SA Health

Safe prescribing of non-Vitamin K antagonist oral anticoagulants, apixaban, rivaroxaban and dabigatran Clinical Guideline

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This document is currently under review and should be considered with approved product information and other information resources.

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Disclaimer

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

- discussing care with consumers in an environment that is culturally appropriate, and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- advising consumers of their choice and ensure informed consent is obtained
- providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- documenting all care in accordance with mandatory and local requirements.

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Author: Senior Pharmacist, Medicines and Technology, Policy and Programs (MTPP)
Audience: Medical, pharmacy, nursing, midwifery and allied health staff in South Australian public health services
Endorsed by: Clinical Governance, Safety and Quality Policy Domain Custodian
Contact: Medicines and Technology Policy and Programs: telephone: 08 8204 1944

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Introduction

Apixaban, rivaroxaban and dabigatran are non-vitamin K antagonist oral anticoagulant medicines often referred to as NOAC, and also known as novel oral anticoagulants or direct acting oral anticoagulants (DOAC). NOACs include dabigatran (direct thrombin inhibitor), apixaban and rivaroxaban (Factor Xa inhibitors). They are listed on the Australian Pharmaceutical Benefits Scheme (PBS) for treatment and prevention of thrombo-embolic disease. NOAC are also available on the South Australian Medicines Formulary (SAMF) for specific indications.

Background

This clinical guideline is intended to assist clinicians with the management of **adult patients only** (excluding pregnant or breastfeeding females) receiving a NOAC. Information in this guideline is based on evidence at the time and should be used in conjunction with Therapeutic Goods Administration (TGA) approved Product information, local protocols and specialist advice.

This clinical guideline does **not** address anticoagulation in:

- Pregnant or breastfeeding females.
    - All NOACs are contraindicated in pregnancy and breastfeeding
- Paediatric patients less than 18 years of age.

Safe and effective use of any anticoagulant requires careful patient selection and clinical monitoring to minimise the risk of thrombosis and of bleeding.

Prescribing a NOAC requires an in-depth knowledge of their pharmacology and clinical use, careful patient selection and monitoring to ensure the best outcomes.

The NOAC are different to existing oral anticoagulants, in particular warfarin, in their clinical monitoring requirements, drug interactions and the limited options available for reversal.

Bleeding complications with NOAC are potentially severe and have been fatal in an often fragile population.

Serious incidents involving NOAC use have been reported due to:

- concurrent prescribing of other anticoagulant medications e.g. heparin
- misinterpretation of coagulation tests and monitoring requirements
- inappropriate or premature cessation prior to procedures
- drug interactions.

This guideline has been developed to assist SA Health staff to safely use NOAC by:

- recognising the medicines by generic and trade name
- managing the risk of thrombosis versus the bleeding risk
- considering individual patient bleeding risk factors
- understanding the significance of different coagulation test results and drug interactions
- making appropriate decisions regarding surgery and neuraxial procedures.

A Clinical Guideline: Management of bleeding associated with apixaban, rivaroxaban and dabigatran is also available.

Abbreviations

AF	Atrial fibrillation
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
$CHADS_2$	Score that estimates stroke risk in patients with atrial fibrillation
CrCl	Creatinine clearance
DVT	Deep vein thrombosis
GI	Gastrointestinal
HIV	Human immunodeficiency virus
INR	International Normalised Ratio
IPU	Individual patient use
LMWH	Low molecular weight heparin
NOAC	Non vitamin K antagonist oral anticoagulant medications
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary embolism
P-gp	P-glycoprotein transporter
PI	Product information
SAMF	South Australian Medicines Formulary
TGA	Therapeutic Goods Administration
T_{max}	Time taken for an oral dose to achieve maximum blood concentration
TT	Thrombin time = Thrombin clotting time
VTE	Venous thromboembolism
WATAG	Western Australian Therapeutic Advisory Group

Standards

The information in this guideline aligns with the Australian Commission on Safety and Quality in Health Care - National Safety and Quality Health Service Standards: Standard 4 - Medication Safety.[1]

- Action item 4.11 - Identifying high-risk medicines in the organisation and ensuring they are stored, prescribed, dispensed and administered safely.

