DOAC Guidelines

Direct Oral Anticoagulants

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Clinical Excellence Commission
Board Chair: Prof Andrew Wilson
Chief Executive: Adjunct Professor Michael C Nicholl

Any enquiries about or comments on this publication should be directed to:
Clinical Excellence Commission
Locked Bag 230
St Leonards NSW 1590
Phone: (02) 9269 5500
Email: CEC-MedicationSafety@health.nsw.gov.au

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Clinical Excellence Commission, 2023, Direct Oral Anticoagulant (DOAC) Guidelines are available at:
https://www.cec.health.nsw.gov.au/keep-patients-safe/medication-safety/high-risk-medicines/anticoagulants

Contents

Introduction

Direct oral anticoagulants (DOAC) are used in adult patients for the prevention of stroke in non-valvular atrial fibrillation (AF), treatment and prevention of venous thromboembolism (VTE) and prevention of major cardiovascular events in patients with atherosclerotic disease.

DOACs approved by the Therapeutic Goods Administration (TGA) for use in Australia include apixaban and rivaroxaban (factor Xa inhibitors), and dabigatran (a direct thrombin inhibitor).[1-3]

The terms 'non-Vitamin K Antagonist Oral Anticoagulant' and 'novel oral anticoagulant' (NOAC) have been used in the past to describe this class of medicines. However, the International Society on Thrombosis and Haemostasis (ISTH), along with several other international societies recommend using the term 'direct oral anticoagulant' (DOAC) as it indicates their pharmacological specificity and is less likely to be misinterpreted.[4]

This guideline is intended to assist clinicians with the inpatient and outpatient management of patients receiving a DOAC. It addresses DOAC use in **adult patients only**.

This DOAC guideline does **not** address anticoagulation in:

Pregnant or breastfeeding patients. DOACs are contraindicated in pregnancy and breastfeeding.[1-3]

Patients less than 18 years of age. The use of DOACs in patients under 18 years is considered off-label due to lack of TGA registration in this population and limited paediatric-specific data. Clinicians must carefully weigh the potential benefits against bleeding risk and absence of reversal agents when considering DOAC therapy for this patient population and obtain informed consent from the patient's legal guardian.

Patients requiring VTE prophylaxis for lower limb injury. The use of DOACs in patients presenting to emergency departments with lower limb injury, not requiring surgical intervention and without a previous history of VTE, is considered off-label due to a lack of TGA approval for this indication. Patients will also be ineligible for supply under the Pharmaceutical Benefits Scheme (PBS) and will be required to pay the full cost of the medication. Clinicians must carefully weigh the potential benefits of DOAC use for this population and obtain informed consent from the patient.

Information within this guideline should be used in conjunction with the TGA approved Product Information, the NSW Health Policy Directive *High Risk Medicine Management* (PD2020_45) and associated Anticoagulant standard, local protocols, and specialist advice.

This guideline was developed in collaboration with a multi-disciplinary expert Anticoagulant Medicines Working Party[a]. Consensus recommendations indicated in the guideline are based on available evidence at the time of publication and the expert opinion of the Working Party.

[a] The Anticoagulant Medicines Working Party members included a consumer, a nursing representative (CNC), pharmacy representatives, a Chief Medical Information Officer and medical representatives including consultants in anaesthetics, cardiology, general medicine, geriatrics, haematology, intensive care, respiratory, stroke neurology and surgical as well as a Junior Medical Officer, Basic Physician Trainee and Advanced Trainee (Haematology).

1. Indications and contraindications

1.1 – Indications

Apixaban (Eliquis®), rivaroxaban (Xarelto®) and dabigatran (Pradaxa®) are DOACs approved by the TGA and listed on the PBS for use in specific clinical conditions. A summary of TGA approved indications[1-3] and PBS listings[5] is presented in Table 1. This table was accurate at the time of publication; prescribers should refer to the TGA and PBS websites for the most up-to-date information.

The PBS listings can be complex as the benefit may apply only to certain strengths. For example, rivaroxaban 2.5 mg and 10 mg tablets are **not** PBS listed for the prevention of stroke in non-valvular AF, however the 15 mg and 20 mg tablets are PBS listed for this indication.

For patients requiring a PBS prescription, the DOACs are all PBS Authority Required (Streamlined). Prescribers eligible to write a PBS prescription should check the PBS website for the relevant streamline authority codes for the indication and duration they are to be prescribing for.

At the time of publication, the NSW Medicines Formulary included all DOACs for initiation in NSW Health facilities with use as per PBS criteria (see NSW Medicines Formulary online platform for further details including restrictions on use).

Table 1: TGA approved indications and PBS listings[1-3,5]

	Apixaban		Rivaroxaban		Dabigatran	
Indication	TGA registered	PBS listed	TGA registered	PBS listed	TGA registered	PBS listed
Prevention of stroke and systemic embolism in non-valvular AF with at least one stroke risk factor[a]	✓	✓	✓	✓	✓	✓
Treatment of VTE	✓	✓	✓	✓	✓	✘
Prevention of recurrent VTE	✓	✓	✓	✓	✓	✘
Prevention of major cardiovascular events in patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD)[b]	✘	✘	✓	✓	✘	✘
Prevention of VTE following total hip replacement (THR) or total knee replacement (TKR)	✓	✓	✓	✓	✓	✓

[a] See Box 1 for PBS listing risk factors.
[b] Must be in combination with aspirin (but not with any other antiplatelet therapy).

Box 1: PBS listing risk factors for developing stroke or systemic embolism[5]

i. Prior stroke (ischaemic or unknown type), transient ischaemic attack (TIA) or non-central nervous system (CNS) systemic embolism.
ii. Age ≥ 75 years.
iii. Hypertension.
iv. Diabetes mellitus.
v. Heart failure and/ or left ventricular ejection fraction ≤ 35%.

1.2 – Contraindications

DOAC use is contraindicated in certain clinical conditions, notably, in patients who have a mechanical heart valve and those with rheumatic mitral stenosis.

Moderate to severe renal impairment or significant hepatic disease is also a contraindication to DOAC treatment.[1-3] When determining renal function, the estimated creatinine clearance (CrCl) should be calculated using the Cockcroft-Gault Equation; the eGFR reported in pathology results should not be used. In the case of a patient with renal impairment, treatment with warfarin may be more appropriate.[6] Box 2 and section 2.5 DOAC dosing provide more information on contraindications and advice regarding DOAC treatment in various degrees of renal impairment.

Whilst DOACs are not absolutely contraindicated in patients with a history of gastrointestinal bleeding, prescribers should use caution and seek specialist advice when prescribing a DOAC in these patients.

DOAC use has not been robustly studied in the treatment of unusual site thrombosis, such as cerebral venous sinus thrombosis, portal and splenic vein thrombosis and non-upper and lower limb DVT. If their use is considered for these types of thromboses, specialist advice from a haematologist should be sought before commencing treatment.

Box 2 provides a list of contraindications to DOAC treatment.

Box 2: Contraindications to DOAC treatment[1-3]

Known hypersensitivity to the active ingredient or to one of the excipients of the formulation
Mechanical heart valve
Rheumatic mitral stenosis
Renal impairment: • Apixaban: CrCl < 25 mL/min • Rivaroxaban: CrCl < 15 mL/min[a] • Dabigatran: CrCl < 30 mL/min
Triple positive antiphospholipid syndrome (aPLS)[b]
Significant inherited or acquired bleeding disorder
Clinically significant active bleeding
Hepatic disease with associated coagulopathy including Child-Pugh C
Lesions or conditions at significant risk of bleeding including intracranial haemorrhage unless under the advice of a neurologist/neurosurgeon
Indwelling spinal or epidural catheter and during the first six hours after removal
Co-administration with strong inhibitors (or inducers) of CYP3A4 and P-glycoprotein (P-gp) (see 2.3 Drug interactions)
Pregnancy or breastfeeding

[a] At the time of publication, rivaroxaban had been studied in a limited number of patients with a CrCl 15 – 29 mL/min; consider its use in these patients only under advice from a specialist.

