WATAG 'Prescribing a NOAC' quick reference

EXCLUSION Criteria:
- Known hypersensitivity to NOAC preparation
- Active significant bleeding
- Pregnant or breastfeeding
- Prosthetic heart valve, valve repair or stenosis
- Valvular Atrial Fibrillation
- Recent stroke, unless advised by a stroke physician

Prior to NOAC initiation:
Record: FBC, renal and liver function

Lab CONTRAINDICATIONS:
- Poor renal function (dabigatran, rivaroxaban* CrCl <30 mL/min, apixaban: <25 mL/min)
- Liver disease (e.g. ALT >2x upper limit of normal)

Take detailed history:
Ensure patient doesn't have any exclusion criteria

Bleeding Risk CONTRAINDICATIONS:
- Disorder of haemostasis e.g. Von Willebrand disease or coagulation factor deficiency
- GI bleed ≤ 12 months, ulcer < 30 days
- Skin ulcer ≤ 30 days ago
- Fibrinolytic treatment last 10 days
- Dual antiplatelet therapy

Assess bleeding risk

CONTRAINDICATED concomitant medications:
Dabigatran
- Systemic azole antifungals (except fluconazole)
- dronedarone
- cyclosporin and tacrolimus
- HIV-protease inhibitors e.g. ritonavir

Rivaroxaban / apixaban
- Systemic azole antifungals (except fluconazole)
- HIV-protease inhibitors e.g. ritonavir

Consider concomitant medications

If the patient is on warfarin:
Discontinue warfarin and start NOAC when INR is 2.0 or less

dabigatran (Pradaxa®):

Total Hip or Knee Replacement (VTE prophylaxis):

CrCl > 50 mL/min: **220mg (2 x 110 mg) once daily**

CrCl 30-49 mL/min: **150mg (2 x 75 mg) once daily**

Hip: up to 30 days | Knee: up to 10 days

Non-Valvular Atrial Fibrillation (therapeutic dose):

CrCl ≥ 50 mL/min: **150mg twice daily**

CrCl 30-49 mL/min or ≥ 75 years: **110mg twice daily**

Treatment or prevention of recurrent DVT/PE:
CrCl ≥ 50 mL/min: **150mg twice daily**
CrCl 30-49 mL/min or ≥ 75 years: **110mg twice daily**

rivaroxaban (Xarelto®):

Total Hip or Knee Replacement (VTE prophylaxis):

CrCl > 50 mL/min: **10mg once daily**

CrCl 30-49 mL/min: **10mg once daily**

*CrCL 15-29mL/min: **10mg once daily with caution**

Hip: up to 30 days | Knee: up to 15 days

Non-Valvular Atrial Fibrillation (therapeutic dose):

CrCl > 50 mL/min: **20mg once daily**

CrCl 30-49 mL/min: **15mg once daily**

Treatment or prevention of recurrent DVT/PE:

CrCl ≥ 30 mL/min: **15mg twice daily** for 3 weeks, then 20mg once daily

apixaban (Eliquis®):

Total Hip or Knee Replacement (VTE prophylaxis):

CrCl > 25mL/min: 2.5mg twice daily

Hip: up to 30 days | Knee: up to 15 days

Non-Valvular Atrial Fibrillation (therapeutic dose):

5mg twice daily

Age ≥ 80 years, weight ≤ 60 kg or SCr ≥ 133 micromol/L**: 2.5mg twice daily**

Treatment of recurrent DVT/PE:
CrCl >25 mL/min: **10mg twice daily** for first 7 days, then 5mg twice daily thereafter

Prevention of recurrent DVT/PE
CrCl > 25mL/min: **2.5mg twice daily** after at least 6 months of treatment

WATAG New Oral Anticoagulant Prescribing Guidelines

The new oral anticoagulants (NOACs), also known as non-Vitamin K antagonist oral anticoagulants (NOACs), novel oral anticoagulant or direct oral anticoagulants (DOACs) currently approved in Australia are dabigatran, rivaroxaban and apixaban.

The NOACs differ from warfarin in that they do not require laboratory monitoring. They need to be used with caution in patients with renal impairment and are contraindicated in patients with renal failure.

Warfarin should be used and NOACs avoided, in patients who have prosthetic or bio-prosthetic heart valves or mitral valve repair and in patients with 'valvular' atrial fibrillation (atrial fibrillation associated with mitral stenosis).

It is important to note that most NOACs do not have specific antidotes and strategies for anticoagulation reversal are limited, although this field is evolving and future changes in knowledge are likely to develop.

