DABIGATRAN 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 Dabigatran 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.* **NOTE: All other indications are NON-FORMULARY at SESLHD. Patients should not be newly commenced on dabigatran for other indications without prior approval from the local Drug and Therapeutics Committee.**
Patient Selection	Before initiating dabigatran 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 swallowing ability. Dabigatran is unsuitable for patients with swallowing difficulties or enteral feeding tubes as capsules cannot be opened. • Consider patient's capacity to manage this medication safely, i.e. compliance with prescribed dosing frequency, need for dose administration aid (dabigatran must be stored in original packaging and cannot be packed into a Webster Pak or Dosette box) • Perform the following: a. Full Blood Count: exclude significant thrombocytopenia or anaemia b. Biochemical Profile including liver function and renal function assessment. 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 dabigatran, 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, when ordering dabigatran. Alerts may not be triggered in other electronic medication management systems. Prescribers should annotate all orders for dabigatran with the word "ANTICOAGULANT" and always include the indication for prescribing.
Contraindications	• **Significant active bleeding and organ 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:** calculated CrCl < 30 mL/min (extreme caution: CrCl 30–50 mL/min – consider warfarin especially if renal deterioration likely) • **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 apixaban 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 – see below)

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 apixaban 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)
- **Drug interactions:** see below

Always consult with haematology if unsure of the appropriateness of dabigatran

Important Drug Interactions

Drug-drug interactions

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 treatment dose in AF dabigatran must be given 2 hours prior to verapamil for first 3 days. Refer to PI or AMH** for VTE prophylaxis and treatment

*SSRI - Selective serotonin re-uptake inhibitor; SNRI - Serotonin noradrenaline re-uptake inhibitors
**AMH – Australian Medicines Handbook

Antithrombotic interactions: The appropriateness of the combination of dabigatran 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	

Dosage

Indication	Renal Function (CrCl mL/min)	Recommended Dose
Prevention of VTE after major orthopaedic surgery of lower limbs	≥ 50	110mg 1-4 hours after surgery, ***then*** 220mg ONCE daily for required duration (10 days for TKR, or 28-35 days for THR)
	30 - 49	75mg 1-4 hours after surgery, ***then*** 150mg ONCE daily for required duration (10 days for TKR, or 28-35 days for THR)
	<30	Do not use
Prevention of stroke in non-valvular AF with ≥ 1 risk factor	≥ 50	*Age < 75 years with no bleeding risk::* 150mg TWICE daily
		*Age ≥ 75 years **OR** elevated risk of major bleeding:* 110mg TWICE daily
	30 - 49	110mg TWICE daily
	<30	**Contraindicated**

Transitioning between anticoagulants

Detailed advice regarding transitioning between dabigatran 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 dabigatran must include: - Drug, dose, route and indication - When prescribed for treatment or prevention of VTE, the intended duration of therapy - the word "ANTICOAGULANT" printed clearly
Administration Instructions	Dabigatran is administered orally. Dabigatran is available in 75mg, 110mg and 150mg capsules. The appropriate strength capsule should be used to administer the prescribed dose. Capsules must be swallowed whole and should not be chewed or opened. Take care to avoid missed doses. If a dose is missed or delayed by > 6 hours, contact pharmacy or consult the CEC NOAC Guidelines for advice.
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 dabigatran experiences a fall, observe and monitor closely for signs of bleeding in accordance with SESLHDPR380 - 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** The Thrombin Time (TT) is the most sensitive routine coagulation assay for determining if any dabigatran is present. A normal APTT suggests that it is unlikely that a high level of dabigatran is contributing to bleeding and a normal TT excludes the presence of clinically significant levels of dabigatran. The Hemoclot assay, a dilute thrombin test, is used to measure dabigatran levels in emergency situations. This assay may be requested on SEALS request form, and two citrated coagulation tubes should be collected. The additional coagulation assays (APTT, PT/INR, Thrombin Time and Fibrinogen) should also be requested in urgent situations. Dabigatran levels can vary widely and the dose, schedule and time of last dose are important information for interpreting levels. 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 **Use of Idarucizumab** • Idarucizumab (Praxbind®) is a monoclonal antibody fragment which is able to immediately reverse the anticoagulant effect of dabigatran. • Idarucizumab is indicated in patients who have life threatening or uncontrolled bleeding or who require immediate reversal for life-saving surgical or invasive procedures which cannot be performed whilst therapeutically anticoagulated. • Idarucizumab must only be used on the advice of a haematologist and is obtained from Blood Bank. • Refer to SESLHD idarucizumab prescribing protocol for further information. • APTT, TT and dabigatran level should be checked within one hour of dosing and again after 24 hours, to ensure that dabigatran has been fully reversed. • A small number of people (and particularly those with renal failure) may have incomplete reversal or a rebound of the dabigatran level. • If there is any ongoing bleeding then consideration of further dosing in consultation with the supervising haematologist may be required. NOTE: Reversing a patient's anticoagulation may carry a risk of thrombosis which needs to be assessed against their risk of ongoing bleeding.
Storage requirements	Dabigatran 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 dabigatran is stored outside of pharmacy, shelf labelling should be used to identify it as an anticoagulant medicine. Dabigatran capsules must be kept in their original packaging until used. They cannot be transferred to dose administration aids (e.g. Webster Paks or Dosette boxes)
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 dabigatran level (Hemoclot assay) in consultation with haematology team.

