

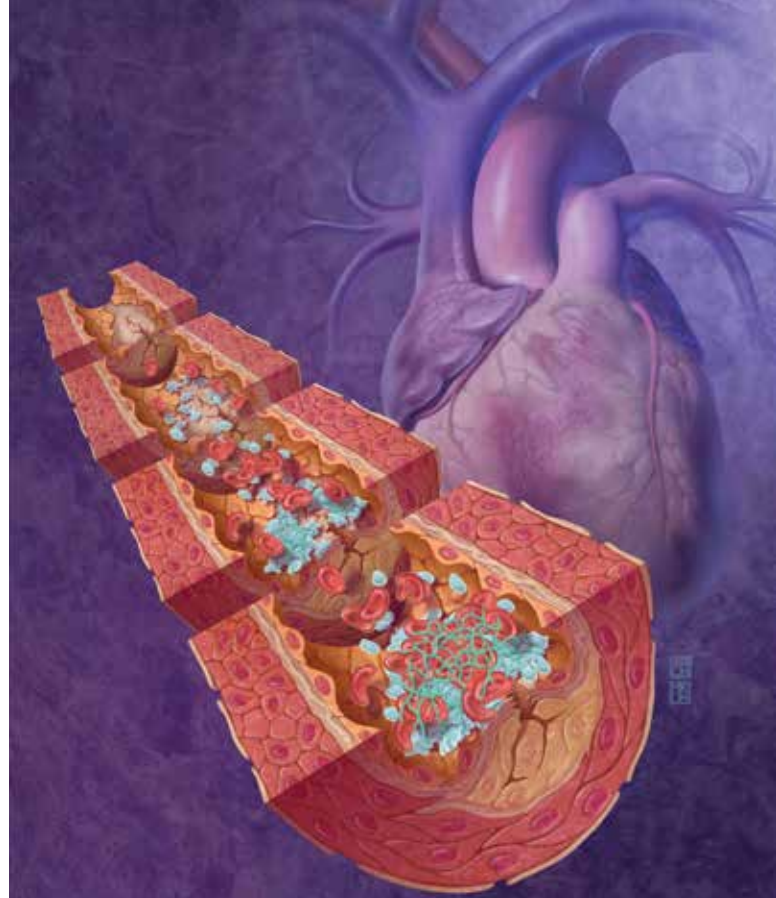
# Practical use of the nonvitamin K antagonist oral anticoagulants

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Six cases illustrate some of the practical issues when determining patient suitability for therapy with a nonvitamin K antagonist oral anticoagulant (NOAC), initiating therapy, managing patients undergoing surgery or with bleeding, and switching between different anticoagulants.

## KEY POINTS

- NOACs (nonvitamin K antagonist oral anticoagulants) are an alternative to vitamin K antagonists such as warfarin for:
  - prevention of stroke in patients with nonvalvular atrial fibrillation and of venous thromboembolism in adults after elective total hip or knee replacement
  - treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE.
- The NOACs dabigatran, apixaban and rivaroxaban differ in their properties, including mode of action and drug interactions; these differences must be taken into account when assessing patient suitability for NOAC therapy.
- Laboratory monitoring required for NOACs differs significantly from that used for warfarin.
- Perioperative use of NOACs is common; management differs between agents, depending on their pharmacokinetic and pharmacodynamic properties.



Warfarin, a vitamin K antagonist (VKA), has been the sole oral anticoagulant for the past 60 years for a range of indications, including prevention of stroke in patients with atrial fibrillation (AF); prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism; prevention of thromboembolism in patients with prosthetic heart valves; and prevention of stroke in patients with previous myocardial infarction and increased embolic risk.<sup>1</sup> Warfarin, however, has a number of limitations, including:

- a narrow therapeutic index
- a delayed onset of action with an initial procoagulant effect
- numerous food and drug interactions
- large interpatient variability in response.

