NOAC GUIDELINES

NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANT

UPDATED JULY 2017

CLINICAL EXCELLENCE COMMISSION

The CEC acknowledges the NSW Health Directors of Clinical Governance who commissioned this guideline and the efforts of the members of the Anticoagulant Medicines Working Party who contributed to its development.

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1. INTRODUCTION

Non-Vitamin K antagonist oral anticoagulants (NOAC) are now widely used in patients with non-valvular atrial fibrillation (AF) and for the treatment and prevention of venous thromboembolism (VTE) in NSW Health facilities. NOACs include dabigatran, (direct thrombin inhibitor), apixaban and rivaroxaban (Factor Xa inhibitors). The term 'DOAC', (Direct Oral Anticoagulant) is also used to describe these medicines.

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

This NOAC guideline does not address anticoagulation in:

- Pregnant or breastfeeding females. All NOACs are contraindicated in pregnancy and breastfeeding[1-3]
- Paediatric patients less than 18 years of age. NOACs have not been tested in this population [1-3].

Information in this guideline should be used in conjunction with Therapeutic Goods Administration (TGA) approved Product Information, local protocols and specialist advice.

This clinical guideline was developed in conjunction with a multi-disciplinary Anticoagulant Medicines Working Party†. Consensus recommendations where indicated in the guideline are based on expert opinion from within the Working Party.

†The Anticoagulant Medicines Working Party members included; a consumer, a Director of Clinical Governance, nurses, pharmacists, medical specialists (a cardiologist, anaesthestist, surgeon, general practitioner and hematologists), and representatives from the NSW Therapeutic Advisory Group and the National Prescribing Service.

2. NOAC INDICATIONS AND CONTRAINDICATIONS

NOACs have been registered by the TGA for use in specific conditions including: the prevention of stroke and systemic embolism in patients with AF with one or more risk factors (see Box 1 for PBS Authority listed risk factors), in the prevention of VTE following hip and knee replacement and the treatment of new and secondary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).

There are conditions in which NOAC treatment is contraindicated, notably, in patients with a mechanical heart valve[1, 2]. NOAC use has not been studied in the following conditions: cerebral venous sinus thrombosis, portal and splenic vein thrombosis and non-lower limb DVT. NOACs are not suitable for use in patients with hemodynamically significant valvular heart disease.

Table 1 outlines registered TGA indications and Pharmaceutical Benefits Scheme (PBS) listings of NOACs as of July 2017. NOAC availability may vary between facilities. Contact the Pharmacy Department at your facility for further information.

Prophylaxis dose in this document refers to the dose used for prevention of VTE following elective total hip replacement (THR) or total knee replacement (TKR).

Therapeutic dose in this document refers to the dose used for stroke prevention in non-valvular AF, or treatment of new and secondary prevention of DVT and PE.

Box 1: PBS Authority listed risk factors[4]

- Prior stroke (ischaemic or unknown type)
- Transient ischaemic attack (TIA) or non-central nervous system (CNS) systemic embolism
- Age 75 years or older
- Hypertension
- Diabetes mellitus
- Heart failure and/ or left ventricular ejection fraction 35% or less.

2.1 Registered indications and Pharmaceutical Benefits Scheme listings of NOACs

Registered indications and PBS listings of NOACs are listed in Table 1. This table was accurate at the time of publication; prescribers should refer to the TGA and PBS websites for updates. For patients requiring a PBS prescription, the prescriber should check the PBS website as a PBS Authority prescription may be required.

Table 1: Registered indications and PBS listings of NOACs

Indication	Dabigatran	Apixaban	Rivaroxaban
Stroke prevention in non-valvular AF with at least one stroke risk factor*	Authority PBS prescription required	Authority PBS prescription required	Authority PBS prescription required
Prevention of VTE after elective THR or TKR	Authority PBS prescription required	Authority PBS prescription required	Authority PBS prescription required
Treatment of VTE	TGA Registered, but not PBS listed for this indication	Authority PBS prescription required	Authority PBS prescription required
Prevention of recurrent VTE	TGA Registered, but not PBS listed for this indication	Authority PBS prescription required	Authority PBS prescription required

*see Box 1 for PBS Authority listed risk factors

2.2 Contraindications to NOAC therapy

NOAC use is contraindicated in certain clinical conditions including moderate to severe renal failure or significant hepatic failure[5]. Estimated creatinine clearance (CrCl) should be calculated using the using the Cockcroft-Gault equation (do **not** use the eGFR reported in pathology results).
In the case of a patient with renal impairment, treatment with warfarin may be more appropriate[5]. Box 2 and Tables 2, 3 and 4 provide general and specific contraindications for NOAC treatment.

Whilst NOACs are NOT ABSOLUTELY contraindicated in patients with a history of gastrointestinal bleeding, prescribers should use caution and seek advice when prescribing to these patients.

Box 2: Contraindications to NOAC therapy[1-3]

Dabigatran (Pradaxa®), Apixaban (Eliquis®) & Rivaroxaban (Xarelto®)
Known hypersensitivity
Renal impairment: • Dabigatran (Pradaxa®): CrCl <30mL/min • Apixaban (Eliquis®): CrCl <25mL/min • Rivaroxaban (Xarelto®): CrCl <30mL/min (Rivaroxaban may be used in patients with CrCl 15-30mL in prevention of VTE after elective THR or TKR see Table 15)
Clinically significant active bleeding
Significant inherited or acquired bleeding disorder
Hepatic disease with coagulopathy
Organ lesions at risk of bleeding including intracranial haemorrhage in previous 6 months
Indwelling spinal or epidural catheter and during the first 6 hours after removal
Mechanical heart valve
Pregnancy or breastfeeding mother

3. COMMENCING TREATMENT

The decision to commence NOAC therapy should be made by a Senior Medical Officer in conjunction with the patient and/ or carer. In addition, contraindications, drug interactions and other patient factors (such as persistent hypertension, falls risk, anaemia and patient compliance), need to be taken into account prior to commencing a patient on a NOAC. NOACs are contraindicated in pregnancy and breastfeeding. In female patients of child bearing age, pregnancy or breastfeeding is to be excluded prior to commencing NOAC therapy.

The following baseline laboratory tests should be performed prior to commencing 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 Test (LFT)
- Renal function:
    - Estimated creatinine clearance (CrCl) should be calculated using the Cockcroft-Gault equation (do **not** use the eGFR reported in pathology results) (see Box 2 for contraindications to a NOAC, based on creatinine clearance)
    - A calculator, such as the AMH Ideal body weight calculator should be used for calculating estimated creatinine clearance in patients who are overweight or obese. For all other patients use actual body weight.