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

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	

Urgent/Unplanned Surgery

- If possible, consider delaying surgery until sufficient time has passed for drug clearance and coagulation screen is normal.
- If surgery must proceed, check dabigatran level (Hemoclot assay), TT, PT, APTT and fibrinogen. Also check EUC, calcium, and perform a Group and Hold.
- If Hemoclot dabigatran level < 40ng/mL, TT, PT and APTT normal, likely minimal residual effect and safe to proceed with procedure.
- Where results are suggestive of a residual anticoagulant effect, consult haematology to discuss a possible indication for idarucizumab. Idarucizumab is able to reverse the anticoagulant effect of dabigatran, and is indicated in patients who require immediate reversal for life-saving surgical or invasive procedures which cannot be performed whilst therapeutically anticoagulated.
- 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 to 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.
- In high risk patients following high-risk procedures, consider restarting therapeutic anticoagulation initially with unfractionated heparin if ongoing concerns for bleeding persist and converting to dabigatran once stable.

Neuraxial anaesthesia in patients on dabigatran	Neuraxial anaesthesia cannot be used in patients who are therapeutically anticoagulated. In this situation neuraxial anaesthesia cannot be performed until laboratory testing establishes the absence of dabigatran effect. There is limited data on the safety of prophylactic dose NOAC use whilst a patient has an epidural catheter in situ. Use of dabigatran for prophylaxis is not recommended in patients who have an epidural catheter in situ. For patients with normal renal function receiving dabigatran for VTE prophylaxis post orthopaedic surgery who require neuraxial anaesthesia: 1. The last dose of dabigatran should be given 48 hours before planned insertion or removal of the epidural catheter 2. The first recommencement dose of dabigatran is to be given no earlier than 6 hours after catheter removal (longer of there are multiple punctures or traumatic insertion - seek haematology advice) 3. Dabigatran 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 dabigatran.

Pharmacist review	Pharmacists should prioritise patients prescribed dabigatran for clinical review during business hours. Within each SESLHD facility, mechanisms should be in place to assist pharmacists with identification of these patients. When clinically reviewing a dabigatran order, 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 dabigatran should be documented according to locally agreed process.
Patient Education	All patients initiated on dabigatran MUST receive specific anticoagulant education. Patients admitted to hospital on dabigatran 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 consumer information about dabigatran (e.g. 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. The importance of good compliance; missed doses lead to the loss of anticoagulation, and the risk of thrombotic events 5. How to take and manage dabigatran capsules, e.g. swallow capsules whole, capsules must be kept in original packaging (not suitable for dose administration aids) etc. 6. How long to take it for 7. Risk of bleeding with surgery or dental procedures, and the need to alert/seek advice from health practitioners if procedures are planned 8. Need to attend GP for review, prescriptions for ongoing supply, and required renal function checks after initiation of dabigatran. 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 NOAC 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. Dansirikul C et al. A combined pharmacometric analysis of dabigatran etexilate in healthy volunteers and patients with atrial fibrillation or undergoing orthopaedic surgery. Thrombosis Haemostasis 2012 107:775 5. Douxfils J et al. Impact of dabigatran on a large panel of routine or specific coagulation assays: Laboratory recommendations for monitoring of dabigatran etexilate. Thrombosis Haemostasis 2012 107:985 6. Huisman M et al. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: Resolving uncertainties in routine practice. Thrombosis Haemostasis 2012 107:838 7. Lindahl TH e al. Effects of the oral direct thrombin inhibitor dabigatran on five common coagulation assays. Thrombosis Haemostasis 2011 105:371 8. NSW Health Safety Notice 014/11 accessed June 2012 at http://www.health.nsw.gov.au/resources/csqg/sabs/pdf/sn_014_11.pdf 9. Queensland Health: Guideline for managing patients on Dabigatran. Effective from 21/05/2013 Accessed at http://www.health.qld.gov.au/qhcss/mapsu/documents/dabigatran_info.pdf 10. CEC NOAC Guidelines: Non-Vitamin K Antagonist Oral Anticoagulant. Accessed 02/06/2021 at https://www.cec.health.nsw.gov.au/keep-patients-safe/medication-safety/high-risk-medicines/anticoagulants 11. Tran, H., et al. New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism. Med J Aust 2019;210:227-35.
Groups consulted in development of this guideline	SESLHD NOACs Working Party.