The recent introduction of the non-VKA oral anticoagulants (NOACs) overcomes many of these problems. Individual NOACs have different mechanisms of action and pharmacokinetic profiles and therefore require different management in regard to starting and stopping therapy, use in patients with renal and hepatic impairment, reversal of anticoagulant effect and periprocedural management, laboratory monitoring and drug interactions. When initiating NOAC therapy, clinicians must understand the application of these new agents, the risks and benefits associated with their use and practical issues in managing patients taking these new agents to ensure that they benefit from their convenience and efficacy.

Currently three NOACs are approved in Australia: dabigatran, apixaban and rivaroxaban. These agents directly inhibit a single specific target in the coagulation pathway, either thrombin (dabigatran) or factor Xa (apixaban and rivaroxaban). In contrast, warfarin inhibits synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, X) and the antithrombotic factors

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**TABLE 1. TGA-APPROVED INDICATIONS AND PBS STATUS OF NOACS AVAILABLE IN AUSTRALIA**

Indication	Dabigatran	Rivaroxaban	Apixaban
Prevention of VTEs in adults after major lower limb orthopaedic surgery (elective total hip or knee replacement)	+ (PBS)	+ (PBS)	+ (PBS)
Prevention of stroke and systemic embolism in patients with nonvalvular AF and at least one additional risk factor for stroke	+ (PBS)	+ (PBS)	+ (PBS)
Treatment of DVT and pulmonary embolism and prevention of recurrent DVT and pulmonary embolism	–	+ (PBS)	+ (in adults)*

Abbreviations: AF = atrial fibrillation; DVT = deep vein thrombosis; NOAC = nonvitamin K antagonist oral anticoagulant; VTE = venous thromboembolic event.

Key: + = TGA approved for indication; PBS = PBS listed for indication.

\* In March 2015, the Pharmaceutical Benefits Advisory Committee recommended the PBS listing of apixaban for the treatment of DVT and pulmonary embolism.

protein C and protein S.<sup>2,3</sup> The clinical considerations when prescribing a NOAC differ from those when prescribing warfarin, including precautions, adverse effects, monitoring and reversal.

### Considerations when initiating NOAC therapy

- Before initiating NOAC therapy, it needs to be decided that anticoagulation is indicated and is clinically appropriate for the patient.
- The choice of NOAC should be based on patient preference, trial evidence and whether there is TGA approval and (if cost is an issue) PBS approval for the specified indication. TGA indications and the current PBS status of the NOACs available in Australia are summarised in Table 1.
- Baseline tests should be completed before initiation of NOAC therapy, including:
  - haemoglobin level
  - a coagulation assay
  - renal function tests
  - liver function tests.
- Education should be provided to the patient regarding the NOAC chosen, and the patient should be involved in the decision-making process.
- After the decision to initiate NOAC therapy, education of the patient regarding adherence is essential, emphasising the risks associated with missing doses.
- The patient should be advised to carry

an alert card to inform healthcare professionals that they are taking an anticoagulant agent.

- Follow-up appointments should be organised, with the first follow-up appointment within one month of initiation of NOAC therapy.
- At each follow-up appointment, the following should be assessed:
  - compliance
  - bleeding events
  - thromboembolic events
  - side effects
  - medication changes
  - patient concerns.
- Blood tests should be performed regularly, as follows:
  - renal function – three to six-monthly for patients with creatinine clearance (calculated by the Cockcroft and Gault method) 30 to 60 mL/min or if on dabigatran and over 75 years of age or frail; yearly if creatinine clearance is more than 60 mL/min<sup>4</sup>
  - haemoglobin level and (for the factor Xa inhibitors) liver function annually, to check for anaemia and liver function abnormalities.

Some of the practical issues in managing patients taking a NOAC are illustrated by the following six cases.

