renal impairment can lead to accumulation and overdosage of DOACs. Accurate estimation of renal function is imperative and the eGFR should not be relied upon. Apixaban and rivaroxaban are also metabolised by the liver and are contraindicated in Child-Pugh Class C cirrhosis, acute hepatitis and liver disease with an associated coagulopathy.

Contraindications to DOACs include active bleeding, planned surgery, lesions at risk of bleeding (recent CVA, active PUD), CrCl <30ml/min, concomitant treatment with strong inhibitors of CYP34A and P-glycoprotein (Clarithromycin, azoles, HIV PIs), pregnancy and lactation.

Other drug interactions include SSRIs and PPIs with dabigatran. Inducers of CYP3A4 and P-gp (phenytoin, carbamazepine, St John's Wort) have been shown to increase bleeding risk when combined with apixaban and are expected to reduce dabigatran concentrations, raising concerns of under-anticoagulation. P-gp inhibitors (amiodarone, clarithromycin, verapamil) should be used with caution and patients kept under close surveillance due to their potential to increase dabigatran levels and potentiate its anticoagulant effect. NSAIDs and anti-platelet agents should be used with caution and only for short periods with any anticoagulant.

Uses

PBS listings for the current drugs are not uniform and may be a potential cause for confusion.

Current approved Australian indications for oral anticoagulants are listed here (see table).

	Rivaroxaban	Dabigatran	Apixaban
Target	Xa	Free and clot bound thrombin (IIa)	Xa
Bioavailability	66%	6.5%	50%
T_{MAX} (hrs)	2-4	0.5-2.0	1-4
$T_{½}$ (hrs)	5-9 (healthy), 11-13 (elderly)	12-17	8-15
Protein binding	95%	35%	87%
Elimination	Renal 66% *, Hepatic 33%	Renal 80-85%, Hepatic 15-20%	Renal 27%
Metabolism	P-gp, CYP 3A4	P-gp	P-gp, CYP 3A4/5
Dosing	(15mg BD initially for VTE) 20mg OD	150mg BD	†
Weight impact	<25%, No dose adjustment	<25%, No dose adjustment	<25%, No dose adjustment
Age impact	1.5 fold higher AUC in >65yrs No dose adjustment	2 fold higher AUC in >65yrs Use 110mg BD in >75yrs	32% higher AUC in >65yrs No dose adjustment ‡
Renal function	If CrCl 30–49 mL/min: ↓ to 15 mg OD Contraindicated if CrCl <30mL/min	If CrCl 30–50 mL/min: ↓ to 110 mg BD Contraindicated if CrCl <30mL/min	‡

* Renal excretion of drug 33%, renal excretion of metabolites 33%
† 10mg BD for 7 days then 5mg BD for VTE Rx, 2.5mg BD for secondary prevention of PE/DVT, NVAF – 5mg BD
‡ 2.5 mg twice daily if patient has two out of three of the following: age, ≥ 80 years; weight, ≥ 60 kg; creatinine, ≥ 133 umol/L.

Perioperative management

The half-lives of the DOACs in patients with a CrCl>50mL/min means that withholding the drug for 24 hrs prior to low risk, or 48-72 hrs for high bleeding risk, procedures is usually sufficient. In impaired renal function (CrCl 30-49mL/min) these extend to 48-72 hrs and 72-96 hrs, respectively.

Pitfalls

Although designed not to require any therapeutic monitoring, certain situations may demand an assessment of coagulation or drug level: patients with low body weight or obesity; children; those with renal or hepatic impairment; accidental or deliberate overdoses; to measure adherence; to evaluate patients with haemorrhagic or thrombotic complications; and to assess levels prior to surgery.

The standard assays of coagulation used to monitor heparin and Warfarin are unsuitable for the DOACs because the assays are either insensitive or too sensitive to the drugs. Clinically important anticoagulation may be predicted. Prolonged APTT and TCT suggest clinically significant dabigatran and an APTT >80sec predicts increased bleeding risk. A prolonged INR (>1.2) indicates clinically significant rivaroxaban levels. Assays developed to determine blood levels have no ratified reference ranges, and analysis is dependent on the timing of the last dose and the strength of the tablets.

Common adverse events for all NOACs include increased liver transaminases and GI upset.

Caution: assays for thrombophilia such as Protein C and S, Lupus anticoagulant and activated protein C resistance, are interfered with by DOACs.

Management of bleeding complications

Minor bleeding: withhold drug for a dose, discontinue if appropriate; apply local measures; assess for aggravating factors; determine renal and liver function.

Moderate bleeding: above plus, hydration to maximise urine output; charcoal if ingestion within 2 hours; platelet transfusion if concomitant thrombocytopenia or antiplatelet agents; administer tranexamic acid.

Severe or ongoing bleeding: dialysis can be used in dabigatran-treated patient; prothrombin complex concentrate (Prothrombinex®-VF) and recombinant factor VII (Novoseven®) for rivaroxaban. Idarucizumab (Praxbind®) is a monoclonal antibody fragment developed to reverse the anticoagulant effects of dabigatran (limited availability).

Drug	Valvular AF	Metal valve replacement	Non valvular AF	THR/TKR Post-Op	VTE – short / long term
Warfarin	✓	✓	✓	×	✓
Rivaroxaban	×	×	✓	✓	✓
Dabigatran	×	×	✓	✓	×
Apixaban	×	×	✓	✓	✓

✓ = PBS listed; × = not PBS listed; VTE – venous thromboembolism (Pulmonary Embolism and Deep Vein Thrombosis); AF – atrial fibrillation; THR – total hip replacement; TKR – total knee replacement