[b] Triple positive aPLS is an autoimmune thrombophilia characterised by recurrent venous and arterial thrombosis associated with circulating antiphospholipid antibodies. A patient who is 'triple positive' will have two positive serum IgG aPL antibodies along with one positive functional plasma lupus anticoagulant (LAC) test result on at least two occasions tested 12 weeks apart. These patients are at an increased risk of thrombosis.

2. Commencing treatment

The decision to commence DOAC treatment should be made by a senior medical officer, in partnership with the patient and/or family or carer, after considering the patient's preference, relevant comorbidities, potential drug interactions and baseline laboratory tests.

2.1 – DOAC choice

There are no completed head-to-head clinical trials of any of the DOACs. In the landmark stroke prevention[7-9] and VTE treatment[10-12] trials, all three available DOACs were compared to warfarin. These trials demonstrated that the safety and efficacy of all three drugs was comparable or superior to warfarin.

In the absence of direct comparison trials, it is not possible to recommend one DOAC over another in all cases, but patient-related factors and dosing regimens may make one agent and dose optimal for individual patients.

The following sections will outline patient-specific comorbidities and significant drug interactions that will need to be considered when starting a DOAC. Factors which may affect the choice of DOAC include the dosing frequency, history, and site of major bleeding (gastrointestinal or intracranial) and if there is a reversal agent available. In all cases, the choice of DOAC should be made after careful consideration of patient-related factors and a thorough clinician-patient discussion.

2.2 – Considerations prior to commencing a DOAC

Patient comorbidities, particularly those which affect the DOAC elimination rate need to be considered when commencing and managing patients taking a DOAC. A summary of these considerations is presented in Table 2.

Table 2: Comorbidities to consider prior to commencing a DOAC[1-3]

Consideration	Clinical advice
Renal impairment	Dose adjustment may be required (see 2.5 DOAC dosing).
Hepatic impairment	All DOACs are contraindicated in hepatic disease with associated coagulopathy, including Child-Pugh C. Apixaban and dabigatran can be used with caution in mild to moderate hepatic impairment (Child-Pugh A or B). Rivaroxaban can be used with caution in mild hepatic impairment (Child-Pugh A) and is contraindicated in moderate hepatic impairment (Child-Pugh B).
Gastrointestinal bleeding	Use with caution and seek specialist advice in patients with any history of gastrointestinal bleeding.
Critically unwell (for example, sepsis)	DOACs should not be commenced in critically unwell patients.
Extremes in body weight	Dose adjustment is not required for extremes of body weight for all agents (excluding apixaban). It is recommended that a reduced dose of apixaban be considered for patients weighing 60 kg or less for stroke prevention in non-valvular AF if another factor is present (see 2.5 DOAC dosing). At the time of publication there has been limited published data for dosing of DOACs in patients with a BMI of over 40 kg/m^2 or a weight over 120 kg. It is important to note that DOAC activity is linked to lean body weight and the relationship becomes inversely proportional for individuals with a total body weight over 100 kg.

Other patient-related factors to be taken into consideration prior to commencing a DOAC are summarised in Table 3.

Table 3: Patient-related factors to consider prior to commencing a DOAC[1-3]

Consideration	Clinical advice
Adherence	DOACs have a rapid offset of action compared to warfarin and missed doses or interruptions in therapy can result in poor anticoagulant coverage (see 2.7 Management of missed DOAC dose).[13]
Dose administration aids	Dabigatran capsules must not be removed from packaging until the time of administration making them unsuitable for patients who are reliant on dose administration aids (see 2.6 DOAC administration).
Dysphagia	Dabigatran capsules must not be opened making them unsuitable for patients unable to swallow a capsule whole (see 2.6 DOAC administration).

2.3 – Drug interactions

There are several drug interactions that need to be considered when commencing and managing patients taking DOACs. Drugs that inhibit or induce CYP3A4 liver enzymes and/or permeability of glycoprotein (P-gp) transporters can have significant interactions with DOACs. Apixaban and rivaroxaban have the same drug interaction profile, however dabigatran is not metabolised by CYP 3A4 enzymes, so the drug interactions vary. Table 4 outlines the details of relevant drug interactions. This is not an exhaustive list; however, it includes those that are considered clinically significant.

Please note, a relative contraindication refers to a situation in which the use of both medications may be considered inappropriate due to an interaction, however their co-administration may be acceptable if potential benefits outweigh the potential risks.

For further information on DOAC drug interactions, NSW Health's Clinical Information Access Portal (CIAP) provides access to a range of medicines information sources including drug interaction checking tools.

Table 4: DOAC-drug interactions[1-3,6]

= coadministration is **contraindicated** = coadministration is a **relative contraindication**

	Drug class	Drugs within class	Effect on DOAC concentration	Clinical advice
Apixaban OR Rivaroxaban	Anticonvulsants	Carbamazepine Phenobarbital Phenytoin	↓↓	Co-administration should be **avoided** due to increased risk of thrombosis. If apixaban or rivaroxaban is being used in the treatment of VTE then co-administration is contraindicated.
	Antidepressant	St John's Wort	↓↓	
	Anti-infectives	Clarithromycin Erythromycin	↑	Co-administration should be used with **caution** due to increased risk of bleeding.
	Anti-infectives	Rifampicin	↓↓	Co-administration should be **avoided** due to increased risk of thrombosis. If apixaban or rivaroxaban is being used in the treatment of VTE then co-administration is contraindicated.
	Azole antifungals	Itraconazole Ketoconazole	↑↑↑	Co-administration is **contraindicated** due to increased risk of bleeding.
	Calcium channel blocker	Diltiazem	↑	Co-administration should be used with **caution.**
	HIV-protease inhibitor	Ritonavir[a]	↑↑↑	Co-administration is **contraindicated** due to increased risk of bleeding.

[a] This includes combination ritonavir products: Kaletra® (lopinavir and ritonavir) used for the management of HIV infection and Paxlovid® (nirmatrelvir and ritonavir) used for the treatment of COVID-19 infection. The co-administration of apixaban with ritonavir in combination with nirmatrelvir (as Paxlovid) may be possible. Dosing recommendations for co-administration depend on the therapeutic indication and dosing of apixaban. Refer to the University of Liverpool COVID-19 Drug Interactions Database for further information.