Table 2 (dabigatran), Table 3 (apixaban) and Table 4 (rivaroxaban) list other factors to be taken into consideration prior to commencing a patient on a NOAC.

Table 2: Considerations prior to commencing dabigatran (Pradaxa®)[1, 6]

Dabigatran (Pradaxa®)	
General	Capsules must not be opened, thus unsuitable for patients unable to swallow a capsule whole Capsules must not be removed from packaging until the time of administration, thus unsuitable for patients who are reliant on dose administration aids
Renal impairment	Contraindicated - CrCl <30 mL/min
	Use with caution - CrCl 30 – 50 mL/min
Hepatic impairment	Contraindicated - Child-Pugh* C
	Use with caution - Child-Pugh A or B
Gastrointestinal bleeding	Use with caution and seek advice in patients with any history of gastrointestinal bleeding
Weight**	No dose adjustment required for extremes of body weight

*Child-Pugh estimates cirrhosis severity, **No published data for extremes of body weight

Table 3: Considerations prior to commencing apixaban (Eliquis®)[3]

Apixaban (Eliquis®)	
Renal impairment	Contraindicated - CrCl <25 mL/min
Hepatic impairment	Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C)
	May be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B)
Gastrointestinal bleeding	Use with caution and seek advice in patients with any history of gastrointestinal bleeding
Weight	Dose adjustment may be required for patients weighing less than 60kg for stroke prevention in patients with non-valvular AF (see Table 11)

Table 4: Considerations prior to commencing rivaroxaban (Xarelto®)[2]

Rivaroxaban (Xarelto®)	
Renal impairment	Contraindicated – • CrCl <30 mL/min for therapeutic dose, • CrCl <15 mL/min for prophylactic dose (prevention of VTE after elective THR or TKR)
	Use with caution - CrCl 30 – 50mL/min
Hepatic impairment	Contraindicated - Child-Pugh B or C
	Use with caution - Child-Pugh A
Gastrointestinal bleeding	Use with caution and seek advice in patients with any history of gastrointestinal bleeding
Weight*	No dose adjustment required for extremes of body weight

*No published data for extremes of body weight

3.1 Drug interactions

There are clinically significant interactions that need to be taken into consideration when prescribing these NOACs[5]. Drugs that interfere with CYP3A4 and P-glycoprotein (P-gp) inhibitors can have significant interaction with NOACs. For considerations with antiplatelet agents and other anticoagulants see Table 7. For other NOAC drug interactions see Tables 5 and 6.

Table 5: Dabigatran (Pradaxa®) drug interactions[1, 7, 8]

Class or medicine *(Not an exhaustive list)*	Advice	Effect on dabigatran activity	Comment
Amiodarone	Caution	Increased activity	
Anticonvulsants: phenytoin, carbamazepine	Caution	Reduced activity	
Azole antifungals e.g. itraconazole voriconazole, posaconazole (separate advice for fluconazole below)	Contraindicated	Increased activity	Potent CYP3A4 and P-gp inhibitors
Dronedarone	Contraindicated	Increased activity	
Fluconazole	Caution	Increased activity	Less potent inhibitor than other azoles
Immunosuppressants (Calcineurin inhibitors) e.g. cyclosporin, tacrolimus	Contraindicated	Increased activity	
Macrolides e.g. clarithromycin, erythromycin	Caution	Increased activity	Not likely to be significant
SSRI/ SNRI* e.g. escitalopram sertraline venlafaxine	Caution	Increased activity	Increased bleeding rates have been noted.
Rifampicin	Caution	Reduced activity	
Verapamil[1]	Relative contraindication	Increased activity	For AF, acute VTE and prevention of subsequent VTE: 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. For VTE prophylaxis: refer to PI or AMH**

*SSRI - Selective serotonin re-uptake inhibitor; SNRI - Serotonin noradrenaline re-uptake inhibitors

**AMH – Australian Medicines Handbook

Table 6: Apixaban (Eliquis®) and rivaroxaban (Xarelto®) drug interactions[2, 3, 7, 8]

Class or medicine *(Not an exhaustive list*)*	Advice	Effect on rivaroxaban or apixaban activity	Comment
Anticonvulsants: phenytoin carbamazepine, phenobarbitone	Caution	Reduced activity	
Azole antifungals e.g. itraconazole voriconazole, posaconazole	Contraindicated	Increased activity	Potent CYP3A4 and P-gp inhibitors
HIV protease inhibitors e.g. ritonavir	Contraindicated	Increased activity	Potent CYP3A4 and P-gp inhibitors
Macrolides e.g. clarithromycin, azithromycin	Caution	Increased activity	
Rifampicin	Caution	Reduced activity	
St John's Wort	Caution	Reduced activity	
Verapamil	Uncertain	Increase in activity	Clinical significance uncertain

* SSRI and SNRI are not listed in the Product Information; however concurrent use may theoretically increase risk of bleeding (Recommendation based on expert opinion of the Anticoagulant Medicines Working Party)

Table 7: Dabigatran (Pradaxa®), apixaban (Eliquis®) and rivaroxaban (Xarelto®) antithrombotic interactions [2, 3, 7]

Action	Example *(Not an exhaustive list)*	Advice	Effect on bleeding rates	Comment
Antiplatelet	NSAIDS Aspirin Clopidogrel Prasugrel Dipyridamole	Caution	Increased bleeding rates seen in studies	Similar to antiplatelets/ warfarin combinations
	Ticagrelor	Apixaban: Caution Rivaroxaban: Caution	Increased risk of bleeding	
		Dabigatran: Relative contraindication		
	Dual-antiplatelets	Relative contraindication	Increased risk of bleeding	Seek specialist advice
Anticoagulant	Warfarin, heparin, Low Molecular Weight Heparin (LMWH)	Contraindicated (unless transitioning between anticoagulants)	Increased	

3.2 NOAC dosing

NOAC dosing is fixed according to indication and specific patient risk factors. Routine laboratory test monitoring of drug levels or anticoagulant effect is not required. Tables 8 – 16 provide information on dosing for each PBS listed NOAC according to indication and risk factors. These tables were accurate at the time of publication; however prescribers should refer to the TGA and PBS websites for updates.

