Ballarat Health Services

DRUG GUIDELINE

Direct Oral Anticoagulants (DOACs)

HIGH RISK MEDICATION

SCOPE (Area): **FOR USE IN:** All ward areas
EXCLUSIONS: Paediatrics (seek Paediatrician advice)
SCOPE (Staff): Medical, Nursing and Pharmacy

BRAND NAMES

Apixaban: Eliquis®
Dabigatran: Pradaxa®
Rivaroxaban: Xarelto®

PHARMACOLOGY AND PHARMACOKINETICS

	Apixaban	Dabigatran	Rivaroxaban
Mechanism	Factor Xa inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor
Time to peak concentration	1.5 to 4 hours (dose dependent)	1 to 6 hours	2 to 4 hours
Half-life (healthy patients)	12 hours	12 to 17 hours	5 to 9 hours
Metabolism (normal renal function)	25%, mainly by CYP3A4	P-gp substrate Not metabolized by CYP450 enzymes	67%, mainly by CYP3A4/5 and CYP2J2
Renal clearance	27%	80 to 85%	33%

INDICATIONS

Non-PBS indications require Individual Patient Usage (IPU) approval.
See Pharmaceutical Benefits Scheme (PBS) criteria for full details (pbs.gov.au)

Indications	Apixaban	Dabigatran	Rivaroxaban
Prevention of stroke/systemic embolism in non-valvular AF or atrial flutter with one or more risk factors for stroke/systemic embolism	YES	YES	YES
Treatment of DVT or PE	YES	NO	YES
Secondary prevention of recurrent VTE	YES	NO	YES
Prevention of VTE after elective total knee or hip replacement	YES	YES	YES
Chronic stable atherosclerotic disease (coronary/peripheral artery disease with at least one risk factor), in combination with aspirin	NO	NO	YES

AF: atrial fibrillation; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism, includes both DVT and PE.

Contact Haematology when there is uncertainty about a listed Contraindication AND/OR when any 'Precautions' apply.

Contact other specialists where appropriate (e.g. Cardiology/Neurology for dose reductions for AF stroke prophylaxis). For perioperative use contact Surgery and see CPP0729 Perioperative Management of Anticoagulant and Antiplatelet Agents.

CONTRAINDICATIONS

- **Active significant bleeding.**
- **Disorder of haemostasis –** e.g. von Willebrand disease or coagulation factor deficiency.
- **Mechanical heart valve.**
- **Renal impairment – use calculated CrCl, not eGFR.** Contraindicated if:
  - CrCl less than 25 mL/min for apixaban.
  - CrCl less than 30 mL/min for dabigatran.
  - CrCl less than 15 mL/min for rivaroxaban.
- **Hepatic impairment –** contraindicated when:
  - ALT is above twice the upper limit of normal, OR
  - Child-Pugh Grade B or C (apixaban may be used with caution in Child-Pugh B),
  - Rivaroxaban may only be used if there is no coagulopathy.
- **Pregnancy or breastfeeding.**
- **Drug interactions** – resulting in significant changes to plasma levels (see Drug Interactions).
- **Known hypersensitivity –** to the chosen DOAC or any of its ingredients.

Rivaroxaban for stable chronic atherosclerosis is contraindicated in patients with ANY of the following:

- High risk bleeding.
- Prior stroke within one month of treatment initiation.
- Previous haemorrhagic or lacunar stroke.
- NYHA class III-IV heart failure symptoms.
- CrCl less than 15 mL/min.
- Requirement for antiplatelet therapy other than aspirin 100 mg daily.
- Indication for higher dose anticoagulant therapy.

PRECAUTIONS

- **Renal impairment – use calculated CrCl, not eGFR.** Dose adjustment required if:
  - CrCl 30-50 mL/min for dabigatran in AF.
  - CrCl 15-50 mL/min for rivaroxaban in AF, limited data if CrCl less than 30 mL/min.
  - Apixaban **may** require dose adjustment if serum creatinine over 133 micromol/L.
- **Elderly –** increased risk of bleeding. Dabigatran dose adjustment required for use in AF if age over 75 years.

- **Body weight –** information may update regularly, contact Haematology if unsure.
    - **Over 120 kg or BMI over 40 kg/m2.** Rivaroxaban usually preferred over apixaban/dabigatran.
    - **Under 50 kg. S**ee also 'Apixaban for AF' below if relevant.
- **Apixaban in AF** – reduce dose if at least 2 of the following factors: age over 80 years, weight under 60 kg and/or serum creatinine over 133 micromol/L.
- **Hepatic impairment (Child-Pugh Grade A cirrhosis)**.
- **Concomitant antiplatelet therapy** – due to increased bleeding risk
- **Combination with dual antiplatelet therapy or 'Triple Therapy'** – bleeding risk versus ischaemic risk should be carefully assessed and individualised to the patient. Treatment duration must be short term and clearly defined. Provide patient clear instructions on which medication to cease and when.
- **Antiphospholipid syndrome** – limited data on the efficacy of DOACs. Warfarin generally preferred.
- **History –** of intracerebral haemorrhage, intra-ocular, spinal, retroperitoneal or atraumatic intra-articular bleed.
- **Clinically significant active or recent bleeding** e.g. (but not limited to) haemorrhagic stroke within the past six months, GI bleed within 12 months.
- **Conditions with an increased risk of bleeding** e.g. severe thrombocytopenia, bleeding disorders, severe renal impairment, GI ulcer (within 30 days), recent fibrinolytic treatment (within the previous 10 days), recent ischaemic stroke, severe uncontrolled hypertension (defined as a BP greater than 160/100 where control cannot be achieved within 24 hours).