Continued Table 4: DOAC-drug interactions[1-3,6]

= coadministration is **contraindicated** = coadministration is a **relative contraindication**

	Drug class	Drugs within class	Effect on DOAC concentration	Clinical advice
Dabigatran	Antiarrhythmic	Dronedarone[a]	↑↑↑	Co-administration is **contraindicated** due to increased risk of bleeding.
	Antiarrhythmics	Amiodarone Quinidine[a]	↑	Co-administration should be used with **caution** due to increased risk of bleeding.
	Anticonvulsants	Carbamazepine Phenobarbital Phenytoin	↓↓	Co-administration should be **avoided** due to increased risk of thrombosis.
	Antidepressant	St John's Wort	↓↓	Co-administration should be **avoided** due to increased risk of thrombosis.
	Anti-infectives	Rifampicin	↓↓↓	Co-administration is **contraindicated** due to increased risk of thrombosis.
	Anti-infectives	Clarithromycin Erythromycin	↑	Co-administration should be used with **caution** due to increased risk of bleeding.
	Antivirals for hepatitis C	Glecaprevir with pibrentasvir	↑↑↑	Co-administration is **contraindicated** due to increased risk of bleeding.
	Azole antifungals	Itraconazole Ketoconazole	↑↑↑	Co-administration is **contraindicated** due to increased risk of bleeding.
	Azole antifungals	Fluconazole Posaconazole Voriconazole	↑	Co-administration should be used with **caution** due to increased risk of bleeding.
	Calcium channel blocker	Verapamil	↑↑↑	**Relative contraindication** If adding verapamil to dabigatran or starting both drugs on the same day, the dabigatran should be given at least 2 hours before verapamil for the first 3 days.
	HIV-protease inhibitors	Nelfinavir[a] Ritonavir[b] Saquinavir[a]	↑	Co-administration should be used with **caution** due to increased risk of bleeding.
	Immunosuppressant	Ciclosporin	↑↑↑	Co-administration is **contraindicated** due to increased risk of bleeding.
	Immunosuppressant	Tacrolimus	↑↑	Co-administration should be **avoided** due to increased risk of bleeding.

[a] These drugs are not currently marketed in Australia.

[b] This includes combination ritonavir products: Kaletra® (lopinavir and ritonavir) used for the management of HIV infection and Paxlovid® (nirmatrelvir and ritonavir) used for the treatment of COVID-19 infection. The co-administration of apixaban with ritonavir in combination with nirmatrelvir (as Paxlovid) may be possible. Dosing recommendations for co-administration depend on the therapeutic indication and dosing of apixaban. Refer to the University of Liverpool COVID-19 Drug Interactions Database for further information.

When prescribing DOACs, it is crucial to consider potential interactions with medications that exhibit antithrombotic or bleeding effects. These medications encompass other anticoagulants and agents with antiplatelet activity such as aspirin, dipyridamole, P2Y12 inhibitors, and glycoprotein IIb/IIIa inhibitors. Co-administration of a DOAC and these agents should be avoided where possible. If deemed necessary, doses of the selected agents should be reviewed to carefully balance between thrombosis prevention and bleeding risk.

Table 5: DOAC-interactions with medications affecting bleeding risk and heamostasis[1-3,6]

= coadministration is **contraindicated** = coadministration is a **relative contraindication**

	Drug	Effect on bleeding rates	Clinical advice
Antiplatelet drugs	Aspirin[a] Clopidogrel Dipyridamole Prasugrel NSAIDs[b]	Increased risk of bleeding	Co-administration should be used with **caution**
	Ticagrelor	Increased risk of bleeding	*Apixaban and rivaroxaban:* Use with **caution** *Dabigatran:* **Relative contraindication**
	Dual antiplatelets		**Relative contraindication** Seek cardiologist advice
Anticoagulants	Warfarin Dalteparin Danaparoid Enoxaparin Heparin Nadroparin	Increased risk of bleeding	Co-administration is **contraindicated** (unless transitioning between anticoagulants)
Other drugs which affect haemostasis	SSRIs and SNRIs[c] for example, escitalopram, sertraline and venlafaxine	Increased bleeding rates seen in studies	Co-administration should be used with **caution** Possible prolonged clotting time, however, the clinical significance of high serotonin is unclear

[a] The decision to provide VTE prophylaxis in a hospitalised patient taking low-dose rivaroxaban and aspirin for stable CAD should be based on an individualised risk assessment and current medical guidelines. It's crucial to weigh the benefits of cardiovascular event prevention against the increased risk of bleeding and VTE associated with this combination therapy. Consulting with a specialist is recommended. If proceeding with VTE prophylaxis, close monitoring of the patient's condition is recommended.

[b] Non-steroidal anti-inflammatory drugs.

[c] Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs).

2.4 – Baseline laboratory tests

The following baseline laboratory tests should be performed prior to commencing DOAC treatment. The patient should be further investigated if results are found to be abnormal:

- Full blood count (FBC)
- Prothrombin time (PT)
- Activated Partial Thromboplastin Time (aPTT)
- Liver function tests (LFT)
- Renal function:
  - Estimated CrCl should be calculated using the Cockcroft-Gault Equation (do not use the eGFR reported in pathology results) (see Box 2 for contraindications based on CrCl).
  - A calculator, such as the Australian Medicines Handbook ideal body weight calculator should be used for calculating estimated CrCl in patients who are overweight or obese (BMI of 30 kg/m^2 or more). For all other patients, use their actual body weight.

DOACs are contraindicated in pregnancy and breastfeeding. In female patients of childbearing age, pregnancy or breastfeeding is to be excluded prior to commencing a DOAC.

2.5 – DOAC dosing

DOAC dosing is complex and is variable based on the DOAC, indication and patient risk factors. Tables 6 to 10 provide information on dosing for each DOAC by the indication, with guidance on appropriate dosing depending on the patient's risk factors. These tables were accurate at the time of publication; however, clinicians should refer to the TGA and PBS websites for updates.

Table 6: DOAC dosing for prevention of stroke and systemic embolism in non-valvular AF[1-3,14]

DOAC	Risk factors	Dose and duration
Apixaban	Patient with CrCl ≥ 25 mL/min	5 mg twice daily Ongoing
	Patient with CrCl ≥ 25 mL/min who has **two or more** of the following risk factors: • Age ≥ 80 years • Weight ≤ 60 kg • Creatinine ≥ 133 micromol/L	2.5 mg twice daily Ongoing
	Patient with CrCl < 25 mL/min	**Contraindicated[a]**
Rivaroxaban	Patient with CrCl ≥ 50 mL	20 mg once daily Ongoing
	Patient with CrCl 15 – 49 mL/min[b]	15 mg once daily Ongoing
	Patient with CrCl <15 mL/min	**Contraindicated**
Dabigatran	Patient with CrCl > 50 mL/min, aged 74 years or younger and who has no bleeding risk[c]	150 mg twice daily Ongoing
	Patient has **one or more** of the following risk factors: • CrCl 30 – 50 mL/min • Age ≥ 75 years • High bleeding risk[c]	110 mg twice daily Ongoing
	Patient with CrCl < 30 mL/min	**Contraindicated**

[a] The use of apixaban in patients with a CrCl < 25 mL/minute is contraindicated as per Australian approved Product Information. Therefore, use in this patient cohort is considered off-label. Studies regarding dosing within this patient cohort are ongoing internationally.

[b] At the time of publication rivaroxaban had been studied in a limited number of patients with AF who have a CrCl 15 – 29 mL/min; consider its use in these patients only under advice from a specialist.

[c] Consider HAS-BLED Score which estimates the risk of major bleeding in patients on anticoagulation.