Table 8: Dabigatran (Pradaxa®) dosing for stroke prevention in non-valvular AF[1]

Indication	Risk factors	Dose	Duration
Prevention of stroke and systemic embolism in non-valvular AF in patients with at least **one** of the following risk factors: • prior stroke, TIA or non-CNS systemic embolism • age ≥75 years • hypertension • diabetes mellitus • heart failure and/ or left ventricular ejection fraction ≤ 35%.	Patient with: CrCl <30 mL/min	Contraindicated	Contraindicated
	Patient with at least **one** of the following risk factors: Age ≥75 years; ***or*** CrCl 30 - 50 mL/min; ***or*** high bleeding risk (consider HAS-BLED* score)	Dabigatran 110 mg twice daily	Indefinite duration
	Patient with: Age <75 years; ***and*** CrCl >50 mL/min; ***and*** no bleeding risk (consider HAS-BLED* score)	Dabigatran 150 mg twice daily	Indefinite duration

*'HAS-BLED' estimates risk of major bleeding for patients on anticoagulation for atrial fibrillation

Table 9: Dabigatran (Pradaxa®) dosing for prevention of VTE in patients undergoing THR or TKR[1]

Indication	Risk factors	Dose	Duration
Prevention of VTE after elective THR or TKR*	Patient with: CrCl <30 mL/min	contraindicated	contraindicated
	Patient with: CrCl 30 – 50 mL/min	Dabigatran 150 mg once daily	THR = 28 – 35 days TKR = 10 days
	Patient with: CrCl >50 mL/min	Dabigatran 220 mg once daily	THR = 28 – 35 days TKR = 10 days

*Dabigatran should be initiated within 1-4 hours of completed surgery with a single capsule (110 mg). If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated as per above table[1]. For patients who have had an epidural or spinal anaesthesia, see 6.1 Epidural, and spinal anaesthesia and lumbar puncture.

Table10: Dabigatran (Pradaxa®) dosing for treatment of VTE and prevention of recurrent VTE[1]

Indication	Risk factors	Dose	Duration
Treatment of, and prevention of recurrent, DVT and/ or PE*	Patient with: CrCl <30 mL/min	Contraindicated	Contraindicated
	Patient with at least **one** of the following risk factors: Age ≥75 years; ***or*** CrCl 30 - 50 mL/min; ***or*** high bleeding risk (consider HAS-BLED score)	Parenteral anticoagulant for at least 5 days, ***then*** Dabigatran 110 mg twice daily	Should be individualised after careful assessment of the treatment benefit against the risk for bleeding. • Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) • Longer durations (> 3 months) should be based on permanent risk factors or idiopathic DVT or PE.
	Patient with: Age <75 years; ***and*** CrCl >50 mL/min; ***and*** no bleeding risk.	Parenteral anticoagulant for at least 5 days, ***then*** Dabigatran 150 mg twice daily	

*At the time of publication dabigatran was not listed with the PBS for this indication. Check the PBS website for updates.

Table 11: Apixaban (Eliquis®) dosing for stroke prevention in non-valvular AF[3]

Indication	Risk factor	Dose	Duration
Prevention of stroke and systemic embolism in non-valvular AF in patients with at least **one** of the following risk factors: • prior stroke, TIA or non-CNS systemic embolism • age ≥75 years • hypertension • diabetes mellitus • heart failure and/ or left ventricular ejection fraction ≤ 35%.	Patient with: CrCl <25 mL/min	Contraindicated	Contraindicated
	Patient with: CrCl ≥25 mL/min and at least **two** of the following risk factors: • *Age* ≥80 years • *Weight* ≤60 kg • *Creatinine* ≥133 micromol/L	Apixaban 2.5 mg twice daily	Indefinite duration
	All other patients with: CrCl ≥25 mL/min	Apixaban 5 mg twice daily	Indefinite duration

Table 12: Apixaban (Eliquis®) dosing for prevention of VTE in patients undergoing THR or TKR[3]

Indication	Risk factor	Dose	Duration
Prevention of VTE for patients following THR or TKR	Patient with: CrCl <25 mL/min	Contraindicated	Contraindicated
	Patient with: CrCl ≥25 mL/min	Apixaban 2.5 mg twice daily	THR = 32 – 38 days TKR = 10 – 14 days

Table 13: Apixaban (Eliquis®) dosing for treatment of VTE and prevention of recurrent VTE[3]

Indication	Risk factor	Dose	Duration
Treatment of VTE	Patient with: CrCl <25 mL/min	Contraindicated	Contraindicated
	Patient with: CrCl ≥25 mL/min	Apixaban 10 mg twice daily	7 days
		then	
		Apixaban 5 mg twice daily	According to patient requirement
Prevention of recurrent VTE	Patient with: CrCl <25 mL/min	Contraindicated	Contraindicated
	Patient with: CrCl ≥25 mL/min	Apixaban 2.5 mg twice daily	Patient dependent (Following at least 6 months of a therapeutic dose anticoagulant)

Table 14: Rivaroxaban (Xarelto®) dosing for stroke prevention in non-valvular AF[2]

Indication	Risk factor	Dose	Duration
Prevention of stroke and systemic embolism in non-valvular AF in patients with at least **one** of the following risk factors: • prior stroke, TIA or non-CNS systemic embolism • age ≥75 years • hypertension • diabetes mellitus • heart failure and / or left ventricular ejection fraction ≤ 35%.	Patient with: CrCl <30 mL/min	Contraindicated	Contraindicated
	Patient with: CrCl 30–49 mL/min	Rivaroxaban 15 mg once daily	Indefinite duration
	Patient with: CrCl ≥50 mL	Rivaroxaban 20 mg once daily	Indefinite duration

Table 15: Rivaroxaban (Xarelto®) dosing for prevention of VTE in patients undergoing THR or TKR[2]

Indication	Risk factor	Dose	Duration
Prevention of VTE after elective THR or TKR*	Patient with: CrCl <15 mL/min	Contraindicated	Contraindicated
	Patient with: CrCl 15 – 29 mL/min	Rivaroxaban 10 mg once daily (use with caution)	THR = 35 days TKR = 14 days
	Patient with: CrCl ≥30 mL/min	Rivaroxaban 10 mg once daily	THR = 35 days TKR = 14 days

*Initial dose should be taken 6-10 hours after surgery provided that haemostasis has been established[2]

Table 16: Rivaroxaban (Xarelto®) dosing for treatment of VTE and prevention of recurrent VTE[2]

Indication	Risk factor	Dose	Duration
Treatment of VTE and prevention of recurrent VTE	Patient with: CrCl <30 mL/min	Contraindicated	Contraindicated
	Patient with: CrCl ≥30 mL/min	Rivaroxaban15 mg **twice** daily	3 weeks
		then	
		Rivaroxaban 20 mg **once** daily	According to patient requirement

3.3 NOAC administration

Table 17 provides guidance on administering NOACs. Information regarding administration of the relevant NOAC should be provided to the patient and/ or their carer.