General

1. **South Australian Medicines Formulary Recommendations**[2]
   The South Australian Medicines Formulary is a list of core medicines which are approved for initiation within SA Public Hospitals and health services.

   1.1. Apixaban (Eliquis®) – *SAMF preferred NOAC*
   - 2.5mg and 5mg tablets as per PBS criteria

   1.2. Rivaroxaban (Xarelto®) - restricted inclusion
   - 10mg, 15mg and 20mg tablets for use when apixaban not appropriate as per PBS criteria

   1.3. Dabigatran (Pradaxa®) – restricted inclusion
   - 150mg capsule for use when apixaban not appropriate as per PBS criteria for patients with:
     - non-valvular atrial fibrillation and one or more risk factors for developing stroke or systemic embolism AND
       - less than 75 years:
       - creatinine clearance (Cockcroft and Gault calculation) > 50mL/min
       - CHADS2 score ≥ 2
       - not taking a strong P- glycoprotein inhibitor
       - does not have active gastrointestinal (GI) disease or a high risk of GI bleeding
       - able to swallow capsules whole
       - does not require a dosage administration aid (Webster, dosette)

2. Pharmacological Characteristics of NOAC

Table 1: Pharmacological Characteristics of NOAC [4,5]

	Apixaban (Eliquis®)	**Rivaroxaban** (Xarelto®)	**Dabigatran etexilate** (prodrug of dabigatran) (Pradaxa®)
Mechanism of action	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct thrombin inhibitor, free and clot bound
T_{max}	1 – 3 hours	2.5 – 4 hours	2 hours
Half-life (hours) if CrCl is 30 - 50 mL/min.	8 - 15	5 - 9 (healthy) 11 - 13 (elderly)	12 – 17
Elimination	Renal 27% (multiple other routes)	Renal 33% Renal metabolites 33% Hepatic 33%	Renal 80% Hepatic 20%

3. Principles for prescribing NOAC

- Prescribing a NOAC requires a knowledge of their pharmacology and clinical use. Careful patient selection and monitoring ensure the best outcomes.
- A risk-benefit assessment should always be conducted prior to prescribing NOAC for any patient.
- It is essential that creatinine clearance is calculated (using the Cockcroft- Gault equation and ideal body weight) and documented before prescribing a NOAC.

  Appendix 1: 'Flowchart for Prescribing Non-Vitamin K antagonist Oral Anticoagulants Apixaban, Rivaroxaban and Dabigatran' provides a summary of the risk factors that must be considered when initiating treatment with these medications.
- Drug accumulation and excessive anticoagulation can occur, especially if renal function is impaired. Renal function must be monitored at least annually, with monitoring increased to 3 or 6 monthly when other factors may indicate declining renal function or dehydration.

4. Drug Interactions

NOAC may have fewer drug interactions than warfarin, however many clinically significant interactions exist. Individual patient bleeding risks must be considered, and specialist advice sought as these are often complex situations.

The European Heart Rhythm Association's 'Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation'[4] provides a useful drug interaction chart that includes advice on NOAC dosage adjustments. The Australian Medicines Handbook (AMH) and consumer product information sheets also provide comprehensive lists of interactions. Note that some recommendations may differ.

Renal function should be rechecked if drugs that may impair renal function are commenced. For example, non-steroidal anti-inflammatory drugs, diuretics or angiotensin-converting enzyme (ACE) inhibitors. These combinations should be avoided wherever possible.

4.1. Thrombolytic agents or antiplatelet agents (e.g. aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine):

Concomitant administration of these agents with NOAC is not recommended unless clinically indicated because dual therapy is associated with higher risks of bleeding and anaemia, especially if there are other risk factors. *Seek specialist advice.*

4.2. Other anticoagulants:

Concomitant administration with NOAC is not recommended. This includes bridging therapy as NOAC have a relatively rapid onset of action.

4.3. Non-steroidal anti-inflammatory drugs (NSAIDs) and Cox 2 inhibitors:

Monitor for risks of bleeding if a NOAC is used with NSAIDs, especially those with half-lives greater than 12 hours (for example, naproxen, piroxicam). This combination should be avoided due to the increased risk of gastrointestinal bleeding.