Table 7: DOAC dosing for treatment of VTE[1-3,14]

DOAC	Risk factors	Dose	Duration
Apixaban	Patient with CrCl ≥ 25 mL/min	10 mg twice daily for 7 days *then* 5 mg twice daily	Between 6 weeks to 6 months, depending on the site of the VTE and if the VTE event was provoked or unprovoked.
	Patient with CrCl < 25 mL/min	**Contraindicated**[a]	
Rivaroxaban	Patient with CrCl ≥ 30 mL/min	15 mg twice daily for 3 weeks *then* 20 mg once daily	
	Patient with CrCl 15 – 29 mL/min	At the time of publication rivaroxaban had been studied in a limited number of VTE patients with a CrCl 15 – 29 mL/min; consider its use in these patients only under advice from a specialist.	
	Patient with CrCl < 15 mL/min	**Contraindicated**	
Dabigatran[b]	Patient with CrCl > 50 mL/min, aged 74 years or younger and who has no bleeding risk[§]	Parenteral anticoagulant for at least 5 days *then* 150 mg twice daily[c]	
	Patient with CrCl 30 – 50 mL/min and has **one or more** of the following risk factors: • Age ≥ 75 years • High bleeding risk[d]	Parenteral anticoagulant for at least 5 days *then* 110 mg twice daily[e]	
	Patient with CrCl < 30 mL/min	**Contraindicated**	

[a] The use of apixaban in patients with a CrCl < 25 mL/minute is contraindicated as per Australian approved Product Information. Therefore, use in this patient cohort is considered off-label. Studies regarding dosing within this patient cohort are ongoing internationally.

[b] Dabigatran is currently not listed on the PBS for this indication. Check the PBS website for updates.

[c] The first dabigatran dose should be given within 2 hours before the next dose of parenteral anticoagulant would have been due.

[d] Consider HAS-BLED Score which estimates the risk of major bleeding in patients on anticoagulation.

[e] Lower dose has not been tested for patients with VTE.

Table 8: DOAC dosing for prevention of recurrent VTE[1-3,14]

DOAC	Risk factors	Dose	Duration
Apixaban	Patient with CrCl ≥ 25 mL/min	2.5 mg twice daily[a]	Duration beyond 6 months may be appropriate for unprovoked VTE or in patients with persistent provoking VTE risk factors[g]
	Patient with CrCl < 25 mL/min	**Contraindicated**[b]	
Rivaroxaban	Patient with CrCl ≥ 15 mL[c]	10 mg once daily[a]	
	Patient with CrCl <15 mL/min	**Contraindicated**	
Dabigatran[d]	Patient with CrCl > 50 mL/min, aged 74 years or younger and who has no bleeding risk	150 mg twice daily	
	Patient with CrCl 30 – 50 mL/min and has **one or more** of the following risk factors: • Age ≥75 years • High bleeding risk[e]	110 mg twice daily[f]	
	Patient with CrCl < 30 mL/min	**Contraindicated**	

[a] For the secondary prevention of VTE after a first event, use of a lower dose of apixaban or rivaroxaban (low-intensity anticoagulant therapy) is safe and effective. Continuing with full-dose anticoagulant therapy (as per Table 7) may be indicated for an extended period with patients who experience multiple prior unprovoked episodes of VTE.

[b] The use of apixaban in patients with a CrCl < 25 mL/minute is contraindicated as per Australian approved Product Information. Therefore, use in this patient cohort is considered off-label. Studies regarding dosing within this patient cohort are ongoing internationally.

[c] At the time of publication, rivaroxaban had been studied in a limited number of VTE patients with a CrCl 15 – 29 mL/min; consider its use in these patients only under advice from a specialist.

[d] Dabigatran is currently not listed on the PBS for this indication. Check the PBS website for updates. Lower dose has not been tested for patients with VTE.

[e] Consider HAS-BLED Score which estimates the risk of major bleeding in patients on anticoagulation.

[f] Lower dose has not been tested for patients with VTE.

[g] Persistent provoking risk factors include antiphospholipid syndrome, active cancer and ongoing non-malignant conditions associated with increased risk of VTE such as inflammatory bowel disease and some other chronic inflammatory states.

Table 9: DOAC dosing for prevention of major cardiovascular events in patients with CAD and/or PAD[1-3,14]

DOAC	Risk factors	Dose and duration
Rivaroxaban[a]	Patient with CrCl ≥ 15 mL/min	2.5 mg twice daily Ongoing
	Patient with CrCl <15 mL/min	**Contraindicated**

[a] Must be in combination with aspirin 100 mg daily (but not with any other antiplatelet therapy). The decision to provide VTE prophylaxis in a hospitalised patient taking low-dose rivaroxaban and aspirin for stable CAD should be based on an individualised risk assessment and current medical guidelines. It is crucial to weigh the benefits of cardiovascular event prevention against the increased risk of bleeding and VTE associated with this combination therapy. Consulting with a specialist is recommended. If proceeding with VTE prophylaxis, close monitoring of the patient's condition is recommended.

Table 10: DOAC dosing for prevention of VTE following THR or TKR[1-3,14]

DOAC	Risk factors	Dose and duration
Apixaban	Patient with CrCl ≥ 25 mL/min	2.5 mg twice daily THR = 32 – 38 days TKR = 10 – 14 days
	Patient with CrCl < 25 mL/min	**Contraindicated**[a]
Rivaroxaban[b]	Patient with CrCl ≥ 15 mL/min	10 mg once daily THR = 35 days TKR = 14 days
	Patient with CrCl < 15 mL/min	**Contraindicated**
Dabigatran[c]	Patient with CrCl > 50 mL/min	220 mg once daily THR = 28 – 35 days TKR = 10 days
	Patient with CrCl 30 – 50 mL/min	150 mg once daily THR = 28 – 35 days TKR = 10 days
	Patient with CrCl < 30 mL/min	**Contraindicated**

[a] The use of apixaban in patients with a CrCl < 25 mL/minute is contraindicated as per Australian approved Product Information. Therefore, use in this patient cohort is considered off-label. Studies regarding dosing within this patient cohort are ongoing internationally.

[b] At the time of publication rivaroxaban had been studied in a limited number of VTE patients with a CrCl 15 – 29 mL/min; consider its use in these patients only under advice from a specialist.

[c] Dabigatran should be initiated within 1 – 4 hours of completed surgery with a single capsule (110 mg for patients with CrCl > 50 mL/min and 75 mg for patients with a CrCl 30 – 50 mL/min). If haemostasis is not achieved, initiation of treatment should be delayed. If treatment commencement on the day of surgery is not feasible, initiation should follow guidance as per Table 10.

2.6 – DOAC administration

Table 11 provides guidance on administering DOACs. Information regarding administration of the relevant DOAC should be provided to the patient and/ or their carer.

Table 11: DOAC administration instructions[1-3,13]

DOAC	Administration instructions
Apixaban	• Swallow whole with or without food. • Can be used in dose administration aids. • Can be crushed (if required) and administered orally or via a gastric tube (See Australian Don't Rush to Crush Handbook).[15]
Rivaroxaban	• **15 mg** and **20 mg** tablet should be **taken with food.** • 2.5 mg and 10 mg tablet may be taken with or without food. • Can be used in dose administration aids. • Can be crushed (if required) and administered orally or via a gastric tube (See Australian Don't Rush to Crush Handbook). [15]
Dabigatran	• Swallow whole with or without food. • Do not chew or open capsule. • Keep in original packaging. • Do not transfer capsule to a dose administration aid.

2.7 – Management of a missed DOAC dose

Table 12 provides guidance for managing a missed DOAC dose. Information regarding missed doses of the relevant DOAC should be provided to the patient and/or their carer.

Table 12: Management of a missed DOAC dose[1-3]

DOAC	Missed dose instructions
If a dose is missed it should be taken as soon as possible.	
Rivaroxaban *Once daily dosing*	• Take within 12 hours of the missed dose, if more than 12 hours omit the dose and continue usual dosing the next day.
Rivaroxaban *15 mg twice daily*	• The missed dose should be taken immediately to ensure intake of a 30 mg total dose per day. In this case two 15 mg tablets may be taken at once. • Continue usual dosing the next day.
Apixaban and dabigatran *Twice daily dosing*	• Take within 6 hours of the missed dose. If more than 6 hours has elapsed since missed dose was due, omit the missed dose and continue usual dosing.