#### Case 1. Is this nonvalvular AF?

*Mrs GB, aged 74 years, presents to her GP for a routine check up. An irregularly irregular pulse and systolic murmur are noted*

*on physical examination. An ECG confirms AF, and an echocardiogram shows mild–moderate aortic stenosis, mild–moderate mitral regurgitation and trivial tricuspid regurgitation. Is this ‘nonvalvular AF’ and can a NOAC be prescribed?*

The trials studying NOACs for stroke prevention in AF excluded patients with ‘valvular’ heart disease.<sup>5–7</sup> The definition of valvular AF in these trials included patients with prosthetic valves, rheumatic mitral stenosis or haemodynamically severe valve lesions. A practical interpretation of this is that NOACs were not studied in patients with a mechanical prosthesis or a valve lesion of such severity that valve surgery was expected in the near future. There has been one study comparing dabigatran with warfarin in patients with mechanical heart valves, which showed that dabigatran was associated with increased rates of thromboembolic and bleeding complications, confirming that NOACs should not be used in this group of patients.<sup>8</sup> NOACs should therefore not be used as an antithrombotic agent for patients with prosthetic heart valve replacement, mitral stenosis or where valve surgery is imminent.

Patients with other valve lesions, including mitral valve prolapse, nonrheumatic valvular lesions, mild–moderate mitral regurgitation or mild–moderate aortic valve conditions were enrolled in the clinical trials comparing NOACs with warfarin and are suitable for NOAC use. *Outcome: Mrs GB was prescribed a NOAC.*

**TABLE 2. PHARMACOKINETIC PROPERTIES OF NOACS AVAILABLE IN AUSTRALIA<sup>4</sup>**

Properties	Dabigatran	Rivaroxaban	Apixaban
Mode of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Bioavailability	3 to 7%	66% without food >80% with food	50%
Prodrug	Yes	No	No
Clearance (nonrenal)	20%	65%	73%
Clearance (renal)	80%	35%	27%
Liver metabolism	No CYP3A4 involvement	Significant CYP3A4 elimination	Minor CYP3A4 elimination
P-glycoprotein transport	Yes	Yes	Yes
Effect of food on absorption	No effect	>39% more absorption with food	No effect
Intake with food recommended	No recommendation	Yes	No recommendation
Time to peak plasma level	2 hours after ingestion (C <sub>max</sub> 0.5 to 2 hours)	2 to 4 hours after ingestion (C <sub>max</sub> 2.5 to 4 hours)	1 to 4 hours after ingestion (C <sub>max</sub> 1 to 4 hours)
Effect of Asian ethnicity	25% increased absorption	No effect	No effect
Plasma trough level	12 to 24 hours after ingestion	16 to 24 hours after ingestion	12 to 24 hours after ingestion
Half-life	12 to 17 hours	5 to 9 hours (young) 11 to 13 hours (elderly)	12 hours

Abbreviations: C<sub>max</sub> = peak plasma concentration; CYP3A4 = cytochrome P450 3A4; NOAC = nonvitamin K antagonist oral anticoagulant.

## Case 2. How do you treat cancer-associated VTE and how do other drugs affect NOAC use?

Mr WD, aged 76 years, presents to hospital with shortness of breath. CT pulmonary angiography shows a pulmonary embolism. Mr WD's past medical history includes metastatic prostate cancer (for which he is receiving antiandrogen therapy) and epilepsy (controlled with carbamazepine). It is recommended that Mr WD begin enoxaparin therapy, but he does not accept the option of long-term injections. Where to from here?

The aim of anticoagulation for Mr WD is to prevent recurrence, extension and embolism of the thrombus while minimising the risk of bleeding associated with anticoagulation therapy. Anticoagulant treatment for venous thromboembolism (VTE) in patients with cancer is complicated by higher than usual rates of VTE recurrence and bleeding. When low molecular weight

heparins (LMWH) were compared with warfarin for the prevention of recurrent VTE in patients with cancer, dalteparin was shown to be more effective in reducing recurrent VTE without increasing the risk of bleeding.<sup>9</sup> Current guidelines recommend using LMWH for long-term anticoagulation in patients with cancer-associated VTE in preference to warfarin. Many patients, however, find the inconvenience of once or twice daily injections unacceptable and prefer oral therapy.

