Health
South Eastern Sydney
Local Health District

RIVAROXABAN IS A HIGH RISK MEDICINE

USE WITH CAUTION AND ENSURE THE DIRECTIONS WITHIN THIS PROTOCOL ARE FOLLOWED CAREFULLY

Areas where applicable	SESLHD Hospitals
Areas where not applicable	None
Authorised Prescribers:	Medical Officers and Nurse Practitioners Rivaroxaban may only be commenced on the advice of a Senior Medical Officer
Indications for use	• Prevention of venous thromboembolism (VTE) after total knee replacement (TKR) or total hip replacement (THR) surgery. • Prevention of stroke or systemic embolism in non-valvular atrial fibrillation in patients with at least one of the following risk factors: *Age ≥ 75 years, Hypertension, Diabetes Mellitis, Heart failure or left ventricular dysfunction (left ventricular ejection fraction < 35%), previous stroke, transient ischaemic attack or systemic embolism.* • Acute treatment of VTE, and prevention of recurrent VTE. • Chronic stable atherosclerotic disease in combination with aspirin. **NOTE: All other indications are NON-FORMULARY at SESLHD. Patients should not be newly commenced on rivaroxaban for other indications without prior approval from the local Drug and Therapeutics Committee**
Patient Selection	Before initiating rivaroxaban undertake clinical evaluation of the patient to ensure it is a suitable and safe therapy: • Ensure no contraindications, drug interactions or significant cautionary factors are present. • Discuss treatment options and confirm patient agreement with choice of therapy. • Consider patient's capacity to manage the medication safely, e.g. compliance with prescribed dosing frequency. • Note: rivaroxaban is suitable for packaging into a dose administration aid (e.g. Webster Pak or Dosette box) if required. • Perform the following: a. Full Blood Count to exclude significant thrombocytopenia or anaemia b. Biochemical profile including liver function and renal function assessment. To assess the appropriateness of rivaroxaban and determine the dosing regimen, creatinine clearance should be calculated using the Cockcroft Gault equation (requires patient gender, age, ideal body weight and serum creatinine). eGFR should NOT be used for this purpose. c. Coagulation profile (PT/APTT) to exclude underlying defect in haemostasis.

Important Safety Considerations	**<u>Duplication of anticoagulants</u>** Errors involving duplication of anticoagulant therapy are common. Before prescribing or administering rivaroxaban, clinicians must ensure that the patient is not currently prescribed any other anticoagulant medications. In eMEDs, an alert is triggered if there is an attempt to order a second anticoagulant drug when one is already prescribed in the system. Prescribers must be aware of the limitations of electronic alerts and always be vigilant to the presence of other anticoagulants, including those that may be prescribed on the IV fluid chart. Alerts may not be triggered in other electronic medication management systems. Prescribers should annotate all orders for rivaroxaban with the word "ANTICOAGULANT" and always include the indication for prescribing.
Contraindications	• **Significant active bleeding and lesions at risk of bleeding** (e.g. current or recent gastrointestinal ulceration, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities) • **Mechanical heart valves** • **Indwelling spinal or epidural catheter and during the first 6 hours after removal** • **Renal impairment:** - For therapeutic anticoagulation rivaroxaban is contraindicated in patients with a calculated CrCl < 30 mL/min - For DVT prophylaxis Rivaroxaban 10mg daily can be used with caution in patients with a CrCl of 15-30 mL/min but is contraindicated in patients with CrCl < 15mL/min Use with caution in patients with CrCl 30-50 mL/min – consider warfarin especially if renal deterioration likely. • **Congenital or acquired coagulation disorder or platelet disorder** (thrombocytopenia, platelets <100 x 10^9/L or functional platelet defects) • **Hepatic disease**: Child-Pugh B or C with coagulopathy (caution: Child Pugh A or B without coagulopathy) • **Pregnancy or breast feeding:** in women of child bearing age a pregnancy test should be performed • **Infective endocarditis** (where the risk of rupture/haemorrhage has not yet been surgically managed) • **Concomitant treatment with any other anticoagulant agent** (except under the circumstances of switching therapy to or from rivaroxaban or when heparin is given at doses necessary to maintain a patent central venous or arterial catheter) • **Concomitant treatment with strong inhibitors of both CYP3A4 and P-gp** (such as azole antifungals or HIV protease inhibitors)