PREGNANCY AND BREASTFEEDING

All DOACs are currently contraindicated in pregnancy and breastfeeding due to a lack of a clinical data. Seek specialist advice before prescribing. Refer to the Royal Women's Pregnancy and Breastfeeding Medicines Guide for more information.

DRUG INTERACTIONS

Complex and variable - refer to the following references or liaise with Pharmacy for more information:

- Interaction checking tools: MIMs or Lexicomp via Clinicals Health Channel
- COVID drugs: Liverpool available from https://www.covid19-druginteractions.org/
- Complementary/alternative medicines: Natural medicines via Clinicians Health Channel
- HIV medicines: Liverpool available from https://www.hiv-druginteractions.org/

Clinically significant drug interactions include but are not limited to:

- **Medicines that increase the risk of bleeding in combination with DOACs –** e.g. antiplatelets (required to be used where indicated), non-steroidal anti-inflammatory drugs (NSAIDs), other anticoagulants, SSRIs, SNRIs.
- **Strong inhibitors/inducers of CYP3A4 and/or P-gp may increase or decrease exposure to DOACs –** e.g. amiodarone, antiretrovirals, carbamazepine, itraconazole, ketoconazole, phenytoin, posaconazole, rifampicin, ritonavir, St John's wort, verapamil.

DOSAGE AND ADMINISTRATION

Refer to standard reference texts for dosing and administration. e.g. Australian Medicines Handbook or Therapeutic Guidelines available via Clinicians Health Channel https://www.clinicians.vic.gov.au/

The clinical pharmacist will provide the patient or carer education and written information about DOACs and document this on the Anticoagulation Education Record section of the NSMC. Where a clinical pharmacist is not on duty, education is the responsibility of the treating team.

Switching anticoagulants

- **Switching from one DOAC to another**

Start the new DOAC when the next dose is due.

- **Switching from warfarin to a DOAC**

Stop warfarin and start the DOAC once the INR is less than 2.5.

- **Switching from DOAC to warfarin**

A cross over period is required due to the slow onset of warfarin (about 5 days). Give the DOAC with warfarin until the INR is greater than 2 for two consecutive days, then cease the DOAC. Check INR just before each DOAC dose and continue to check INR after DOAC is ceased.

Estimated cross over period required when switching from DOAC to warfarin		
Creatinine clearance	**Rivaroxaban/apixaban**	**Dabigatran**
Greater than 50 mL/min	Stop 4 days after starting warfarin	Stop 3 days after starting warfarin
31-50 mL/min	Stop 3 days after starting warfarin	Stop 2 days after starting warfarin
15-30 mL/min	Stop 2 days after starting warfarin	Stop 1 day after starting warfarin

- **Switching from low molecular weight heparin (LMWH e.g. enoxaparin) to DOAC**

Start the DOAC when the next LMWH dose is due.
For treatment of VTE, use loading dose of apixaban to commence even if the patient has already been on therapeutic enoxaparin.

- **Switching from unfractionated heparin to DOAC**

Start DOAC immediately once the heparin infusion is ceased.

- **Switching from DOAC to LMWH (e.g. enoxaparin) or unfractionated heparin**

Cease the DOAC and start unfractionated heparin **(without a bolus)** or LWMH when the next dose of DOAC was due (note this is either 12 or 24 hours depending on the DOAC dosing frequency for the patient).

MONITORING (INCLUDING BLOOD TESTS)

- Baseline coagulation studies, FBE, LFT (including albumin) and pregnancy test (if appropriate)
- Monitor for any signs of bleeding (external bruising, abdominal distension/pain, back pain, hypotension and shock, collapse, neurological symptoms, macroscopic haematuria, haemoptysis, epistaxis, GI blood loss, headache, dyspnoea, stridor, unexplained fall in haemoglobin)
- Regular monitor renal function via calculated CrCl (especially for the elderly) to review whether dose adjustment is required or therapy has become contraindicated.
- DOACs do not require routine coagulation monitoring. Consider coagulation studies in the following situations:
    - Bleeding secondary to overdose or if DOAC is thought to be contributing to bleeding. **See CPG0390 Direct Oral Anticoagulant (DOAC) Overdose, Toxicity and Reversal for interpretation of coagulation tests.**
    - Change in clinical scenario e.g. urgent surgery, new or worsening renal impairment, recurrence/extension of thromboembolism
    - Drug interactions where there is no data in available and the combination is unavoidable
    - Following stroke or thromboembolism in a patient already taking a DOAC

ADVERSE EFFECTS

- **ALL DOACs**
  Common: **bleeding**, signs of bleeding (e.g. anaemia).
  Rare: **anticoagulant-related nephropathy (ARN)** following DOAC use, presenting as acute kidney injury. See TGA Medicines Safety Update for more information.
- **Dabigatran**
  Common: gastritis, dyspepsia, GI bleeding.
  Infrequent: oesophageal ulcers, increased liver enzymes and bilirubin
- **Apixaban**
  Common: nausea. Infrequent: thrombocytopenia, abnormal liver function tests.
  Rare: allergic reactions
- **Rivaroxaban**
  Common: peripheral oedema, itch, skin blisters, muscle spasm. Rare: hepatotoxicity.

For management of DOAC overdose or toxicity see CPG0390 Direct Oral Anticoagulant (DOAC) Overdose, Toxicity and Reversal

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DRUG PRESENTATIONS AND STORAGE

Apixaban: 2.5 mg and 5 mg film coated tablets. Store below Store below 30°C.
Dabigatran: 75 mg, 110 mg and 150 mg capsules. Capsules should not be opened, this may increase bioavailability of dabigatran. Do not put the capsules in dose administration aids, unless capsules can be maintained in the original package. Store below 30°C.
Rivaroxaban: 2.5 mg, 10 mg, 15 mg and 20 mg film coated tablets. Store below 30°C.