3. Patient follow up and ongoing monitoring

3.1 – Primary care follow up

Patients commenced on a DOAC should have medical follow up during the first seven days of therapy to review clinical progress and possible signs of bleeding.

The treating team should ensure appropriate information is communicated to the patient and their family or carer as well as to the patient's primary care providers on discharge from hospital. This includes information such as the rationale for the choice of DOAC, current renal function and any dose changes that may be required (for example, apixaban and rivaroxaban require dose reduction after a period of one or three weeks respectively when treating VTE).

3.2 – Ongoing renal function monitoring

Ongoing monitoring of renal function is recommended for all patients at least every 6 to 12 months. More frequent monitoring may be required if the patient's clinical condition changes, there are changes to their medications or if the patient has impaired renal function.

3.3 – Laboratory tests and other monitoring

Routine laboratory testing of drug levels or anticoagulant effect is not usually required for DOACs. There is variable and limited ability to monitor DOACs using laboratory testing in NSW Health facilities.

Table 13 provides some advice on the effect of DOACs on routine coagulation tests. Specific testing is required to quantify drug presence. Local advice should be sought.

Table 13: Effect of DOAC on routinely performed coagulation assay[16]

Effect	Apixaban	Rivaroxaban	Dabigatran
Significant anticoagulant effect unlikely	Normal PT[a] **does not** exclude presence of therapeutic apixaban	PT[a] normal	TT normal aPTT normal
Anticoagulant effect present	PT[a] prolonged or normal	PT[a] prolonged	TT prolonged aPTT prolonged
Specific assays to quantify drug presence	Modified anti-Xa assay specific for apixaban	Modified anti-Xa assay specific for rivaroxaban	Dilute thrombin clotting time (Hemoclot® assay)

Key: PT = Prothrombin time, TT = Thrombin time, aPTT = activated partial thromboplastin time.

[a] PT sensitivity to DOACs will vary according to local laboratory reagents. In some laboratories, PT will be insensitive to DOACs. Check with local laboratory.

Other monitoring that is recommended for patients on DOAC therapy includes:

- Full Blood Count (FBC) every 6 months
- iron studies every 12 months.

In addition, patients should also be monitored for the development of conditions that may affect DOAC half-life such as weight gain or loss.

4. Transitioning between anticoagulants

Transitioning between anticoagulants should be undertaken by a senior medical officer or in consultation with a specialist. It is currently recommended that patients who are stable on warfarin continue warfarin therapy.[6]

4.1 – Transitioning from IV UFH, LMWH or warfarin to a DOAC

Before transitioning to a DOAC, the prescriber should check contraindications and other factors as outlined in Section 1.

Table 14 provides guidance on transitioning from intravenous (IV) unfractionated heparin (UFH), low molecular weight heparin (LMWH) or warfarin to a DOAC.

Table 14: Transitioning from IV UFH, LMWH or warfarin to a DOAC[a 1-3, 17]

From IV UFH to a DOAC
Stop IV UFH. Start DOAC within one hour.
From LMWH to a DOAC[b]
Stop LMWH. Start DOAC when the next dose of LMWH would have been due.
From warfarin to a DOAC
Stop warfarin. Measure INR daily. Wait until INR is less than 2.5. Start DOAC.

[a] Generalised advice is provided, taking into account the variations among Australian registered DOAC agents. For more specific advice, please refer to the individual Product Information for each DOAC.

[b] The duration of initiation dosing for DOAC therapy is variable and based on clinical trial data. Individual patient factors must be considered when determining duration of initiation dose.

4.2 – Transitioning from a DOAC to IV UFH, LMWH or another DOAC

Before transitioning to a LMWH or another DOAC patients should have their renal function (determined by calculating CrCl) checked. This will inform if the patient needs to wait longer before transitioning over and what the appropriate dose should be.

Table 15 provides guidance on transitioning from a DOAC to IV UFH, LMWH or another DOAC.

Table 15: Transitioning from a DOAC to IV UFH, LMWH or another DOAC[1-3, 17]

From a DOAC to IV UFH
Stop DOAC. If apixaban or rivaroxaban: • Start IV UFH when the next DOAC dose would have been due.[a] If dabigatran, check renal function (CrCl): • If CrCl ≥ 30 mL/min, start IV UFH when the next dabigatran dose would have been due.[a] • If CrCl < 30 mL/min, start IV UFH 48 hours after the last dabigatran dose.[a]
From a DOAC to a LMWH
Stop DOAC. Check renal function (CrCl): • If CrCl ≥ 30 mL/min, start LMWH when the next DOAC dose would have been due. • If CrCl < 30 mL/min, seek specialist advice.
From one DOAC to another DOAC
Stop DOAC and start the other DOAC when the next dose of the first DOAC would have been due.

[a] Decision based on expert consensus taking into account relative real function and pharmacokinetics of dabigatran. IV UFH infusions are to be given according to local protocol and specialist advice should be sought regarding the need for a bolus dose of IV UFH.

4.3 – Transitioning from a DOAC to warfarin

Transition from a DOAC to warfarin should be undertaken in consultation with a specialist as the process will depend on the acuteness of the risk of recurrent thrombosis, the clinical context and the DOAC being transitioned from. The transition carries a risk of thrombosis and bleeding which requires an individualised anticoagulant management plan.

When transitioning from a DOAC to warfarin, the DOAC half-life (which is affected by renal function) needs to be considered as well as the delay in onset of action of warfarin; steady state is around 5 days although most clinicians measure an INR on Day 4. A starting dose of warfarin 5 mg or less is recommended.

When transitioning from a DOAC to warfarin it is necessary to consider that INR results can be affected by both the DOAC and warfarin. Upon starting warfarin, the INR should be measured daily to inform ongoing warfarin dosing. Laboratory INR testing should be used as point-of-care INR testing is not suitable when transitioning from a DOAC to warfarin.[6]

Table 16 provides guidance on transitioning from a DOAC to warfarin.

Table 16: Transitioning from a DOAC to warfarin

From a DOAC to warfarin CrCl ≥ 50 mL/min
1. Start warfarin while still taking the DOAC. 2. Measure INR daily, with the blood sample for the test being taken immediately before the DOAC dose, i.e., a 'trough' level. 3. Continue taking both the warfarin and DOAC until the INR has been greater than the patient's 'baseline' INR plus 1.0 for two consecutive days.[a] *For example, if the patient's baseline INR is 1.7, the DOAC should be ceased when INR has been greater than 2.7 (i.e., 1.7 plus 1.0) on two consecutive days.* 4. If the baseline INR is NOT elevated (i.e. ≤ 1), then cease the DOAC when the INR has been greater than 2 for two days. 5. Ongoing warfarin dosing is according to the usual target range for the patient's specific indication.
From a DOAC to warfarin CrCl < 50 mL/min
Reduced clearance of a DOAC can increase the risk of bleeding, the transition should be taken with a high degree of caution under the direction of a specialist.

[a] Recommendation based on expert opinion of the Anticoagulant Medicines Working Party.

5. Perioperative management and other considerations

The perioperative management of DOACs includes patients who are established on DOAC therapy and require surgery or an invasive procedure.