For information and advice on NOAC reversal or uncontrolled bleeding please refer to your local hospital guidelines or consult with a haematologist.

These guidelines are based on evidence available at the time and do not replace expert medical judgement; for more comprehensive guidance please refer to a local haematologist and the manufacturer's product information.

Contraindications – Do Not Use
Known hypersensitivity to ingredients in NOAC Active significant bleeding Increased bleeding risk – this includes previous pathologies and/or interventions, and future planned interventions (see PI for product specifics) Poor renal function: • dabigatran CrCl <30 mL/min* • rivaroxaban CrCl <30 mL/min* (rivaraoxaban 10 mg may be used with caution for DVT prophylaxis for Total Knee Replacement (TKR)/Total Hip Replacement (THR) in patients with CrCl 15-29 mL/min*) • apixaban CrCl < 25 mL/min* Liver disease (Child-Pugh Grade B or C, or ALT >2 times ULN) Valvular Atrial Fibrillation Mechanical or bio-prosthetic heart valve replacement, mitral valve repair or valvular disease including mitral valve stenosis. Disorder of haemostasis e.g. Von Willebrand disease or coagulation factor deficiency Pregnancy or breast-feeding Other anticoagulants Recent fibrinolytic treatment (≤ 10 days) Concomitant contraindicated medications Recent stroke - Recent stroke (unless advised by a stroke physician) GI bleed or ulcer (see PI for product specifics)

*** Creatinine Clearance should be calculated using the Cockcroft Gault formula.**

Precautions – Use with Caution
Renal impairment 30 – 50 mL/min – dose adjustment required, see dosing instructions Unstable renal function or likely to continue deteriorating. Hepatic impairment: Child-Pugh A. Recent surgery ≤ 1 month ago Weight ≤ 60 kg – see dosing instructions Age ≥ 75 years – see dosing instructions Concomitant medications – see drug interactions Concomitant antiplatelet therapy Previous pathologies and/or interventions, and future planned interventions (see PI for product specifics) Haemorrhagic risk

Drug interactions: **See PI for a comprehensive list of medication interactions**

Contraindications: dabigatran	Contraindications: rivaroxaban/apixaban
Via P-glycoprotein competition and CYP3A4 inhibition: Systemic azole antifungals e.g. ketoconazole (except fluconazole), dronedarone, cyclosporin, tacrolimus, ritonavir (and other HIV protease inhibitors)	Via P-glycoprotein competition and CYP3A4 inhibition: Systemic azole antifungals e.g. ketoconazole (except fluconazole), ritonavir (and other HIV protease inhibitors)
Caution – avoid use or seek advice, dose change may be warranted	
Less potent P-gp inhibitors and/or CYP3A4 inhibitors: amiodarone, clarithromycin, erythromycin, fluconazole, quinidine, verapamil	Less potent P-gp and/or CYP3A4 inhibitors: amiodarone, clarithromycin, erythromycin, cyclosporin, diltiazem, dronedarone erythromycin, fluconazole, quinidine, tacrolimus, verapamil
P-gp/CYP3A4 inducer: carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort	
Antiplatelet agents: e.g. clopidogrel, prasugrel, ticagrelor	
Nonsteroidal anti-inflammatory drugs (NSAIDs): e.g. naproxen, celecoxib, ibuprofen	

Prescribing a New Oral Anticoagulant – Dosing Instructions

Dabigatran				
	THR (up to 35 days)	**TKR** (up to 10 days)	**Non-Valvular AF**	**Treatment and Prevention DVT/PE**
CrCl >50mL/min	220mg (2 x 110 mg) once daily	220mg (2 x 110 mg) once daily	150mg twice daily	150mg twice daily
CrCl 30-49 mL/min	150mg (2 x 75mg) once daily	150 mg (2 x 75mg) once daily	110mg twice daily	110mg twice daily
CrCl <30 mL/min	contraindicated	contraindicated	contraindicated	contraindicated
Special Considerations	nil	nil	Older than 75 years: 110mg twice daily	Older than 75 years: 110mg twice daily

Rivaroxaban				
	THR (up to 35 days)	**TKR** (up to 14 days)	**Non-Valvular AF**	**Treatment and Prevention DVT/PE**
CrCl >50mL/min	10mg once daily	10mg once daily	20mg once daily	15mg twice daily for first 3 weeks, then 20 mg once daily thereafter
CrCl 30-49 mL/min	10mg once daily	10mg once daily	15mg once daily	15mg twice daily for first 3 weeks, then 20 mg once daily thereafter
CrCl 15-29 mL/min	10mg once daily with caution	10mg once daily with caution	contraindicated	contraindicated
CrCl <15 mL/min	contraindicated	contraindicated	contraindicated	contraindicated
Special Considerations	nil	nil	nil	nil