Precautions

- **Increased bleeding risk**: carefully assess risk vs benefit and consider use of alternative anticoagulant
  - History of intracranial haemorrhage, spinal, retroperitoneal or atraumatic intra-articular bleeding
  - History of retinal bleeding, vascular proliferative retinopathy or eye surgery
  - History of bronchiectasis or pulmonary haemorrhage
  - Recent malignancy or irradiation
  - Uncontrolled hypertension i.e. systolic BP >180mmHg or diastolic BP > 110mmHg
  - Thrombocytopenia (platelets < 100 $x10^9$/L - discuss with haematology)
  - Age >75 years and the presence of other risk factors for bleeding (including drug interactions)
  - Weight < 50 kg (dose adjustment may be required)
- **Malignancy:** Low molecular weight heparin is the current preferred treatment for VTE related to active malignancy
- **Antiphospholipid syndrome related VTE:** inadequate data in this group of patients. Warfarin remains the standard of care.
- **Poor compliance:** missing rivaroxaban doses results in inadequate and inconsistent anticoagulation due to the short half-life; consider use of warfarin
- **Upper limb thrombosis or unusual site thrombosis** such as cerebral vein thrombosis, portal and splenic vein thrombosis (NOACs have not been studied in these groups)
- **Age > 70 years with high risk of falls**
- **Drug interactions:** see below

Always consult the haematology team if unsure of the appropriateness of rivaroxaban

Important Drug Interactions

Drug-drug interactions

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)

Antithrombotic interactions: the appropriateness of the combination of rivaroxaban and antiplatelet drugs should be confirmed with a senior medical officer.

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 Dabigatran: Relative contraindication	Increased risk of bleeding	
	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	

	Indication	Renal Function (CrCl mL/min)	Recommended Dose
Dosage	Prevention of VTE after major orthopaedic surgery of lower limbs	≥ 30	10mg ONCE daily for 14 days (knee replacement surgery) or 35 days (hip replacement surgery). Commence 6-10 hours after surgery provided haemostasis is established
		15 – 29 *USE WITH CAUTION*	
		< 15	**Contraindicated**
	Prevention of stroke in non-valvular AF with ≥ 1 risk factor (see indications section for risk factors)	≥ 50	20mg ONCE daily
		30 - 49	15mg ONCE daily
		15 – 29 *USE WITH CAUTION*	
		<15	**Contraindicated**
	Treatment of VTE and Prevention of recurrent VTE	≥ 30	15mg TWICE daily for 3 weeks ***then*** reduce dose to 20mg ONCE daily for 6 to 12 months ***then*** maintain 20mg ONCE daily or consider* 10mg ONCE daily
		15 – 29 *USE WITH CAUTION*	
		< 15	**Contraindicated**
	Treatment of CAD and/or PAD	≥ 30	2.5mg TWICE daily with aspirin 100mg ONCE daily
		15 – 29 *USE WITH CAUTION*	
		< 15	**Contraindicated**
	*Based on individual assessment of the risk of recurrent DVT or PE against the risk of bleeding, dose reduction to 10mg Rivaroxaban ONCE daily may be considered.		
Transitioning between anticoagulants	Detailed advice regarding transitioning between rivaroxaban and other anticoagulants is available in the CEC NOAC Guidelines. The process of transitioning between anticoagulants should be done under the close guidance of a Senior Medical Officer.		