4.4. Strong inhibitors of CYP3A4 or P-glycoprotein (P-gp) transporter:

All three NOAC are substrates for the P-glycoprotein transporter. Apixaban and rivaroxaban are also metabolised largely by CYP3A4. Inhibitors of these systems increase NOAC bioavailability. See flowchart, Appendix 1 and Table 2a for a list of common drugs affected.

NOAC are contraindicated with drugs that are strong inhibitors of both of these pathways including:

- systemic azole antifungals.
- protease inhibitors

4.5. Less potent inhibitors or drugs inhibiting only one of these two pathways

These drugs may significantly contribute to increased bleeding risk if administered with apixaban or rivaroxaban when there are other bleeding risk factors; however, they are not currently contraindicated. A dose reduction may be appropriate and concomitant administration should be considered on an individual basis.

- cardiac medicines – *consider cardiology advice*
- fluconazole
- immunosuppressants
- macrolides
- others; for example, dipyridamole, tamoxifen.

4.6. Strong inducers of CYP3A4:

Concomitant use of a NOAC with strong P-gp or CYP3A4 inducers may lead to reduced plasma levels of the NOAC and increase the risk of a thrombo-embolic event. Examples of strong inducers of CYP3A4 include:

- rifampicin, phenytoin, carbamazepine, phenobarbitone or St John's Wort

The combination with apixaban or dabigatran is contraindicated.

If using rivaroxaban in these situations, a dose change should be considered but the combination is preferably avoided as there is no way to monitor the effectiveness of the NOAC.

4.7. Contraindicated drug combinations

Avoid concomitant use due to clinically significant increased plasma levels and increased bleeding risk.

Table 2a: Contraindicated drug combinations with NOAC[4,5]

Apixaban, Rivaroxaban and Dabigatran	Dabigatran
Systemic azole antifungals: - ketoconazole, itraconazole, voriconazole, posaconazole (except fluconazole) Protease inhibitors: - for example, ritonavir, saquinavir	Simultaneous initiation with verapamil

4.8. Drug combinations that are preferably avoided

Consider alternative therapy due to increased bleeding risk or seek advice as dose change may be warranted.

The presence of renal or hepatic impairment may make these interactions significant, even with weak inhibitors.

During concomitant use, monitor patients closely for bleeding and encourage them to report signs of bleeding.

Table 2b. Drug combinations that are preferably avoided with all NOAC[4,5]

Apixaban and Rivaroxaban and Dabigatran
Increased plasma level of NOAC and increased bleeding risk **Less potent P-gp and/or CYP3A4 inhibitors:** > cardiac medications – *consider cardiology advice* > amiodarone, diltiazem, quinidine, verapamil – especially simultaneous initiation > clarithromycin, erythromycin > cyclosporin, tacrolimus > fluconazole > grapefruit juice.
Reduced plasma levels of NOAC and increased thromboembolic risk **Potent P-gp/CYP3A4 inducers:** > carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's Wort
Pharmacodynamic interactions that increase bleeding risk > antiplatelet / anticoagulant / antithrombotic agents: > for example, aspirin, cox-2 inhibitors, fish oil, clopidogrel, ticagrelor, heparins, warfarin, alteplase > systemic steroid therapy > chemotherapy
Some antidepressants: > for example, selective serotonin (SSRI) or serotonin-noradrenaline(SNRI) reuptake inhibitors

5. Transitions of care

The following factors must be communicated through all transitions of care:

- Monitor renal function at least annually, or when other patient factors such as dehydration or declining renal function suggest that an increased frequency of monitoring is necessary. For example, in older people (≥ 75 years) or in reduced renal function, monitoring every 3–6 months may be warranted.
- Declining renal function or concomitant use of agents that affect renal function are important factors in increasing the bleeding risk associated with NOAC.
- Any planned dose change or expected limits on duration of treatment must be clearly documented, for example with rivaroxaban when used for the treatment and subsequent prevention of acute and recurrent DVT or PE.
- Patient counselling should include:
  - communicating the discharge from hospital care plan with patient / carer
  - encouraging regular and adequate follow up
  - educating the patient and carer, including information on how to recognise and respond to bleeding by seeking medical attention immediately if bleeding is suspected.