Table 17: NOAC administration[1-3, 6]

NOAC	Administration instructions
Dabigatran (Pradaxa®)	• 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.
Apixaban (Eliquis®)	• Swallow whole with or without food • Can be used in dose administration aids • Can be crushed (if required) and administered orally or via a nasogastric tube (See Australian Don't Rush to Crush Handbook[9]).
Rivaroxaban (Xarelto®)	• 10 mg tablet may be taken with or without food • 15 mg and 20 mg tablet should be taken **with** food • Can be used in dose administration aids • Can be crushed (if required) and administered orally or via a nasogastric tube (See Australian Don't Rush to Crush Handbook[9]).

3.4 Management of a missed dose

Tables 18, 19 and 20 provide guidance for managing missed NOAC doses for patients discharged on a NOAC. This information may be adapted for inpatients depending on the clinical circumstances.

Table 18: Management of a missed dose of dabigatran (Pradaxa®)[1]

Instructions
• A missed dose may still be taken up to six hours prior to the next scheduled dose • If within 6 hours of next due dose, omit the missed dose • The dose should not be doubled to make up for a missed dose • Continue with the remaining daily doses at the same time on the next day.

Table 19: Management of a missed dose of apixaban (Eliquis®)[3]

Instructions
• The missed dose should be taken as soon as possible on the same day • The dose should not be doubled to make up for a missed dose • Twice daily administration should resume.

Table 20: Management of a missed dose of rivaroxaban (Xarelto®)[2]

Dose	Instructions
Rivaroxaban 10 mg, 15 mg, or 20 mg tablets taken **once** a day	• The missed dose should be taken as soon as possible on the same day • The dose should not be doubled to make up for a missed dose • The following day, the once daily dose administration should resume.
Rivaroxaban 15 mg tablets taken **twice** a day	• The missed dose should be taken immediately to ensure the intake of 30 mg total dose per day. In this case two 15 mg tablets may be taken at once. • The following day the 15 mg twice daily dose administration should resume.

4. PATIENT FOLLOW-UP AND MONITORING

There is variable and limited ability to monitor NOACs using laboratory testing in NSW Health facilities. Patients commenced on a NOAC should have medical follow up during the first seven days to review clinical progress and monitor for signs of bleeding.

In addition patients on:

- RIVAROXABAN FOR VTE TREATMENT should be followed up after THREE weeks for dose modification[2]
- APIXABAN FOR VTE TREATMENT should be followed up after ONE week for dose modification[3].

4.1 Ongoing renal function monitoring

The patient's renal function should be checked at least annually and whenever their clinical circumstances or medications change to avoid inadvertent overdose. There may be a risk of bleeding if there is deterioration in renal function[5]. More frequent monitoring of renal function will be required in patients considered to have impaired renal function.

Table 21 provides some advice on the effect of NOACs on anticoagulation tests. Routine monitoring of drug levels or anticoagulant effect is not required. Local advice should be sought on availability of relevant coagulation tests.

Table 21: Effect of NOAC on routinely performed coagulation assays[10]

Effect	Dabigatran	Rivaroxaban	Apixaban
Significant anticoagulant effect unlikely	aPTT and thrombin time (TT) normal	PT* normal	Normal PT* **DOES NOT** exclude presence of therapeutic apixaban
Anticoagulant effect present	TT prolonged aPTT prolonged	PT* prolonged	PT* prolonged or normal
Specific assays to quantify drug presence	Dilute thrombin clotting time (Hemoclot assay)	Modified Anti Xa assay specific for rivaroxaban	Modified Anti Xa assay specific for apixaban

*PT sensitivity to NOACs will vary according to local laboratory reagents. In some laboratories, PT will be insensitive to NOACs. Check with local laboratory.

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5 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 therapy continue on warfarin therapy[5].

5.1 Transitioning from anticoagulant therapy to a NOAC

Before transitioning to a NOAC, the prescriber should check contraindications and other factors as outlined in NOAC Indications and contraindications. When transitioning between a NOAC and warfarin laboratory International Normalised Ratio (INR) testing should be used. Point-of-care INR testing is NOT suitable for patients transitioning between a NOAC and warfarin.

Table 22 provides guidance on transitioning from low molecular weight heparin (LMWH), intravenous (IV) unfractionated heparin (UFH) or warfarin to a NOAC. Caution should be used when transitioning patients with renal impairment to LMWH[1-3, 5].

Table 22: Transitioning from an anticoagulant (IV UFH, LMWH or warfarin) to a NOAC[1-3, 5]

Anticoagulant	Instructions
From IV UFH infusion to NOAC	• Stop IV UFH • Commence NOAC immediately (when aPTT in or below therapeutic range)
From LMWH to NOAC	• Stop LMWH • Commence NOAC when next dose of LMWH due
From warfarin to NOAC	• Stop warfarin • Measure INR daily • Wait until INR is less than 2.5 • Commence NOAC

5.2 Transitioning from a NOAC to IV UFH or LMWH

Figures 1 – 5 provide guidance on transitioning from a NOAC to IV UFH or LMWH. This guidance should be used in conjunction with local IV UFH protocols and specialist advice.

Figure 1: Transitioning from dabigatran (Pradaxa®) to IV UFH[5]

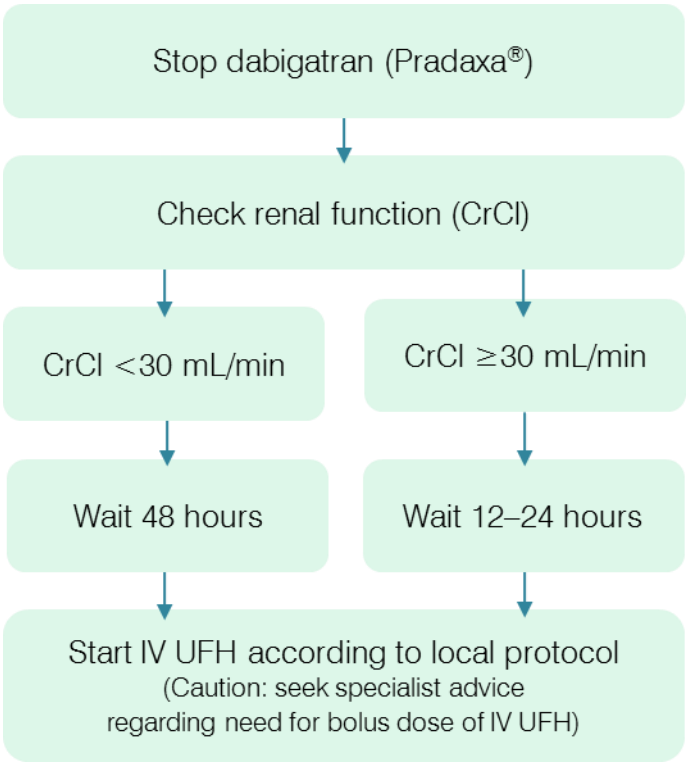


Figure 2: Transitioning from dabigatran (Pradaxa®) to LMWH[5]