Prescription Requirements	All medication orders for rivaroxaban must include: - Drug, dose, route and indication - the intended duration of therapy when prescribed for treatment or prevention of VTE - the word “ANTICOAGULANT” printed clearly
Administration Instructions	Rivaroxaban should be administered orally with food Rivaroxaban is available in 2.5mg 10mg, 15mg and 20mg film-coated tablets (can be crushed if required) Missed doses: - **Where patient is on a ONCE daily regimen** 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. Resume at the normal time the next day. - **Where patient is on a TWICE daily regimen** the missed dose should be taken immediately to ensure the total daily dose is administered. Two tablets may be taken at once if necessary. Resume twice daily dosing the next day.

Monitoring Requirements	**Routine monitoring** Patients should be monitored for signs of bleeding and educated on how to self-monitor (see 'Patient Education' section). If a patient on rivaroxaban experiences a fall, observe and monitor closely for signs of bleeding in accordance with SESLHDPR/380 - Falls prevention and management for people admitted to acute and sub-acute care. In patients with normal renal function, renal function should be checked at least annually, and more often if the patient's clinical circumstances change. In patients with impaired renal function, with risk factors for bleeding or taking interacting medications, more regular monitoring is required. Even a small decline in renal function can result in a significantly increased risk of bleeding in these patients. **Investigations for bleeding** • Routine coagulation tests cannot be used to assess the degree of anticoagulation. PT/INR and APTT may or may not be affected by rivaroxaban. • Rivaroxaban levels can be assessed using a specific anti-Xa assay • Drug levels may be useful to assist in determining if there has been an overdose or if therapeutic anticoagulation is contributing to bleeding. • Drug assays may be requested on the pathology request form. One citrate (blue top) tube should be collected; noting that the patient is on rivaroxaban, their current dose and the time of last dose. • Results should be interpreted in consultation with the haematology team. Note: There is no role for routine monitoring of drug levels or anticoagulant effect. Doses should NOT be adjusted in response to laboratory tests.
Management of Complications	**Management of bleeding** Refer to flowchart in Appendix A Note: No effective reversal agent for rivaroxaban is available in Australia at the current time. Due to high plasma protein binding rivaroxaban is not dialyzable.
Storage requirements	Rivaroxaban must not be stored in clinical areas where use is infrequent and any dispensed products that are no longer required should be removed from these areas at the earliest opportunity. In areas where rivaroxaban is stored outside of pharmacy, shelf labelling should be used to identify it as an anticoagulant medicine.

Peri-procedural management of anticoagulation

Routine Surgery

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.

It is recommended that the following laboratory results are reviewed preoperatively:

- CrCl (calculated using the Cockcroft-Gault equation)
- FBC
- LFT

For urgent or high bleeding risk elective surgery the following laboratory results should **also** be reviewed:

- PT, TT, APTT
- Consider Anti-Xa level in consultation with haematology team.

Specialist advice should be sought regarding when rivaroxaban should be stopped prior to surgery. The following table is a guide:

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.	

Urgent/Unplanned Surgery

- No agent can reverse rivaroxaban. Consider delaying surgery until coagulation screen normal or sufficient time has passed for drug clearance. Consult with haematology for urgent lifesaving surgery.
- If surgery must proceed, check rivaroxaban Anti-Xa level, PT, APTT and fibrinogen. Also check EUC, calcium and perform a Group and Hold.
- If PT prolonged or Anti-Xa level significant and surgery cannot be delayed, consider use of Prothrombinex VF 50 international units/kg. Continue supportive measures such as maintenance of BP and urine output to optimise drug clearance and consider transfusion support for the management of bleeding.
- Epidural and spinal anaesthesia are contraindicated

Post-Procedure

ALWAYS LIASE WITH THE PROCEDURAL TEAM REGARDING SATISFACTION WITH HAEMOSTASIS PRIOR TO ANY ANTICOAGULATION COMMENCEMENT

General principles:

- For low bleeding risk procedures, consider restarting therapeutic anticoagulation 24 hours post operatively
- For high bleeding risk procedures, consider restarting therapeutic anticoagulation 48 – 72 hours post operatively