Apixaban				
	THR (32 to 38 days)	**TKR** (10 to 14 days)	**Non-Valvular AF**	**Treatment and Prevention DVT/PE**
CrCl >25mL/min	2.5mg twice daily	2.5mg twice daily	5mg twice daily	Treatment: 10mg twice daily for the first 7 days, then 5mg twice daily thereafter. Prevention: 2.5mg twice daily after at least 6 months of treatment
CrCl <25 mL/min	contraindicated	contraindicated	contraindicated	contraindicated
Special Considerations	nil	nil	If at least 2 of: ▪ Older than 80 y ▪ Weight ≤60 kg ▪ creatinine ≥133 micromol/L Then: 2.5mg twice daily	

Switching anticoagulants (See PI for further details)

Switching From	Switching To	Instructions
LMWH or subcut Heparin	Dabigatran/rivaroxaban/apixaban	Start NOAC when next dose of LMWH or subcut Heparin due.
Heparin infusion	Dabigatran/rivaroxaban/apixaban	Start NOAC immediately once infusion ceased
Dabigatran	LMWH or Heparin	Wait 12-24 hrs where CrCl ≥ 30mL/min, or 48 hrs where CrCl < 30mL/min, after last dose of dabigatran before starting the parenteral anticoagulant.
Rivaroxaban or apixaban	LMWH or Heparin	Commence 12-24 hrs (1-2 half lives of the NOAC) after the last NOAC dose. No bolus dose of unfractionated heparin is required.
Warfarin	Dabigatran/rivaroxaban/apixaban	Discontinue warfarin and monitor INR. The NOAC can be started immediately when the INR is <2 or the day after the INR is 2.0-2.5.
Dabigatran/rivaroxaban/apixaban	Warfarin	INR is generally not reliable. It is necessary to take into account that the elimination half-life of a NOAC is affected by renal function, there is a delay in the onset of warfarin (typically 5 days) and the INR readout may be affected by both the NOAC and warfarin. See below recommendations; discussion with a haematologist may be needed.

*****IT IS HIGHLY RECOMMENDED THAT A HAEMATOLOGIST IS CONSULTED BEFORE SWITCHING FROM A NOAC TO WARFARIN BECAUSE OF THE POTENTIAL FOR COMPLICATIONS.**

Switching dabigatran to warfarin:
CrCl >50 mL/min: start warfarin 3 days before ceasing dabigatran CrCl 31 to 50 mL/min: start warfarin 2 days before ceasing dabigatran CrCl 15 to 30 mL/min: start warfarin 1 day before ceasing dabigatran CrCl <15mL/min: consult with haematology service

Switching rivaroxaban or apixaban to warfarin:
CrCl >50 mL/min: start warfarin 4 days before ceasing rivaroxaban or apixaban CrCl 31 to 50 mL/min: start warfarin 3 days before ceasing rivaroxaban or apixaban CrCl 15 to 30 mL/min: start warfarin 2 day before ceasing rivaroxaban or apixaban CrCl 15mL/min: consult with haematology service

Management of Patients Undergoing Surgery

For patients taking a NOAC who require surgery, the risk of thrombosis when the drug is withheld relative to the risk of excessive bleeding if continued must be considered. Advance planning is essential as there are no strategies for immediate reversal and strategies to manage bleeding during and after surgery are anecdotal.

Elective surgical intervention classification – this is not an exhaustive list.

High bleeding risk	Minor bleeding risk	Low bleeding risk (consider continuing NOAC)
Complex left-side ablation	Endoscopy with biopsy	Some dental interventions
Spinal or epidural anaesthesia	Prostate/bladder biopsy	Ophthalmology – cataract, glaucoma
Thoracic, abdominal or major orthopaedic surgery	Electrophysiological/radiofrequency catheter ablation	Endoscopy without surgery
Liver or kidney biopsy	Angiography or pacemaker/ICD implantation	Superficial interventions

Peri-operative NOAC interruption - Recommended dose withholding time before surgery

Further consultation with specialist haematologist and consideration of specific risks of bleeding vs. risks of thrombosis in each case is recommended. Details below are suggestions only.

Dose adjustments reflect half-lives and renal function.