6. Laboratory Tests

- Regular routine monitoring of International Normalised Ration (INR) or other coagulation parameters is **not** necessary.
- The anticoagulant effect of the NOAC should be measured if:
  - the patient is bleeding severely
  - urgent surgery is required
  - a thrombotic event occurs or there is a recurrence or exacerbation of thromboembolism.
- The time of the last NOAC dose is required to interpret the results.
- Interpretation of coagulation tests must consider the clinical setting.
- When the results of coagulation test results are prolonged, extend testing to confirm the likelihood of a drug effect with Hemoclot or anti-Xa, and refer to Table 3.
- All 'standard' coagulation assays (PT, aPTT, TT) may be normal in the presence of significant levels of apixaban.
- Specific assays to assess drug level (anti-Xa assay for rivaroxaban and apixaban, Hemoclot for Dabigatran) are not available at all sites or 24 hours a day. If needed urgently, consult with the on-call clinical Haematology Service.

Table 3: Effect of Non-Vitamin K antagonist Oral Anticoagulants on Laboratory Coagulation Tests[5]

Tests	Apixaban	Rivaroxaban	Dabigatran
Prothrombin time (PT) and International Normalised Ratio (INR)	Insensitive PT and INR not recommended	Relatively insensitive A 1.5 to 2.0 fold increase will be seen at peak concentrations	Insensitive A prolonged PT in the absence of other causes often indicates excess drug levels
Activated Partial Thromboplastin Time (aPTT)	Insensitive	aPTT is prolonged dose dependently, but is less sensitive than PT	Variable sensitivity A normal aPTT excludes high drug levels
Thrombin Time (TT)	Insensitive	Insensitive	Very sensitive. A normal TT excludes the presence of Dabigatran
Chromogenic anti-Xa assay	Use modified anti-Xa assay for apixaban	Use modified anti-Xa assay for rivaroxaban	Insensitive
Hemoclot (Not always available)	Not suitable	Not suitable	Can quantify drug level

Protocols

1. Total Hip and Knee Replacement

Haemostasis must be established prior to initiating NOAC.

Table 4: Dose for prevention of venous thromboembolism (VTE) for total hip or total knee replacement[6]

Creatinine clearance	Apixaban *SAMF preferred NOAC for this indication*	Rivaroxaban
CrCl > 30 mL/min	2.5 mg twice daily	10 mg once daily
CrCl 25 – 29 mL/min	2.5 mg twice daily	Seek haematologist advice
CrCl 15-25 mL/min	contraindicated	Seek haematologist advice
CrCl < 15 mL/min	contraindicated	contraindicated

- Duration of therapy:
  - Hip - apixaban: 32-38 days, rivaroxaban: 5 weeks
  - Knee - apixaban: 10-14 days; rivaroxaban: 2 weeks

Table 5: Time of the first dose of NOAC following total hip or knee replacement[6]

	Apixaban	Rivaroxaban
Time elapsing between surgery and the first dose after surgery	12 – 24 hours	6 – 10 hours

For other surgery and use of NOAC for other indications refer to Tables 8 and 9.

2. Deep vein thrombosis, pulmonary embolism and atrial fibrillation

- In general, the risk-benefit balance in AF and PE favour the use of an anticoagulant regardless of age and renal function. Both the stroke risk and the bleeding risk increase with age, and renal function declines. Being over 75 years of age, declining renal function and other patient factors may increase the bleeding risk and outweigh benefit of NOAC therapy.
- It is recommended that prescribers measure renal function and consider this with the patient's bleeding risk (HASBLED score) and stroke risk (CHADSVASC score). NOAC administration should not necessarily be avoided in favour of warfarin (or no treatment) if renal function is reduced, and where CrCl ≥ 30 mL / min. *Seek specialist advice in complex situations*.

2.a. Acute and Recurrent Deep Vein Thrombosis or Pulmonary Embolism

Rivaroxaban and apixaban are approved by the TGA and PBS for the initial and continuing treatment of venous thromboembolism and pulmonary embolism.