The CEC *Guidelines on Perioperative Management of Anticoagulants and Antiplatelet Agents* (available here) provides recommendations for the perioperative management of patients taking DOACs as well as other anticoagulant and antiplatelet agents. The guideline is separated into four broad perioperative patient groups, including those taking:

1. warfarin (vitamin K antagonist)
2. warfarin requiring perioperative bridging therapy
3. DOACs
4. antiplatelets.

In general, interrupting anticoagulation for surgery or an invasive procedure transiently increases the risk of thromboembolism, and at the same time the bleeding risks from the procedure are increased if a patient is anticoagulated. A balance between reducing the risk of thromboembolism and preventing excessive bleeding must be decided for each patient.[18]

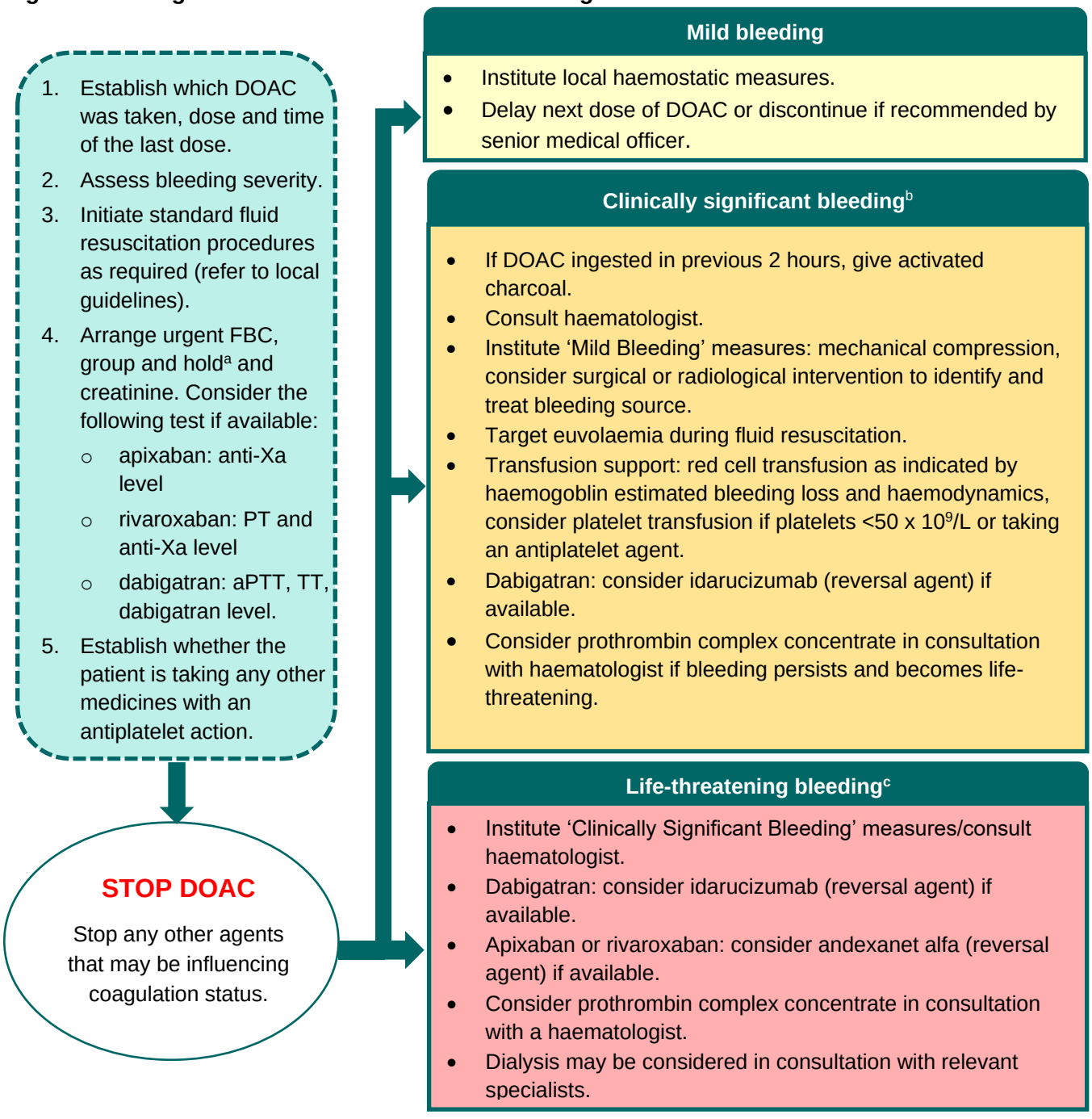
The following should be considered when managing patients taking a DOAC in the perioperative period:

- Thromboembolic risk and bleeding risk. The balance will depend on the reason the patient is taking an anticoagulant and the bleeding risk of the surgical procedure they are undergoing.
- The half-life of the DOAC, time of the last dose and the patient's renal function. DOACs have shorter half-lives compared to warfarin, often making them easier to discontinue and resume rapidly.
- Bridging anticoagulation is usually not required for patients taking DOACs.[18]

6. Managing bleeding

Figure 1 provides guidance on managing bleeding in patients taking DOACs. Clinicians should refer to their local bleeding management guidelines. In regional or rural health services where results from laboratory tests may not be readily available, bleeding should be managed on a case-by-case basis according to the patient's condition in consultation with a haematologist or senior medical officer.

Figure 1: Management of DOAC associated bleeding[6]



[a] "Group and hold" refers to the procedure where a patient's blood is collected and tested in advance to determine blood type and perform compatibility testing with potential donor blood.

[b] Clinically significant bleeding: reduction in Hb ≥ 20g/L, transfusion of ≥ 2 units of red cells.

[c] Life-threatening bleeding: bleeding in critical area or organ (intraocular, intracranial, intraspinal, compartment syndrome, retroperitoneal or pericardial), hypotension not responding to resuscitation.

6.1 – Reversal agents

The need for rapid reversal of anticoagulation provided by DOACs may arise for emergent life-saving surgery or life-threatening bleeding events.

When considering pharmacological agents such as idarucizumab or andexanet alfa, clinicians **must** review the listing on the NSW Medicines Formulary prior to use within NSW Health facilities (see NSW Medicines Formulary online platform for further details including any restrictions on use). Where relevant, refer to NSW Health Policy Directive *Approval Process for Medicines and Their Use* (PD2022_056) for guidance on the use of medicines not listed on the NSW Medicines Formulary via the Individual Patient Use approval pathway.

6.1.1 Idarucizumab[19]

Idarucizumab (Praxbind®), a monoclonal antibody that reverses effects of dabigatran was registered for use in Australia by the TGA in May 2016.

Indications

Idarucizumab is indicated for when rapid reversal of the anticoagulant effects of dabigatran is required for urgent surgery or invasive procedures and in life-threatening bleeding when it will have a clinically relevant benefit.[19]

An analysis of dabigatran reversal with idarucizumab in patients with clinically significant or life-threatening bleeding, or who required an urgent procedure, demonstrated that idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.[20,21] Though the anticoagulant effect is reversed, achieving haemostasis will be dependent on identifying and treating the source of bleeding.

In cases of mild bleeding or for patients in need of non-urgent surgery or invasive procedure, discontinuation of dabigatran and administration of appropriate supportive care is usually sufficient unless bleeding continues.