Dabigatran (150 mg twice daily)		
Surgical Bleeding Risk	**Low Risk**	**High Risk**
CrCl >50 mL/min (Half-life 12 – 17 hrs)	Last dose 24hr before surgery	Last dose 48 -72hr before surgery
CrCl 30-49 mL/min (Half-life 13 – 23 hrs)	Last dose 48-72hr before surgery	Last dose 96hrs before surgery

Rivaroxaban (20mg once daily)		
Surgical Bleeding Risk	**Low Risk**	**High Risk**
CrCl >50 mL/min (Half-life 5 – 9 hrs)	Last dose 24hr before surgery	Last dose 48 -72hr before surgery
CrCl 30-49 mL/min (Half-life 9 – 13 hrs)	Last dose 48hr before surgery	Last dose 72hrbefore surgery

Apixaban (5mg twice daily)		
Surgical Bleeding Risk	**Low Risk**	**High Risk**
CrCl >50 mL/min (Half-life 7 -8 hrs)	Last dose 24hr before surgery	Last dose 48-72hr before surgery
CrCl 30-49 mL /min (Half-life 18 – 18 hrs)	Last dose 48hr before surgery	Last dose 72hr before surgery

Urgent surgical intervention when patient is on NOAC therapy
• If possible, delay surgery until at least 12 – 24 hr after last dose of NOAC   • If surgery cannot be delayed, measure anticoagulant effect and seek haematologist advice

Post-operative NOAC recommencement – recommended management

For patients at high risk of thrombosis/thromboembolism an earlier reduced dose may be suitable (e.g. on the evening following surgery). Specialist haematologist advice is recommended.

	Resumption of NOAC
Low Bleeding Risk	Resume 24 hr after surgery
High Bleeding Risk	Resume 48-72 hr after surgery

For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran (e.g. 75mg once daily) on the evening after surgery and on the following day (first postoperative day) after surgery.

Consider a reduced dose (i.e. rivaroxaban 10mg once daily or apixaban 2.5mg twice daily) in patients at high risk for thromboembolism.

LMWH such as enoxaparin 40mg once daily, unfractionated heparin 5000 units twice or three times daily or mechanical prophylaxis such as intermittent pneumatic compression (IPC) can be considered until therapeutic anticoagulation can be re-introduced.

Management of Bleeding with New Oral Anticoagulants

Bleeding patient on a NOAC
Identify any other concurrent anticoagulants/antiplatelet agents

Seek early advice from a haematologist
Optimal care will be guided by this advice in each instance

In addition to routine care as clinically indicated:
Measure: FBE, UEC, LFT, standard Coagulation Profile, Group & Hold, and: • dabigatran: TT, dabigatran level • rivaroxaban: PT, rivaroxaban level • apixaban: apixaban level

Mild bleeding
• local haemostatic measures • delay or discontinue NOAC as required

Clinically significant bleeding (reduction in Hb >20 g/L or requiring RBC transfusion > 2 units)
• **Stop NOAC therapy** • **Give oral charcoal if NOAC ingested < 2 hours ago** • Local haemostatic measures: mechanical compression and consider surgical/radiological intervention to identify and treat bleeding source • Maintain adequate hydration to aid drug clearance • RBC transfusion as per Hb level • Consider platelet transfusion if on antiplatelet therapy or if platelets < 50 x 10^9/L

Life-threatening / persistent bleeding or clinical instability
Consider use of one of the following agents: • Prothrombinex-VF 25-50 IU/kg • Factor Eight Inhibitor Bypassing Activity (FEIBA) 50 IU/kg • Tranexamic acid 15-30mg/kg IV +/- infusion for mucosal bleeds **Consider dialysis for dabigatran** (Note evidence around efficacy/risk of these options is unclear; specialist advice is recommended)

Note on laboratory tests for different NOACs:

In general, routine coagulation assays do not reliably reflect the presence/efficacy of NOAC therapy, so interpretation and management requires specialist input. In addition, some of the recommended assays are dependent upon laboratory capabilities. N.B. At the time of writing this guideline no WACHS laboratories had the capacity to measure levels.

Dabigatran: TT is the most sensitive assay. A normal TT excludes the presence of dabigatran. A normal APTT suggests it is unlikely a high level of dabigatran is contributing to bleeding.

Rivaroxaban: PT is the most sensitive assay. A normal PT suggests significant rivaroxaban effect is unlikely.

Apixaban: An apixaban level is necessary to estimate accurately the anticoagulant effect.

Disclaimer

Clinical material in this guideline should not replace or remove clinical judgement or professional care for each patient within the context of local resources and expertise.

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