Table 6: Treatment or prevention of acute and recurrent DVT or PE[6]

Creatinine clearance	Apixaban 2.5mg and 5mg	Rivaroxaban 15 and 20 mg
CrCl ≥ 30 mL/min	10 mg twice daily for 7 days, then 5 mg twice daily. Consider reducing dose after 6 months to 2.5 mg twice daily if extended treatment is needed.	15 mg twice daily with food for 3 weeks, followed by 20 mg once daily.. Therapy should be continued as long as the VTE risk persists. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding; haematology referral is suggested if the risk/benefit of continued anticoagulation is unclear.
CrCl 25 – 29 mL/min	10 mg twice daily for 7 days, then 5 mg twice daily. Consider reducing dose after 6 months to 2.5 mg twice daily if extended treatment is needed.	Seek haematologist advice
CrCl < 15-25 mL/min	Contraindicated	Seek haematologist advice
CrCl < 15 mL/min	Contraindicated	Contraindicated

2.b. Non-valvular Atrial Fibrillation

Table 7: Dose for non-valvular atrial fibrillation[6]

Creatinine clearance	Apixaban	Rivaroxaban*	Dabigatran
CrCl > 50 mL/min	5 mg twice daily **or** if any 2 of the following are present (even if CrCl > 25 mL/min: > older than 80 years > weight ≤ 60 kg > serum creatinine ≥133 micromol / L **then use:** 2.5 mg twice a day	20 mg once daily	150 mg twice daily not recommended by SAMF if there are bleeding risk factors other than renal function
CrCl 31 - 50 mL/min		15 mg once daily	not recommended
CrCl 25 - 30 mL/min		15 mg once daily	contraindicated
CrCl 15 – 25 ml/min	contraindicated	15 mg once daily	contraindicated
CrCl < 15 mL/min	contraindicated	contraindicated	contraindicated

* Rivaroxaban must be taken with food as there is increased absorption from 66% in fasted state to nearly 100% with food.

3. Surgery

- Consider the risk of thrombotic complications in the perioperative period if the NOAC is stopped, relative to the risk of bleeding if it is continued.
- Discontinuing the NOAC may not be essential, especially with very minor procedures.
- Time the surgery to coincide with minimal residual anticoagulant effect as per the elimination half- life of the NOAC in relation to the patient's renal function, based on calculated creatinine clearance, and the bleeding risk.

3.a. Urgent Surgery

- If possible delay surgery until coagulation screen is normal or sufficient time has passed for drug clearance.
- Seek haematologist's advice if surgery cannot be sufficiently delayed.

3.b. Pre-operative interruption of NOAC

Table 8: Suggested time between last dose of NOAC and surgery[4,5]

Renal Function and related half-life*	NOAC and current dose	Low bleeding risk† surgery (2 to 3 half-lives between last dose and surgery) Time of last dose before surgery (hours)	High bleeding risk‡ surgery (4 to 5 half-lives between last dose and surgery) Time of last dose before surgery (hours)
CrCl ≥ 50 mL/min (half-life 7 - 8 hours)	**apixaban** 5mg twice daily	24	48 - 72
CrCl 30 - 49 mL/min) (half-life 17 - 18 hours)		48	72
CrCl ≥ 50 mL/min (half-life 5 - 9 hours)	**rivaroxaban** 20mg once daily	24	48 - 72
CrCl 30 - 49 mL/min) (half-life 9 - 13 hours)		48	72
CrCl ≥ 50 mL/min (half-life 12 - 17 hours)	**dabigatran** 150 mg twice daily	24	48 - 72
CrCl 30 - 49 mL/min) (half-life 13 - 23 hours)		48 - 72	96

* Estimate of half-life is based on calculated renal clearance using the Cockcroft-Gault equation
† Aim for mild to moderate residual anticoagulant effect at surgery (<12-25%)
‡ Aim for no or minimal residual anticoagulant effect at surgery (<3-6%)

3.c. Post-operative NOAC recommencement

- Ensure that renal and hepatic functions are normal before restarting NOAC.
- Time the resumption of a NOAC based on the anticipated surgical bleeding risk, the extent of intra-operative or post-operative bleeding and the patient's risk of thromboembolism.
- In patients undergoing a procedure associated with high bleeding risk, the resumption of therapeutic anticoagulation with a NOAC should normally be delayed 48 to 72 hrs. Appropriate anticoagulant therapy should be administered during this time as indicated for the procedure. Management of patients at high risk of thrombotic complications (see local guidelines) should be guided by a consultant and refer to Table 12 for converting the patient to NOAC.
- Consider intermittent pneumatic compression if prophylactic anticoagulation cannot be safely administered.