Contraindications and precautions

- There are no contraindications to the use of idarucizumab.
- Idarucizumab binds specifically to dabigatran and will not reverse the effects of other anticoagulants.
- Treatment can be used in conjunction with standard supportive measures which should be considered as medically appropriate.
- In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be recorded in the patient's medical record.
- Reversal of dabigatran therapy exposes patients to the thrombotic risk of their underlying disease – to reduce the risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate.
- The use of idarucizumab in patients with a known hypersensitivity to idarucizumab or any listed excipients must be weighed cautiously against the potential benefit of the treatment
- The recommended dose of idarucizumab contains 4 g sorbitol and must be used with caution in patients with hereditary fructose intolerance.
- Idarucizumab causes transient proteinuria as a phycological reaction to renal protein overflow; the transient proteinuria is not indicative of renal damage which should be considered for urine testing.

- In some patients, recurrence of plasma concentrations of unbound dabigatran and concomitant, elevated coagulation parameters have occurred up to 24 hours after administration. If reappearance of clinically relevant bleeding together with elevated coagulation is observed after administration, administration of an additional 5 g dose may be considered.
- Each dose of idarucizumab contains 2.2 mmol or 50 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

Special patient populations

Renal impairment
No dose adjustment is required in renally impaired patients.

Hepatic impairment
An impact of hepatic impairment on the pharmacokinetics of idarucizumab has not been observed. No dose adjustment is required in patients with hepatic impairment.

Use in the elderly
Age does not have a clinically meaningful effect on the pharmacokinetics of idarucizumab and dose adjustment is not required.

Paediatric use
The safety and efficacy of idarucizumab in children and adolescents have not been established.

Effects on fertility
Studies to assess the potential effects of idarucizumab on human fertility have not been performed. Preclinical results do not suggest a risk to fertility or embryofetal development,

Use in pregnancy – Category B2
No data is available from the use of idarucizumab in pregnancy. It is not recommended during pregnancy or in women of childbearing potential not using contraception.

Use in lactation
No studies have been conducted to assess the presence of idarucizumab in human milk.

Drug interactions

No formal interaction studies with idarucizumab and other medicines have been conducted. Clinically relevant interactions with other medicines are considered unlikely.

Monitoring

The following laboratory tests should be conducted before idarucizumab administration and 30 minutes after idarucizumab administration:

- aPTT
- PT
- Fibrinogen
- TT.

A normal TT rules out the presence of dabigatran. The TT is extremely sensitive, even to clinically insignificant levels of dabigatran. Repeat doses of idarucizumab should not be based on repeat TT results in isolation. Waiting for these test results is not necessary in the setting of known dabigatran ingestion and life-threatening bleeding.

Dosage and administration

The total dose of idarucizumab is 5 g (given as two consecutive doses of 2.5 g) by slow intravenous bolus injection or IV infusion. If administering via IV injection, the second 2.5 g dose should be given within 5 to 10 minutes of the first 2.5 g dose. No dose adjustment is required for renal impairment.

Preparation and storage

Idarucizumab must not be mixed with other medicinal products. A pre-existing IV line may be used for administration. Flush with sterile sodium chloride 0.9% solution prior to and at the end of infusion. No other infusion should be administered in parallel via the same IV access.

Prior to use, the unopened vial may be kept at room temperature (up to 30°C) for up to 48 hours if stored in the original package and protected from light.

Once solution has been removed from the vial, chemical and physical in-use stability has been demonstrated for up to 5 hours at room temperature.

IV injection

Withdraw 2.5 g/50 mL from one vial into a syringe and withdraw another 2.5 g/50 mL into a second syringe. Inject one after the other, each over 5 to 10 minutes.

IV infusion

Hang and infuse 2 vials, one after the other each over 5 to 10 minutes.

Discard any residue.

Restarting anticoagulation

Reversing dabigatran exposes patients to the thrombotic risk of their underlying disease. Resumption of anticoagulant therapy should be considered as soon as medically appropriate. Specialist advice should be sought. Dependent on patient circumstances, treatment can be initiated 24 hours after administration of idarucizumab.

Idarucizumab may not be available in all facilities. Clinicians should confirm availability with their local Pharmacy Department (or blood bank).

6.1.2 Andexanet alfa[23-26]

Andexanet alfa (Andexxa®), a reversal agent for direct factor Xa inhibitors (apixaban and rivaroxaban) was registered for use in Australia by the TGA in July 2023. For further information refer to the Product Information.

TGA approved indication for use

Andexanet alfa has provisional approval in Australia for adult patients treated with a direct factor Xa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Contraindications and precautions

- There are no listed contraindications to the use of andexanet alfa.
- Andexanet alfa may interfere with the anticoagulant effect of heparin in addition to factor Xa inhibitors. If anticoagulation is needed following administration of andexanet alfa, consider using an alternative to heparin, such as a direct thrombin inhibitor in consultation with Haematology.
- Andexanet alfa has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any factor Xa inhibitors other than apixaban or rivaroxaban.
- The safety of andexanet alfa has not been evaluated in patients who have received prothrombin complex concentrates, recombinant factor VIIa, or whole blood products within 7 days prior to the bleeding event.

Special patient populations

Renal impairment
The effect of renal impairment on andexanet alfa exposure levels has not been evaluated. Based on the existing data on clearance, no dose adjustment is recommended.

Hepatic impairment
The safety and efficacy of andexanet alfa has not been studied in patients with hepatic impairment.

Use in the elderly
No dose adjustment is required in elderly patients (aged 65 years and over).

Paediatric use
The safety and efficacy of andexanet alfa in children and adolescents have not been established. Use is limited to patients 18 years and older.

Effects on fertility
No data available on the effects of andexanet alfa on human fertility.

Use in pregnancy – Category B2
No data is available from the use of andexanet alfa in pregnancy. It is not recommended during pregnancy or in women of childbearing potential not using contraception.

Use in lactation
No studies have been conducted to assess the presence of andexanet alfa in human milk. A risk to breastfed newborns/infants cannot be excluded. Breastfeeding should be stopped during treatment with andexanet alfa.

Drug interactions

No formal drug interaction studies between andexanet alfa and other medicines have been conducted.

Monitoring

Monitoring of therapy should primarily be based on clinical parameters indicating an adequate response (for example, achieving haemostasis), lack of efficacy (for example, rebleeding) and adverse events (for example, thromboembolic episodes). Monitoring of andexanet alfa therapy should not be based on anti-factor Xa activity, as commercially available anti-factor Xa activity assays are not appropriate for measuring anti-factor Xa activity after andexanet alfa administration.[25-26] These assays may show falsely elevated levels of anti-factor Xa activity, leading to a significant underestimation of andexanet alfa's reversal activity.

Dosing

Andexanet alfa is administered following a **low dose** or **high dose** regimen based on the specific factor Xa inhibitor, the dose taken, and time since last dose (see Table 17).

Table 17. Determining the dose of andexanet alfa

Factor Xa inhibitor	Dose taken	Time since last dose taken	
		< 8 hours or unknown	≥ 8 hours to 18 hours[a]
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg or unknown	High dose	
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg or unknown	High dose	

[a] Andexanet alfa **should not** be administered if more than 18 hours has elapsed since the last dose of apixaban or rivaroxaban.

Preparation

Andexanet alfa **does not** need to be brought to room temperature (≤ 25°C) before reconstitution or administration to the patient.

- Reconstitute the 200 mg vial of andexanet alfa by slowly injecting 20 mL of water for injection solution toward the inside wall of the vial to minimise foaming.
- Dissolve by gently swirling each vial. **Do not shake** as this can lead to foaming. The dissolution time for each vial is approximately 3 to 5 minutes.
- Inspect the vials for particulate matter and/or discolouration. Do not use if opaque particles or discolouration are present.
- After reconstituting the required number of vials of andexanet alfa, transfer the reconstituted solution (**10 mg/mL**) without further dilution to sterile large volume syringes if using a syringe pump for administration, or to suitable empty IV bags comprised of polyolefin (PO) or polyvinyl chloride (PVC) material. Multiple syringes or bags may be required for the high dose protocol.