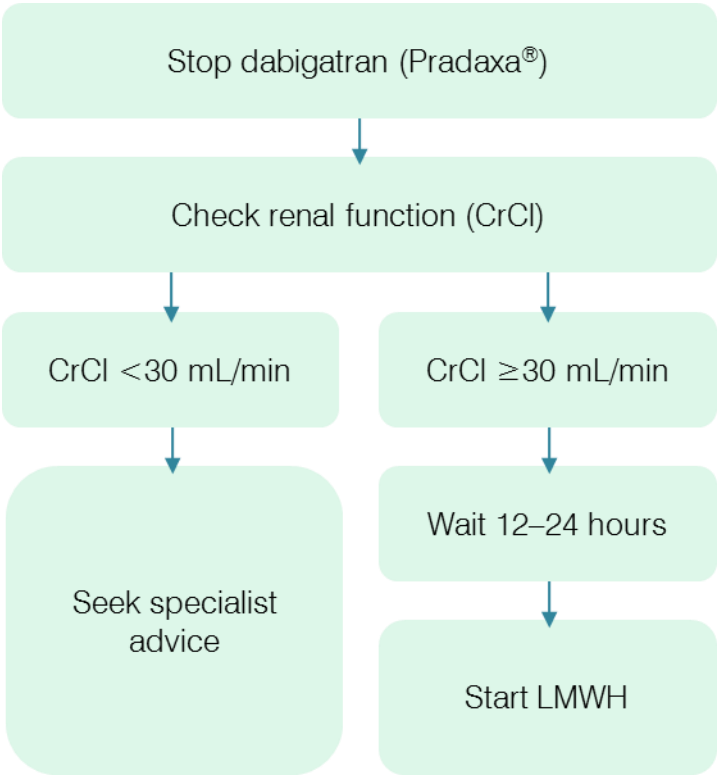


Figure 3: Transitioning from apixaban (Eliquis®) or rivaroxaban (Xarelto®) to IV UFH[5]

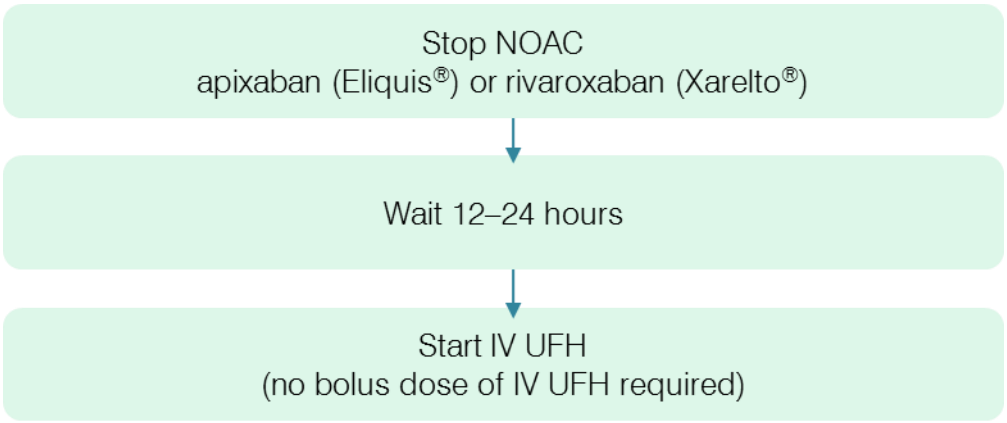


Figure 4: Transitioning from apixaban (Eliquis®) to LMWH[5]

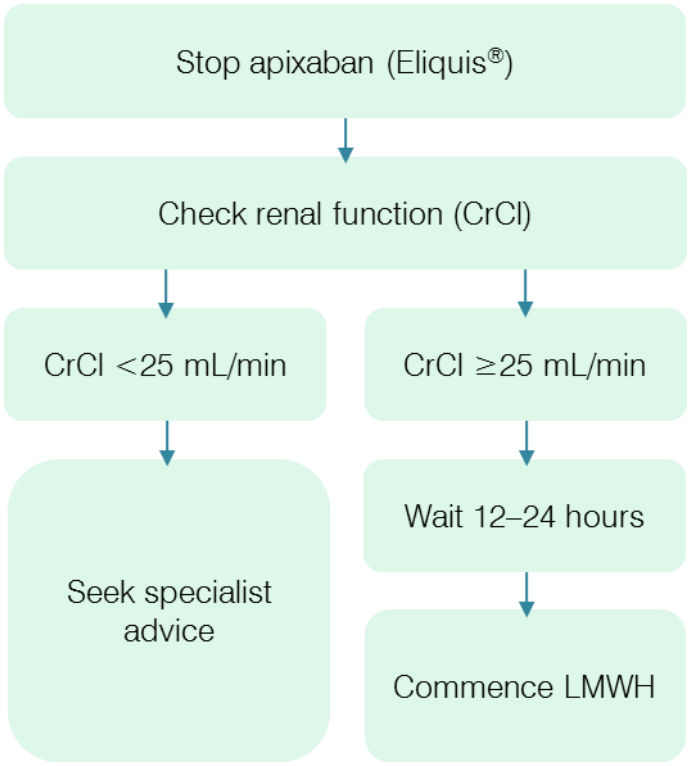
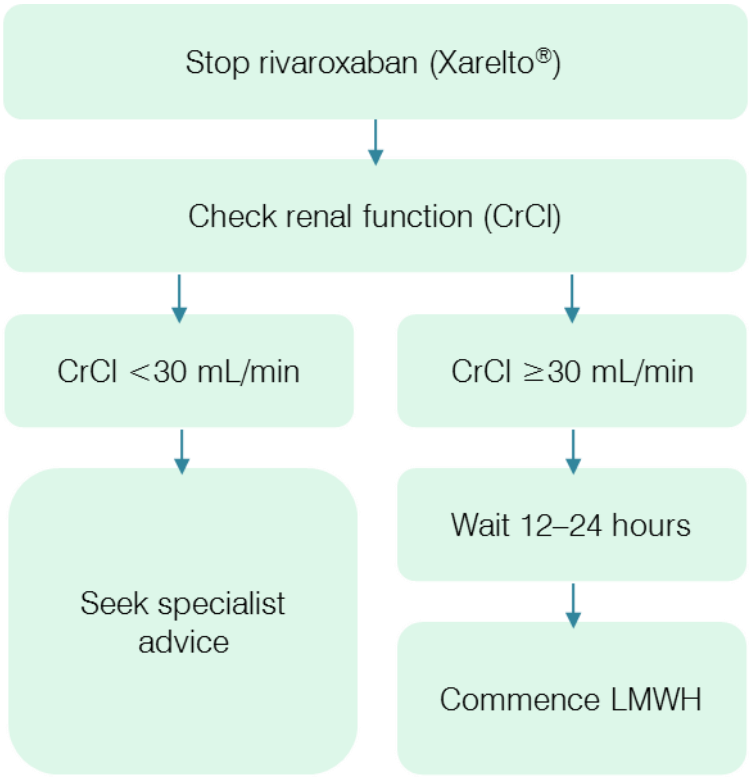