Table 9: Suggested time between surgery and resumption of NOAC[4,5]

(For timing of first NOAC dose following total hip or knee replacement, refer to Table 5).

	Low bleeding risk	High bleeding risk
NOAC*	Resume 24 hours after surgery	Resume 48 -72 hours after surgery

***** For patients at high risk of thromboembolism consider commencing NOAC sooner, but with a reduced dose, in the evening after surgery and on the following day:

- dabigatran: 75 mg once daily
- rivaroxaban: 10 mg once daily
- apixaban: 2.5 mg twice daily for 2 days or until it is safe to resume therapeutic anticoagulation.

4. Neuraxial anaesthesia (or lumbar puncture)

- A patient is at risk of developing an epidural or spinal haematoma if a neuraxial procedure is undertaken when anticoagulated.
- There is a lack of published evidence regarding the safety of neuraxial anaesthesia in patients therapeutically anticoagulated with NOAC.
- Avoid neuraxial procedures until laboratory testing (if available) establishes the absence of any anticoagulant effect or wait until five renally adjusted half-lives have elapsed since the last NOAC dose.
- Always monitor carefully for signs and symptoms of neurological impairment.
- Seek specialist advice from Haematology, Anaesthesia or Acute Pain Service.

5. Switching anticoagulants

5.a. Switching from warfarin to a NOAC

When deciding whether to transition a patient from warfarin to a NOAC the following should be considered:

- patients stable on warfarin (i.e. INR is within range for > 65% of time in 3 months) should continue on warfarin
- patient preference
- lack of reliable agents to reverse severe NOAC related bleeding
- access to INR testing versus the added convenience of NOAC therapy
- the potential for enhanced efficacy and the reduced risk of intracranial bleeding with NOAC, as compared with warfarin in correctly selected patients
- other risk factors such as drug interactions and consistency of dietary vitamin K intake.

Recommended strategy:

- Discontinue warfarin and start NOAC when INR ≤ 2.5.

5.b. Switching from a NOAC to warfarin

When converting a patient from NOAC to warfarin it is necessary to consider the following:

- the elimination half-life of the NOAC is affected by renal function
- there is typically a 5-day delay in the onset of warfarin effect
- the INR may be affected by both NOAC and warfarin, hence the INR will better reflect warfarin only after the NOAC has been stopped for at least two days.

Recommended strategy:

- Start daily warfarin dose of ≤ 5mg. Higher initiation doses are not recommended.[5]
- Continue NOAC
- Measure the first INR on day 2 or 3 after initiating warfarin. The main purpose is to identify high levels of warfarin and maintain caution with ongoing doses.
- Do not use point of care monitors during the changeover period between NOAC and warfarin.
- Stop NOAC when INR ≥ 2 on two consecutive days, taking into account the NOAC effect on INR.
- Consult haematology services for further advice.

Table 10: Recommended time between initiating warfarin and ceasing NOAC[5, 6]

Calculated creatinine clearance	Number of days after initiating warfarin that **apixaban or rivaroxaban** should be stopped	Number of days after initiating warfarin that **dabigatran** should be stopped
> 50 mL/min	4 days	3 days
31 to 50 mL/min	3 days	2 days
15 to 30 mL/min	2 days	Consult haematology service
< 15 mL/min	Consult haematology service	

Table 11: Converting from injected anticoagulants to NOAC[5]

Converting from	**Converting to**	**Instructions**
Low molecular weight heparin (LMWH)	NOAC	Discontinue LMWH and start NOAC when the next dose of LMWH would have been due
Continuous heparin infusion	NOAC	Discontinue the infusion and start NOAC immediately

Table 12: Converting from NOAC to injected anticoagulants[5]