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GOVERNANCE	
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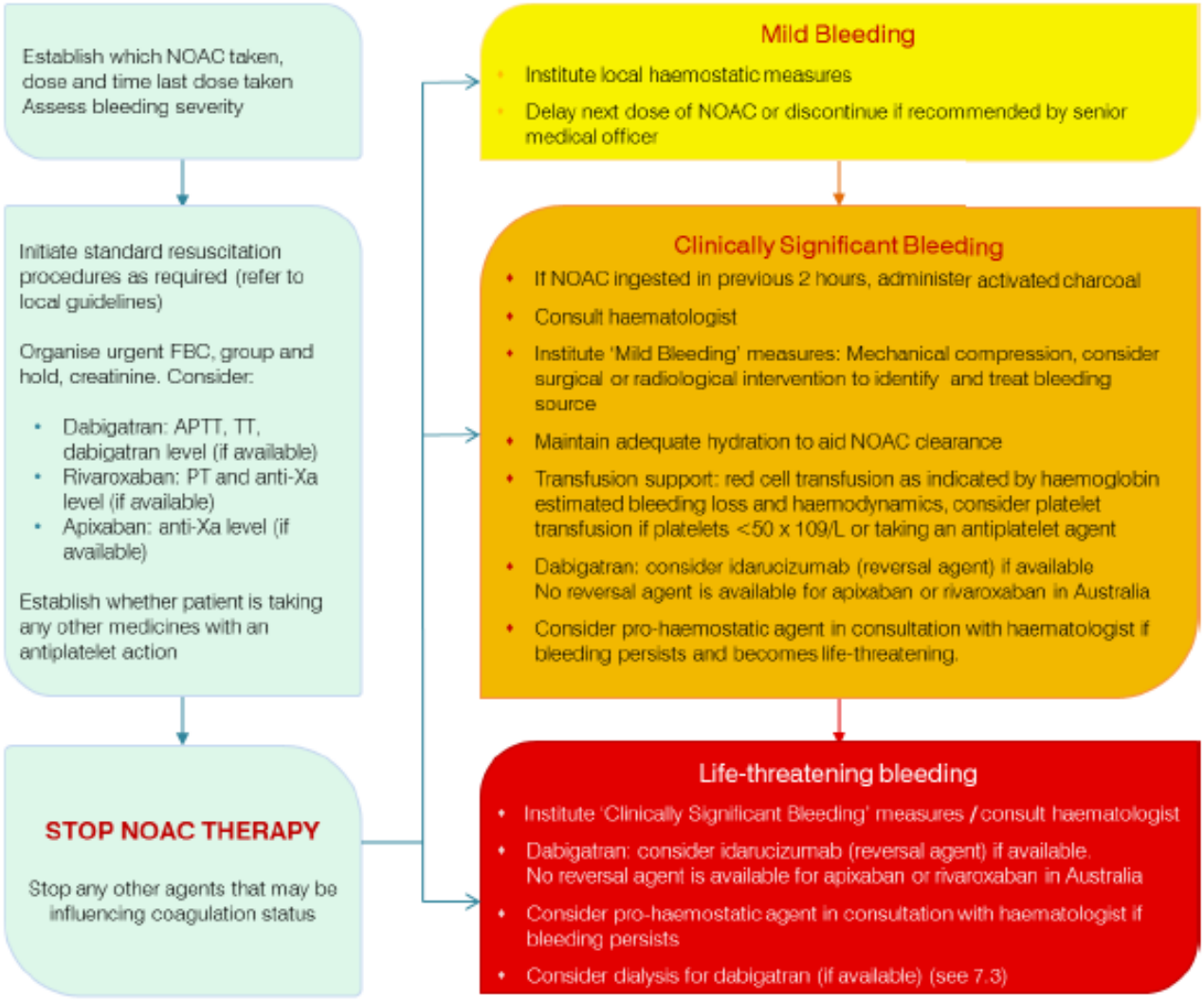
Appendix A: Management of NOAC associated bleeding



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