Figure 5: Transitioning from rivaroxaban (Xarelto®) to LMWH[2, 5]



5.3 Transitioning from NOAC to warfarin

Transition from a NOAC to warfarin should be undertaken in consultation with specialist advice as transition carries a risk of thrombosis and bleeding. Important points to consider in converting from a NOAC to warfarin are the NOAC half-life which is affected by renal function, and the delay in onset of warfarin. A starting dose of warfarin 5 mg or less is recommended[5].

When transitioning from a NOAC to warfarin it is necessary to take into account that INR results can be affected by both the NOAC and warfarin[5]. Upon commencing warfarin, the INR should be measured daily to identify high levels thereby maintaining caution with ongoing warfarin dosing. Laboratory INR testing should be used. Point-of-care INR testing is NOT suitable when transitioning between a NOAC and warfarin.

5.3.1 Patients with impaired renal function (estimated CrCl <50mL/min)

Specialist advice must be sought for patients with impaired renal function (< 50mL/min) as reduced clearance of a NOAC may increase exposure and therefore may increase bleeding risk.

5.3.2 Patients with estimated CrCl ≥50mL/min

For patients with estimated CrCl ≥50mL/min, the NOAC should be ceased when the INR has been greater than 'baseline' INR plus 1.0 on two consecutive days[∞]. The baseline INR should be a 'trough' level, that is, the blood sample is taken from the patient immediately prior to the next dose of the NOAC.

For example, if the patient's baseline INR is 1.7, the NOAC should be ceased when INR has been greater than 2.7 (that is, 1.7 plus 1.0) on two consecutive days.

If the baseline INR is NOT elevated, then cease the NOAC when the INR has been greater than 2 for two days.

Ongoing warfarin dosing is according to the usual target range for the patient's specific indication.

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

6. PERIOPERATIVE MANAGEMENT AND OTHER CONSIDERATIONS

The bleeding risk of surgery, timing of the last dose and half-life of the drug adjusted for renal function will determine duration of treatment cessation before surgery[11]. A recent CrCl result should be available. Table 23 lists the 2-day risk of major bleed for common procedures.

For urgent[5] or high bleeding risk elective surgery the following laboratory tests should be conducted∞.

For dabigatran:

- Estimated CrCl (calculated using the Cockcroft-Gault equation)
- FBC
- PT, aPTT, TT
- Consider drug level (where available)

For apixaban:

- Estimated CrCl (calculated using the Cockcroft-Gault equation)
- FBC
- Consider drug level (where available)

For rivaroxaban:

- Estimated CrCl (calculated using the Cockcroft-Gault equation)
- FBC
- PT
- Consider drug level (where available).

Refer to Table 21, Effect of NOAC on routinely performed coagulation assays.

∞Recommendation based on expert opinion of the Anticoagulant Medicines Working Party

Table 23: Risk of procedural bleeding (2-Day risk of major bleeding)[12]

Minimal bleeding risk procedures	Low bleeding risk procedures (2-day risk of major bleed < 2%)	High bleeding risk procedures (2-day risk of major bleed ≥ 2%)
• Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) • Cataract procedures • Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings • Pacemaker or cardioverter-defibrillator device implantation*	• Arthroscopy • Cutaneous/lymph node biopsies • Shoulder/foot/hand surgery • Coronary angiography • Gastrointestinal endoscopy +/- biopsy • Abdominal hysterectomy • Laparoscopic cholecystectomy • Abdominal hernia repair • Haemorrhoidal surgery • Bronchoscopy +/- biopsy • Epidural injections with INR <1.2	• Major surgery with extensive tissue injury • Cancer surgery • Major orthopaedic surgery • Reconstructive plastic surgery • Urologic or gastrointestinal surgery • Transurethral prostate resection, bladder resection, or tumor ablation • Nephrectomy, kidney biopsy • Colonic polyp resection** • Bowel resection • Percutaneous endoscopic gastrotomy placement, endoscopic retrograde cholangiopancreatography • Surgery in highly vascular organs (kidneys, liver, spleen) • Cardiac, intracranial or spinal surgery • Any major operation (procedure duration of > 45 min)

*Interruption of NOAC therapy is currently recommended[13, 14]

**The size of the polyp influences the risk of bleeding. It may be appropriate to categorise polyps less than 1 cm in size as low bleeding risk[15]

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Withholding of NOACs for patients who are having minimal or selected low bleeding risk procedures (see Table 23) may not be required. The treating surgeon should advise whether NOAC therapy needs to be withheld. If the decision is made to withhold NOAC therapy, the NOAC should be withheld according to the guidelines (see Tables 24 - 26). Bridging therapy[β] is not required for patients receiving NOACs.

Table 24: Timing for ceasing dabigatran (Pradaxa®) prior to surgery[1, 11]

Dabigatran (Pradaxa®) (110 or 150 mg twice a day)	Low bleeding risk surgery	High bleeding risk surgery
Normal renal function (CrCl ≥80 mL/min)	Last dose 24 hours before surgery	Last dose 48 hours before surgery
Mildly impaired renal function (CrCl 50-80 mL/min)	Last dose 24–48 hours before surgery	Last dose 48–72 hours before surgery
Moderately impaired renal function (CrCl 30-49 mL/min)	Last dose 48 – 72 hours before surgery	Last dose 96 hours (4 days) before surgery
CrCl <30 mL/min	Seek specialist advice. Dabigatran is contraindicated. Stop at least 5 days before high-risk surgery	

Table 25: Timing for ceasing apixaban (Eliquis®) prior to surgery[3]

Apixaban (Eliquis®) (2.5 mg or 5 mg twice a day)	Low bleeding risk surgery	High bleeding risk surgery
Normal/ mildly impaired renal function (CrCl >50 mL/min)	Last dose 24 hours before surgery	Last dose 48–72 hours before surgery
Moderately impaired renal function (CrCl 30-50 mL/min)	Last dose 48 hours before surgery	Last dose 72 hours before surgery
CrCl <30 mL/min	Seek specialist advice	

Table 26: Timing for ceasing rivaroxaban (Xarelto®) prior to surgery[2]

Rivaroxaban (Xarelto®) (15 mg or 20 mg once a day)	Low bleeding risk surgery	High bleeding risk surgery
Normal/ mildly impaired renal function (CrCl >50 mL/min)	Last dose 24 hours before surgery	Last dose 48–72 hours before surgery
Moderately impaired renal function (CrCl 30-50 mL/min)	Last dose 48 hours before surgery	Last dose 72 hours before surgery
CrCl <30 mL/min	Seek specialist advice.	