Converting from	**Converting to**	**Instructions**
apixaban or rivaroxaban	Low molecular weight heparin (LMWH) or unfractionated heparin	Discontinue NOAC and start LMWH or heparin 12-24 hours after the last dose of NOAC. A bolus dose of unfractionated heparin is not required
dabigatran	LMWH	**If CrCl ≥ 30 mL/min:** > discontinue dabigatran and start LMWH 12 - 24 hours after last dose of dabigatran. **If CrCl < 30 mL/min:** > LMWH is not recommended and dabigatran is contraindicated
dabigatran	unfractionated heparin	**If CrCl ≥ 30 mL/min:** > discontinue dabigatran and start unfractionated heparin 12 - 24 hours after last dose of dabigatran **If CrCl < 30 mL/min:** > discontinue dabigatran and start unfractionated heparin 48 hours after the last dose of dabigatran.

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Interim update undertaken in October 2022 by the Office of the Chief Pharmacist pending full review.

Appendices

1. **Flowchart for Prescribing Non-Vitamin K antagonist Oral Anticoagulants (NOAC) Apixaban, Rivaroxaban and Dabigatran.**

   This flowchart summarises the factors that must be taken into account when considering the initiation of treatment with apixaban, rivaroxaban or dabigatran.

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Flowchart for Prescribing NOAC Apixaban, Rivaroxaban and Dabigatran

Calculate and record creatinine clearance (CrCl)
(use Cockcroft - Gault equation)
Record full blood count and liver function

Take a detailed history
Check all laboratory considerations and exclusion criteria

Assess bleeding risk

Consider concomitant medicines

If the patient is on warfarin and
if all other patient factors warrant the changeover to a NOAC then stop warfarin and see guideline instructions for converting patient from warfarin to NOAC

Laboratory considerations

Renal function

- rivaroxaban is contraindicated if:
  CrCl < 15 mL /min
- apixaban is contraindicated if:
  CrCl < 25 mL/min
- dabigatran is contraindicated in SA Health, for initiation of therapy if:
  CrCl < 50 mL/min (see dabigatran below)

Liver disease

Contraindicated if alanine transaminase (ALT) > 2 x upper limit of normal,

or for apixaban Child-Pugh C (if B use with caution)

or rivaroxaban and dabigatran Child-Pugh B and C.

Full Blood Count

Anaemia Hb ≤ 100 g/L

Assess bleeding risk (seek specialist advice if 'yes' to any of the following):

- history of significant bleeding
- surgery ≤ I month ago
- gastro-intestinal (GI) bleed ≤ 12 months ago
- GI ulcer ≤ 30 days ago
- fibrinolytic treatment ≤ 24 hours ago
- on any anticoagulation agent
- on dual antiplatelet therapy
- platelet count < 100 x 10^9/L

Exclusion criteria

- < 18 years
- known hypersensitivity to NOAC
- pregnant or breastfeeding
- active significant bleeding or disorder of haemostasis (von Willebrand's or coagulation deficiency)
- prosthetic heart valve or severe valvular disease
- recent stroke – relative contraindication *(seek specialist advice)*
- thrombus and recent stent *(seek cardiologist advice)*
- active cancer – relative risk *(seek specialist advice)*

This is not an exhaustive list – refer to guideline. The European Heart Rhythm Association provides a useful decision making chart.

Concomitant medicines Contraindicated:

- ***Potent P-glycoprotein (P-gp) competitors and CYP3A4 inhibitors:***
  - *ketoconazole, itraconazole, posaconazole, voriconazole*
  - *protease inhibitors*
  - *dronedarone*
- ***Enzyme inducers:*** *contraindicated with apixaban and dabigatran e.g. rifampicin, St John's Wort, carbamazepine, phenytoin, and phenobarbitone. Preferably avoid with rivaroxaban.*

Preferably avoided: known or expected increases in NOAC blood levels may occur with the following medicines and a NOAC dose reduction may be appropriate; consider on an individual basis:

- *Cardiac medicines – consider cardiologist advice*
- *fluconazole*
- *cyclosporin, tacrolimus*
- *erythromycin, clarithromycin*

- ***If antiplatelet, anticoagulant or antithrombotic agents are required seek haematologist advice***

Apixaban (Eliquis®)

Total hip or knee replacement (VTE prophylaxis)
2.5 mg twice a day
hip: 32-38 days / knee: 10--14 days