Prior to administration, extension tubing, 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter should be used.

Storage

Unopened vials should be stored refrigerated at 2-8°C and protected from light.

Once reconstituted, use immediately.

Reconstituted andexanet alfa in IV bags is stable at room temperature (≤ 25°C) for up to 8 hours.

Administration

Both dosing regimens are administered as an initial intravenous (IV) bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose). The continuous IV infusion should be commenced within 2 minutes of bolus dose completion. The continuous IV infusion should be administered for 120 minutes (see Table 18).

Table 18. Administering the dose of andexanet alfa

Dose	Initial IV bolus	Continuous IV infusion	Total number of 200 mg vials needed
Low dose	400 mg (= 40 mL) over 15 minutes Rate of 160 mL/hour (approximately 30 mg/minute)	480 mg (= 48 mL) over 2 hours Rate of 24 mL/hour (approximately 4 mg/minute)	**5 vials** (2 vials bolus + 3 vials infusion)
High dose	800 mg (= 80 mL) over 30 minutes Rate of 160 mL/hour (approximately 30 mg/minute)	960 mg (= 96 mL) over 2 hours Rate of 48 mL/hour (approximately 8 mg/minute)	**9 vials** (4 vials bolus + 5 vials infusion)

Note – the safety and efficacy of additional doses have not been established.

Restarting anticoagulation

Reversing factor Xa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. Resumption of anticoagulant therapy should be considered as soon as medically appropriate. Specialist advice should be sought.

Andexanet alfa may not be available in all facilities. Clinicians should confirm availability with their local Pharmacy Department.

6.2 – Prothrombin Complex Concentrate

There is limited evidence on the use of prothrombin complex concentrate in DOAC related bleeding. Where available, it is only reasonable to consider the use of prothrombin complex concentrate, in the circumstance of life-threatening bleeding unable to be managed with supportive measures and in consultation with a haematologist. The risk of thrombotic complications may be significant. The use of rFVIIa (NovoSeven®) in DOAC related bleeding is not recommended.[6]

6.3 – Use of dialysis in life-threatening bleeding for patients treated with dabigatran

When idarucizumab is not available, dialysis may be considered in patients treated with dabigatran who have life-threatening bleeding when:

- the patient has renal function impairment, or
- dabigatran is present in excess indicated by aPTT > 80 seconds or a dabigatran level > 500 mg/mL.[6,22]

There is no role for dialysis in rivaroxaban and apixaban related bleeding due to high protein binding.[6]

6.4 – Blood management guidelines

For patients requiring transfusion support, evidence-based patient blood management guidelines are available on the Australian National Blood Authority website.

7. Information and education for patients, families and carers[27,28]

Patients and/or their family or carer who are discharged home on a DOAC should be provided with verbal and written information on their medication. They should be given the opportunity to discuss their therapy with a member of the health care team, including the use of Professional Health Care Interpreters for patients who are not fluent in English or who are Deaf.

Provision of DOAC information and education should be recorded in the patient's health care record.

Information and education for patients, families and carers should address the following:

Name of their DOAC

The patient should be aware of both the generic (active ingredient) and brand name of their DOAC.

What their DOAC is used for and how it works

An explanation that their medicine belongs to a group of medicines called anticoagulants and that sometimes they are referred to as 'blood thinners' should be provided. Also, a simple description of how they work to lower the risk of blood clots and the specific reason (indication) that it is being prescribed for them.

How to take their DOAC

The patient should be provided with instructions on their **dose** (including dosage adjustments which may be the case in the treatment of VTE) and **how to take** their DOAC safely (see 2.5 DOAC dosing and 2.6 DOAC administration). This should include a discussion on the importance of not missing a dose and instructions on what to do in the case of a **missed dose** (see 2.7 Management of a missed DOAC dose).

Intended duration of DOAC treatment

The duration of DOAC treatment will depend on the indication and individual patient risk factors. Some people need treatment for a short time for example, three months, while others will need to continue on an ongoing basis. It is important that the patient does not stop taking their DOAC unless advised by their treating doctor. The intended duration of therapy should be communicated to the patient.

Bleeding and what to do

Patients should be provided with information on bleeding and what to do if they have a bleed. This includes:

- The signs and symptoms of bleeding to watch for, including those that may be indicative of more serious bleeding such as red or dark urine or bowel motions, coughing blood, unexplained bruising that gets bigger without a cause.
- What to do in the case of bleeding, including going to the nearest emergency department if bleeding is severe.
- Ways to minimise the risk of injury for example, avoiding contact sports, using an electric razor instead of a blade, using a soft bristled toothbrush.

DOAC drug interactions

Patients should check with their primary care provider or pharmacist before starting any medication, this includes prescription medicines, vitamins, mineral and herbal supplements or any other medicine bought without a prescription from a pharmacy, supermarket or health food store.

Monitoring DOAC treatment

DOACs do not require a test to monitor their effect on blood clotting like other anticoagulants such as warfarin, however, other blood tests such as those to check kidney function are important. If there are changes in kidney function the DOAC dose may need adjusting.

The patient should have regular check-ups with their primary care provider to monitor their condition and for any side effects.

Alerting health care professionals they are taking a DOAC before surgical, medical or dental procedures

Patients should tell their health care professional that they are taking a DOAC well before any planned surgical, medical or dental procedure as the risk of bleeding may be increased. For minimally invasive procedures the patient may continue taking their DOAC. Other procedures may require their DOAC to be stopped for a short period. In such cases, the health care professional should advise the patient on what to do.

Patients taking a DOAC may want to consider carrying an alert card or medical ID tag (for example, MedicAlert®). Carrying an up-to-date list of all their medicines is recommended.

Any specific storage and administration requirements

Some DOACs have specific requirements when it comes to storage and packing in dose administration aids, these should be communicated to the patient (see 2.6 DOAC administration).

Pregnancy and breastfeeding

DOACs are not recommended during pregnancy or while breastfeeding. If the patient plans on becoming pregnant, they should speak with primary care providers about appropriate alternatives.

7.1 – Written consumer information

Consumer Medicine Information (CMI) is available via the TGA website and should be provided to the patient and/or their family or carer.

Written information for patient's, families and carers developed by the CEC is available on the CEC High-Risk Medicines Anticoagulants webpage.

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9. Appendix

9.1 – Abbreviations

Abbreviation	Term
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
CMI	Consumer Medicine Information
CNS	Central nervous system
COVID-19	**Co**rona**vi**rus **d**isease 20**19**
CrCl	Creatinine clearance (estimated using the Cockcroft-Gault equation)
CYP 3A4	Cytochrome P450 3A4
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
FBC	Full blood count
HIV	Human immunodeficiency virus
INR	International normalised ratio
ISTH	International Society on Thrombosis and Haemostasis
LFT	Liver function tests
LMWH	Low molecular weight heparin
NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary embolism
P-gp	P-glycoprotein
PT	Prothrombin time
SNRI	Serotonin norepinephrine re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
TGA	Therapeutic Goods Administration
THR	Total hip replacement
TIA	Transient ischaemic attack
TKR	Total knee replacement
TT	Thrombin time
UFH	Unfractionated heparin
VTE	Venous thromboembolism