### NOACs in patients with cancer

Dabigatran, rivaroxaban and apixaban have each been studied in patients with acute VTE.<sup>10-12</sup> In the dabigatran trial, patients received initial LMWH for at least five days; in the rivaroxaban and apixaban trials these drugs were used as monotherapy with no initial LMWH mandated. In each of the trials, the NOAC was non-inferior to conventional anticoagulation in efficacy and at least as safe. However, the

number of patients with active cancer in these trials was small, and it is uncertain whether the overall trial results apply in this high-risk subgroup. At present, rivaroxaban and apixaban have an indication in Australia for the treatment of VTE and are appropriate first-line therapy for most patients with acute VTE. It is also reasonable to use these NOACs in patients with acute VTE and active cancer, particularly in those who do not wish to have regular injections of LMWH.

### Drug interactions

The second consideration for Mr WD is the potential for drug interactions between carbamazepine and NOACs. A major advantage of NOACs over warfarin is their relatively lower potential for drug interactions (see Table 2).<sup>4</sup> Dabigatran has a high renal clearance and less hepatic clearance than rivaroxaban and apixaban. Both rivaroxaban and apixaban are metabolised by cytochrome P450 3A4 (CYP3A4) and

**TABLE 3. DRUGS THAT INTERACT WITH NOACS, MECHANISM OF INTERACTION, EFFECT ON NOAC PLASMA LEVELS AND CLINICAL CONSIDERATIONS FOR NOAC DOSING<sup>13-21</sup>**

Interacting drug	Mechanism of interaction	Effect on NOAC plasma levels (AUC)*		
		Dabigatran (Substrate of P-gp)	Rivaroxaban (Metabolised by CYP3A4, substrate of P-gp)	Apixaban (Metabolised by CYP3A4, substrate of P-gp)
Atorvastatin	P-gp and CYP3A4 inhibition	Increase in AUC of 18% <sup>13</sup>	No effect <sup>14</sup>	No data
Digoxin	P-gp competition	No effect <sup>15</sup>	No effect <sup>16</sup>	No data
Verapamil	P-gp competition Weak CYP3A4 inhibition	Increase in AUC of 12 to 180% <sup>17</sup>	Increase in AUC of 23% <sup>18</sup>	No data
Diltiazem	P-gp competition Weak CYP3A4 inhibition	No effect <sup>19</sup>	Minor effects	Increase in AUC of 40%
Amiodarone	P-gp competition	Increase in AUC of 12 to 60% <sup>19</sup>	Minor effects	No effect
Ketoconazole, itraconazole, voriconazole, posaconazole	P-gp and BCRP competition CYP3A4 inhibition	Increase in AUC of >140 to 150%	Increase in AUC of >160% <sup>20</sup>	Increase in AUC of >100%
Fluconazole	Moderate CYP3A4 inhibition	No data	Increase in AUC of >42% <sup>20</sup>	No data
H2RA/PPI		Decrease in AUC of 12 to 30% <sup>21</sup>	No effect	No data
Cyclosporin, tacrolimus	P-gp competition	No data	Increase in AUC of 50%	No data
Clarithromycin, erythromycin	P-gp competition CYP3A4 inhibition	Increase in AUC of 15 to 20%	Increase in AUC of 30 to 54%	No data
HIV protease inhibitors	P-gp and BCRP competition or inducer CYP3A4 inhibition	No data	Increase in AUC of up to 153%	Strong increase
Rifampicin, St John's wort, carbamazepine, phenytoin	P-gp/BCRP and CYP3A4/ CYP2j2 inducers	Decrease in AUC of 66%	Decrease in AUC of up to 50%	Decrease in AUC of 54%
<b>Key to colours</b>				
Contraindicated/not recommended		Dose reduction recommended	Consider dose adjustment. Do not use if another yellow drug is present	

Abbreviations: AUC = area under curve; BCRP = breast cancer resistance protein; CYP2j2 = cytochrome P450 2j2; CYP3A4 = cytochrome P450 3A4; H2RA = H<sub>2</sub> receptor antagonists; NOAC = nonvitamin K antagonist oral anticoagulant; P-gp = P-glycoprotein; PPI = proton pump inhibitor.