Non-valvular AF
5 mg twice a day
or
If any 2 of the following are present:
age ≥ 80 years,
weight ≤ 60 kg or
serum creatinine ≥ 133 micromol/L
2.5 mg twice daily

Rivaroxaban (Xarelto®)

SAMF restricted to:

Total hip or knee replacement (VTE prophylaxis)
10 mg once daily
hip: 32-38 days / knee: 10-14 days

Initial and continuing treatment of deep vein thrombosis (DVT)
and pulmonary embolism (PE)
(If CrCl > 30 mL/min)
15 mg twice daily for 3 weeks,
then reduce to 20 mg daily

Dabigatran (Pradaxa®)

Streamlined Individual Patient Use Authority for:
Non-valvular AF
150 mg twice daily only in selected patients
(if CrCl ≥ 50 mL/min)
also refer to SA Medicines Formulary

References

1. Australian Commission on Safety and Quality in Health Care - National Safety and Quality Health Service Standards: Standard 4 - Medication Safety
2. South Australian Medicines Formulary (SAMF)
3. Pharmaceutical Benefits Scheme. Available from: http://pbs.gov.au/pbs/home
4. Heidbuchel H et al. European Heart Rhythm Association. Practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* (2013) 15, 625-651. Available from: http://www.escardio.org/The-ESC/Communities/European-Heart-Rhythm-Association-(EHRA)/Publications/Novel-Oral-Anticoagulants-for-Atrial-Fibrillation
5. Tran et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. *Internal Medicine Journal* 44 (2014); 525-536. Available from: http://asth.org.au/downloads/NOAC_imj_12448.pdf
6. Australian Medicines Handbook. Available from: https://amhonline.amh.net.au/

Related documents and references

1. Prescribing information – MIMS ONLINE
1. Apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto): Information for health professionals (TGA, All alerts)
2. Dabigatran (Pradaxa) and the risk of bleeding: Information for health professionals (TGA, All alerts)
3. NPS Medicinewise (For health professionals)
4. Newer Oral Anticoagulants (Update): New South Wales Health, Safety notice 002/14
5. European Society of Cardiology Guidelines
6. Massicotte A. A practice tool for the new oral anticoagulants. *Can Pharm J (Ott)* 2014; 147: 25-32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3908617/
7. SA Health. Clinical Guideline: Management of bleeding related to apixaban, rivaroxaban and dabigatran.
8. SA Health Incident Management Guideline Incorporating Open Disclosure Response Available from: http://www.sahealth.sa.gov.au/wps/wcm/connect/public%20content/sa%20health%20internet/about%20us/publications%20and%20resources/policies%20and%20guidelines?WCM_PI=1&WCM_Page.e835508043e5a0419ae4bfd404a53267=3
9. SA Health Preventing Adverse Drug Events: Policy Directive and Guideline. Available from: http://www.sahealth.sa.gov.au/wps/wcm/connect/public%20content/sa%20health%20internet/about%20us/publications%20and%20resources/policies%20and%20guidelines?WCM_PI=1&WCM_Page.e835508043e5a0419ae4bfd404a53267=6
10. Anticoagulant Guideline for Hospitalised Adult Patients: Queensland Health Feb 2022

Patient information

1. Living with a new Oral Anticoagulant NOAC (WATAG) - patient guideline 2013
2. NPS Medicinewise
3. Dabigatran (Pradaxa) safety update: Information for consumers: (TGA, All alerts)
4. Apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto): Information for consumers (TGA, All alerts)

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Safe Prescribing of New Oral Anticoagulants Apixaban, Rivaroxaban and Dabigatran Clinical Guideline

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02/12/2022	V1.2	Domain Custodian, Clinical Governance, Safety and Quality	Interim review (Dec 2022) Minor updates include terminology of non-Vitamin K antagonist oral anticoagulants (NOAC), South Australian Medicines Formulary recommendations, examples of drug interactions and renal function dosing in line with current TGA approved product information
01/07/2015	V1.1	SA Health Safety and Quality Strategic Governance Committee	Update based on feedback
01/03/2015	V1	SA Health Safety and Quality Strategic Governance Committee	Original