	• In high-risk patients, consider prophylactic anticoagulation with enoxaparin or heparin, starting the evening following the procedure until therapeutic anticoagulation can be commenced. • If ongoing concerns for bleeding persist following high-risk procedures, consider restarting therapeutic anticoagulation initially with unfractionated heparin and converting to rivaroxaban once stable.
Neuraxial anaesthesia in patients on rivaroxaban	Neuraxial anaesthesia is contraindicated in patients who are therapeutically anticoagulated. Neuraxial anaesthesia cannot be performed until laboratory testing establishes the absence of rivaroxaban effect. There is limited data on the safety of prophylactic doses of NOACs whilst a patient has an epidural catheter in situ. Use of rivaroxaban for VTE prophylaxis is not recommended for patients who have an epidural catheter in situ. For patients with normal renal function receiving rivaroxaban for VTE prophylaxis who require neuraxial anaesthesia: 1. The last dose of rivaroxaban should be given 24 hours before planned insertion or removal of the epidural catheter 2. The first recommencement dose of rivaroxaban should be given no earlier than 6 hours after catheter removal (longer of there are multiple punctures or traumatic insertion - seek haematology advice) 3. Rivaroxaban is not recommended in patients undergoing anaesthesia with postoperative indwelling catheters Monitor carefully for symptoms and signs of neurological impairment due to an increased risk of epidural or spinal haematoma in patients receiving rivaroxaban.
Pharmacist review	During business hours, pharmacists should prioritise patients prescribed rivaroxaban for clinical review and provision of education. Within each SESLHD facility, mechanisms should be in place to assist pharmacists with identification of these patients. When clinically reviewing an order for rivaroxaban, the pharmacist is responsible for ensuring the appropriateness of the drug, formulation, dose, route and frequency in the context of the individual patient's parameters. The pharmacist should also ensure that all prescribing requirements (above) have been met. Once satisfied with the order, the pharmacist should annotate the medication chart in the pharmacy section with their initials and the date. In electronic systems, the order should be electronically verified. Any interventions involving rivaroxaban should be documented according to locally agreed process.

Patient Education	All patients initiated on rivaroxaban MUST be educated regarding anticoagulation as they would be on warfarin. Patients admitted to hospital on rivaroxaban should be assessed for their level of knowledge and receive further education as appropriate. Wherever possible, education should be provided by a clinical pharmacist. Pharmacy should be contacted as early as possible to request anticoagulant education. If a pharmacist is unavailable, the medical officer should provide written and verbal education. The patient must be provided with the specific patient booklets about rivaroxaban (e.g. locally developed patient information booklets or CEC information leaflet) and an anticoagulation card to carry on their person (available from pharmacy) Patient education should include the following; 1. The reason the patient is being commenced on an anticoagulant 2. How to minimise risk of bleeding (lifestyle considerations, drug interactions e.g. NSAIDs), signs of bleeding and what to do in case of bleeding or a fall 3. Signs of venous thromboembolism 4. How to take rivaroxaban and the importance of good compliance; missed doses lead to the loss of anticoagulation and the risk of thrombotic events 5. How long to take it for 6. Risk of bleeding with surgery or dental procedures, and the need to alert/seek advice from health practitioners if procedures are planned 7. Need to attend GP for review, prescriptions for ongoing supply, and required renal function checks after initiation of rivaroxaban Provision of anticoagulant education must be documented in the patient's medical record.
Additional Resources	Guidelines on the management of Non-Vitamin K oral anticoagulants, summary information for each drug and patient information brochures are available from the CEC: https://www.cec.health.nsw.gov.au/keep-patients-safe/medication-safety/high-risk-medicines/anticoagulants
Basis of Protocol	1. Tran H et al. New Oral Anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Internal medicine Journal 2014, 44:6, 525-536 2. Wood P et al. New Oral Anticoagulants: An emergency department overview. Emergency Medicine Australasia 2013, 25,503-514 3. ASTH NOAC guide: New Oral Anticoagulant – A practical guide on behalf of ASTH. Accessed 08/09/2014 at http://www.asth.org.au 4. Patel MR, Mahaffey KW, Califf RM, et al; for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

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Groups consulted in development of this guideline	SESLHD NOACs Working Party.