\* AUC is the area under the plasma drug concentration versus time curve, a measure of drug exposure.

are therefore prone to drug interactions with inhibitors or inducers of this enzyme. All three NOACs are substrates for the P-glycoprotein (P-gp) transporter and therefore interact with P-gp inhibitors or inducers. Table 3 summarises the significance of some of these drug interactions and the associated recommendations

when prescribing these medications.<sup>13-21</sup> Carbamazepine is an inducer of CYP3A4 and may increase the metabolism of rivaroxaban. The effect is unlikely to be clinically significant, so rivaroxaban can be prescribed in this situation. If an additional CYP3A4 inducer, such as St John's wort, was also being taken then

rivaroxaban should not be used. The most important drug classes with major interactions with the NOACs are the antiretrovirals and the azole antifungals; and NOACs are contraindicated in the presence of these drugs.

*Outcome: Rivaroxaban is prescribed for Mr WD.*



**TABLE 4. RECOMMENDED TIME OF FINAL ANTICOAGULANT DOSE BEFORE ELECTIVE SURGERY**

Procedural bleeding risk	Renal function*	Dabigatran	Rivaroxaban	Apixaban
Low	Normal	24 h	24 h	24 h
	Moderately reduced	48 to 72 h	48 h	48 h
High	Normal	48 to 72 h	48 to 72 h	48 to 72 h
	Moderately reduced	96 h	72 h	72 h

\* Renal function definitions: normal = calculated creatinine clearance >50 mL/min; moderately reduced = calculated creatinine clearance 30 to 49 mL/min.

### Case 3. What is the impact of NOAC therapy on surgery?

Mrs JM is a 73-year-old woman with paroxysmal AF, and is currently receiving anticoagulation therapy with dabigatran (150 mg twice daily). Her past medical history includes hypertension and diabetes mellitus. Mrs JM is admitted to hospital with acute right upper quadrant abdominal pain and fever. Her last dose of dabigatran was 18 hours ago. A surgical consultation confirms acute cholecystitis, and surgery later today is recommended. Coagulation studies are performed and show: activated partial thromboplastin time (APTT), 27 s (normal range [NR], <35 s); prothrombin time, 10 s (NR <12 s); INR, 1.1 (NR <1.2); thrombin time, 12 s (NR <15 s).

The surgeon wants to know whether Mrs JM has an increased risk of surgical bleeding.

### Interpretation of coagulation assays in patients taking NOACs

NOAC therapy does not require routine monitoring of coagulation, but a coagulation assay should be undertaken before initiating these agents to exclude any pre-existing coagulation abnormality.

The main value of performing coagulation studies in patients taking a NOAC is to determine whether any anticoagulant effect is present. This may be clinically useful for patients requiring urgent surgery or with active bleeding, to determine whether surgery may be safely performed or whether the NOAC is likely to be contributing to bleeding, respectively. Coagulation studies

may also be useful to assess drug adherence. A normal result indicates that no anticoagulant effect is present; prolongation of anticoagulation measures indicates that an anticoagulant effect is present but does not give information about the intensity of this effect or the risk of bleeding.

For patients taking dabigatran, a normal APTT makes any significant dabigatran effect unlikely, and a normal thrombin time excludes a dabigatran effect. Prothrombin time and INR are not useful.