The treating surgeon should advise when to recommence NOAC therapy. Table 27 provides guidance on when therapeutic dose NOACs should be recommenced post-operatively (consult Table 23 to determine bleeding risk). THR and TKR prophylaxis with NOAC may be recommenced after 24 hours.

[β]Bridging anticoagulation involves the administration of a short-acting anticoagulant, typically a LMWH during the interruption of a longer-acting anticoagulant.

Table 27: Recommencing NOAC post-operatively[5]

	Recommencing NOAC post-operatively
Low bleeding risk surgery	Start or resume 24 hours after surgery
High bleeding risk surgery	Do not resume therapeutic dosing until 48 – 72 hours after surgery Consider alternative VTE prophylaxis in the interim

6.1 Epidural, and spinal anaesthesia and lumbar puncture

There is limited safety data on epidurals and NOAC use. Specialist medical advice should be sought for patients receiving a NOAC who require an epidural or spinal anesthesia.

Spinal or epidural anesthesia is contraindicated in patients currently receiving a therapeutic dose of NOAC. If a decision has been made to cease therapeutic dose NOAC prior to surgery to enable planned epidural or spinal anaesthesia, the NOAC should be ceased according to perioperative guidelines (Tables 24, 25 or 26).
If the NOAC has not been ceased for sufficient time to predict absence of anticoagulant effect then epidural or spinal anesthesia should be avoided unless laboratory testing establishes the absence of anticoagulant effect (see Table 21).

There is limited data on the safety of prophylactic dose NOAC use whilst a patient has an epidural catheter in situ. Prophylactic dose NOAC administration is not recommended for patients who have an epidural catheter in situ.

Specialist medical advice should be sought for patients receiving a NOAC requiring therapeutic or diagnostic lumbar puncture.

Table 28 provides general guidance regarding timing of VTE prophylactic NOAC doses in relation to epidural or spinal anesthesia. Longer periods apply for patients with renal impairment. The recommendations in this table should be used in consultation with specialist medical advice.

Table 28: Timing of VTE prophylactic dose in relation to epidural or spinal anaesthesia in patients without reduced renal function[5, 16]

Timing of VTE prophylactic dose	Dabigatran (Pradaxa®) 220 mg or 150 mg daily	Apixaban (Eliquis®) 2.5 mg twice daily	Rivaroxaban (Xarelto®) 10 mg daily
Last **prophylactic** dose prior to spinal or epidural catheter insertion	48 hours	24 hours	24 - 48 hours
Last **prophylactic** dose prior to spinal or epidural catheter removal	48 hours	24 hours	24 - 48 hours
Next **prophylactic** dose post catheter insertion (if indwelling epidural catheter in-situ)	Not recommended		
Next **prophylactic** dose after epidural catheter removal*	At least 6 hours*		

*A longer delay is required if there are multiple punctures or traumatic insertion of spinal or epidural catheter.

6.2. Acute coronary syndrome and stroke admissions

The management of patients who present with acute coronary syndrome who are receiving a NOAC will depend on a variety of patient factors as well as the treatment options available at the facility. Specialist cardiology advice should be sought for patients presenting with acute coronary syndrome who are receiving a NOAC.

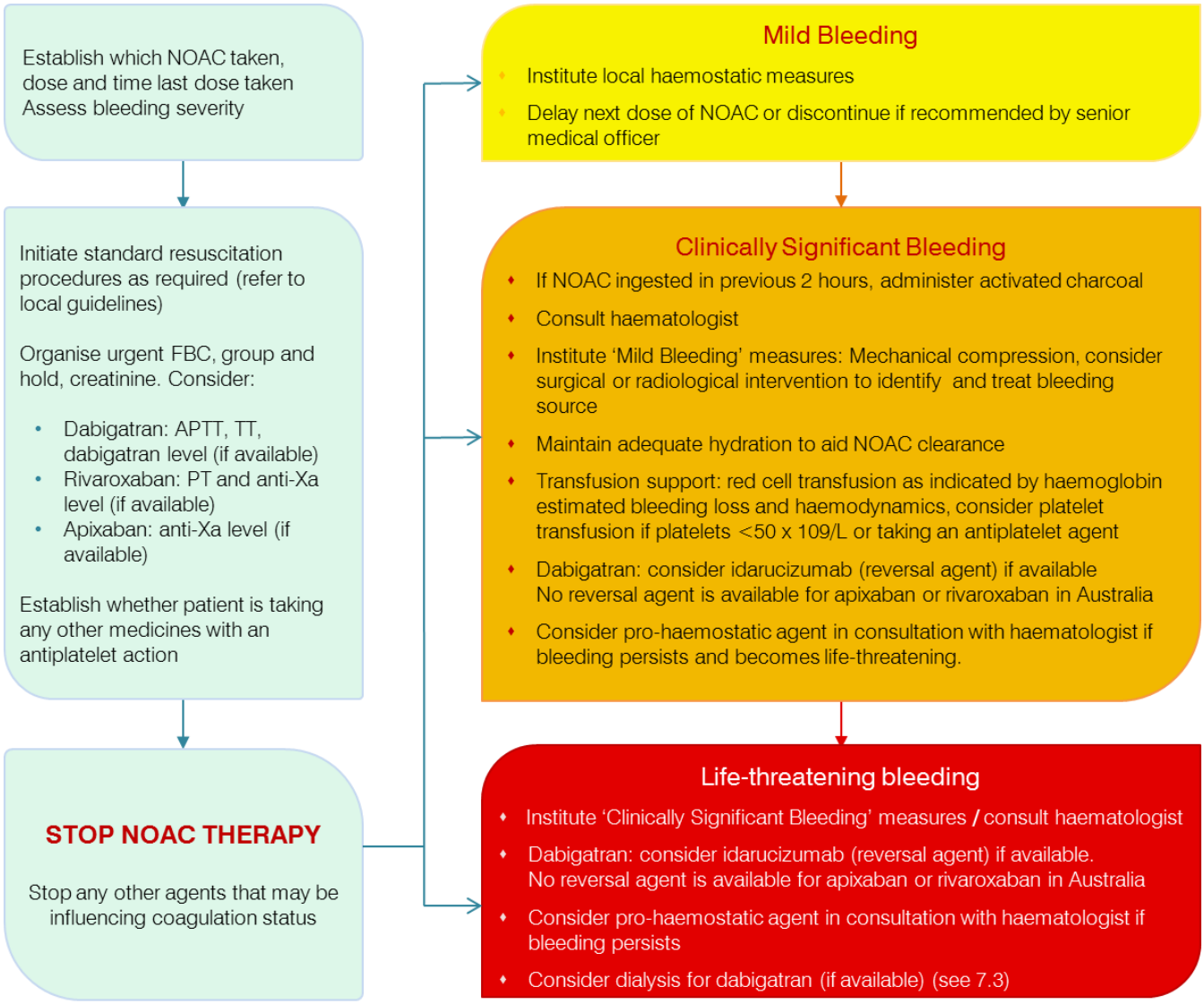
Urgent specialist advice should be sought for patients presenting with haemorrhagic strokes on NOACs as haemorrhagic stroke represents critical bleeding (See Section 7 Managing Bleeding). Urgent specialist advice should also be sought for patients on NOACs who present with an acute ischaemic stroke who would otherwise meet criteria for intravenous thrombolysis therapy or interventional neuroradiology clot retrieval.