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GOVERNANCE	
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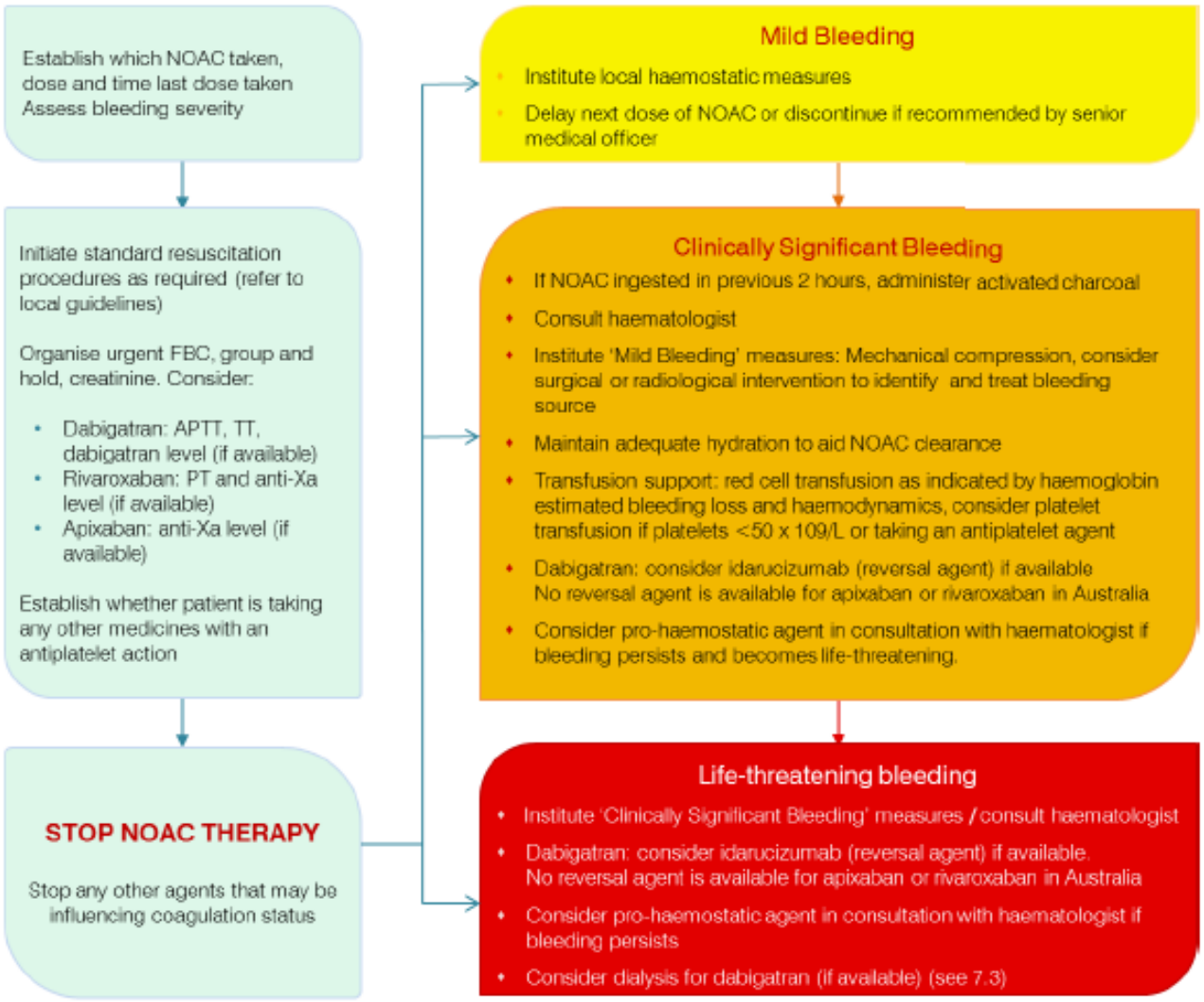
Appendix A: Management of NOAC associated bleeding



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