Where a patient presents with acute ischaemic stroke on a NOAC, specialist advice is needed to consider continuation or cessation of anticoagulation in the acute period.

7. MANAGING BLEEDING

Figure 6 provides some guidance on managing bleeding. Clinicians should refer to their local bleeding management guidelines. In rural/ regional sites where results from laboratory tests may not be readily available, bleeding should be managed on a case-by-case basis according to patient condition in consultation with a haematology specialist or senior medical officer.

Figure 6: Management of NOAC associated bleeding[5]



Adapted from Tran et al (2014) with permission[α]

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7.1 Reversal agents

Idarucizumab (monoclonal antibody that reverses effects of dabigatran) was registered by TGA in May 2016. At the time of publication, reversal agents for the factor Xa inhibitors (apixaban and rivaroxaban) were not available.

Indications

Idarucizumab is indicated for when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/ urgent procedures and in life-threatening or uncontrolled bleeding[17].

An analysis of dabigatran reversal with idarucizumab in patients with serious bleeding or who required an urgent procedure, demonstrated that idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes[18, 19]. Though the anticoagulant effect is reversed, achieving haemostasis will be dependent on identifying and treating the source of bleeding.

In mild or moderate bleeding e.g. patients presenting with a non-life threatening bleed or in need of non-urgent surgery or invasive procedure, discontinuation of dabigatran and administration of appropriate supportive care is usually sufficient.

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.

IDARUCIZUMAB is only indicated if the TT is prolonged. 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.

Dosage and administration

The recommended dose of IDARUCIZUMAB is 5 g (2 x 2.5 g/ 50 mL). Administer intravenously as two consecutive infusions over 5 to 10 minutes each or as a bolus injection. No dose adjustment is required for renal impairment.

Restarting DABIGATRAN

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 verify availability with their relevant Drug and Therapeutics Committee and Pharmacy Department.

An idarucizumab information sheet is available on the Clinical Excellence Commission High-Risk Medicines webpage.

7.2 Pro-haemostatic agents

There is limited evidence on the use of pro-haemostatic agents in NOAC related bleeding[5]. Where available, it is only reasonable to consider the use of pro-haemostatic agents, 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 in NOAC related bleeding is not recommended[5].

7.3 Use of dialysis in life-threatening bleeding for patients treated with dabigatran[5, 20]

Where 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.

There is no role for dialysis in rivaroxaban and apixaban related bleeding due to high protein binding[5].

7.4 Blood management guidelines

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

8. INFORMATION AND EDUCATION FOR PATIENTS, FAMILIES AND CARERS

All patients and/ or their carer should receive education on their medications. Patients should also be advised to carry an alert card or provide Medic/Alert™ information.

Education regarding NOACs should address:

- Information about bleeding risk, what to do in case of bleeding, and the importance of alerting health care professionals that they are being treated with a NOAC
- Importance of not missing doses
- Actions to be taken if they miss a dose (see 3.4 Management of a missed dose) or take a duplicate dose
- Advice to check with the prescriber before starting any medication, including complementary and alternative medicines. For example, St John's Wort which may reduce the anticoagulant effect
- Dietary requirements, such as avoiding grapefruit juice as it can increase the anticoagulant effect
- The need to reassess kidney function in case dose adjustment is required (patient may believe that no monitoring is required)
- Actions to be taken if they sustain a fall
- Instructions for taking their NOAC (see Table 17)
- For rivaroxaban and apixaban, in the treatment of VTE, the requirement for a dosage adjustment of the anticoagulant at one week (apixaban) or three weeks (rivaroxaban) after commencement
- The need for regular clinical review by their GP.

Up to date Consumer Medicine Information (CMI) (available via TGA website) should be provided to the patient and/ or their carer:

- Dabigatran (Pradaxa® Capsules)
- Apixaban (Eliquis®)
- Rivaroxaban (Xarelto®)

The following resources may also be useful:

Clinical Excellence Commission:

- Dabigatran (Pradaxa®) Information for Patient's, Families and Carers
- Apixaban (Eliquis®) Information for Patient's, Families and Carers
- Rivaroxaban (Eliquis®) Information for Patient's, Families and Carers

These documents have also been translated into the following languages: Arabic, Traditional Chinese, Simplified Chinese, Greek, Korean and Vietnamese. The translated versions are available on the Clinical Excellence Commission High-Risk Medicines Webpage.

Government of Western Australia:

- Living with a NOAC (2013)

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APPENDIX

1. Abbreviations used

Abbreviation	Term
AF	Atrial fibrillation
aPTT	Activated Partial Thromboplastin Time
CMI	Consumer Medicine Information
CNS	Central nervous system
CrCl	Creatinine clearance (estimated using the Cockcroft-Gault equation)
DVT	Deep vein thrombosis
FBC	Full blood count
INR	International normalised ratio
ICH	Intracranial haemorrhage
IV	Intravenous
LFT	Liver Function Test
LMWH	Low molecular weight heparin
NOAC	Non-vitamin k antagonist oral anticoagulant
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary embolism
P-gp	P-glycoprotein
PBS	Pharmaceutical Benefits Scheme
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

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