For patients taking factor Xa inhibitors, rivaroxaban leads to prolongation of prothrombin time and INR, so normal results for these tests exclude a significant rivaroxaban effect. Apixaban does not reliably prolong prothrombin time and INR, so a calibrated anti-factor Xa level is required to detect apixaban activity.

Recent Australian recommendations for the management of patients receiving NOACs who require a surgical procedure are summarised below.<sup>22</sup>

### Perioperative management of patients taking NOACs

Perioperative management of patients taking a NOAC depends on whether the surgery is urgent or elective.<sup>22-24</sup>

#### Before urgent surgery

1. Stop NOAC.
2. Perform specific coagulation tests and interpret results according to the NOAC being taken, as follows.

- Dabigatran – if normal APTT and thrombin time or normal APTT

and prolonged thrombin time then proceed to surgery; if prolonged APTT and prolonged thrombin time then go to step 3

- Rivaroxaban – if normal prothrombin time then proceed to surgery
- Apixaban – if normal factor Xa level then proceed to surgery
- Factor Xa inhibitors – if prolonged prothrombin time and prolonged APTT then go to step 3.

3. Maintain blood pressure and urine output, control any bleeding, give transfusion if required.<sup>25</sup>

- If surgery can be delayed then refer to elective surgery guide
- If surgery can be delayed four to 12 hours then consider haemodialysis for dabigatran (requires specialist advice)
- If immediate surgery is required then seek specialist advice.

#### Before elective surgery

- Determine the renal function of the patient and the bleeding risk of the procedure. Table 4 shows the time when the final dose of the NOAC should be administered before surgery.
- Perioperative laboratory monitoring of patients treated with NOACs is not usually required because of their rapid offset of action.
- The rapid offset of NOAC therapy obviates the need for preoperative bridging therapy with LMWH.

#### When to restart NOACs

For surgical procedures that do not carry a high postoperative bleeding risk, it is reasonable to re-start the NOAC 24 hours after the procedure. For procedures with a high postoperative bleeding risk recommencement of the NOAC should be delayed for 48 to 72 hours. If the patient is at risk of VTE, it is reasonable to initiate prophylactic LMWH six to eight hours after haemostasis has been achieved, and to continue to withhold therapeutic anticoagulation until safe (see Table 5). There is no evidence to support reducing the postoperative dose of NOAC

in patients with AF undergoing surgery. *Outcome: Mrs JM's normal thrombin time indicates that no anticoagulant effect of dabigatran is present. She is able to undergo surgery safely, and recommences taking dabigatran on day 3 postoperatively.*

#### Case 4. How do you manage bleeding in patients taking NOACs?

*Mr CR is a 78-year-old man with permanent AF, who is receiving anticoagulation therapy with rivaroxaban 20 mg daily. His past medical history includes hypertension, diabetes mellitus and congestive cardiac failure. Mr CR is admitted to hospital with haematemesis and melaena. On admission he has a creatinine clearance of 85 mL/min, haemoglobin level of 62 g/L and systolic blood pressure of 80 mmHg, which improves to 120 mmHg after a fluid bolus is given. His last dose of rivaroxaban was eight hours previously. What would you do?*

A major current concern about prescribing NOACs is the lack of a specific reversal agent. In clinical trials, however, major bleeding with NOACs was rare and fatal bleeding very infrequent. Of note, there are no reversal agents for aspirin, clopidogrel, prasugrel or LMWH. Although there are reversal agents for warfarin, observational studies have shown that in practice it takes a number of hours for them to be administered. During this time, the effect of NOACs would have reduced because of their short half-lives. Management strategies for patients experiencing bleeding while taking a NOAC are well established.<sup>26</sup>

#### Management of NOAC therapy during bleeding episodes

When a patient treated with a NOAC is bleeding, the cause of the bleed and any residual or excessive anticoagulant effect should be assessed. If the bleeding is minor then cessation of the NOAC and supportive management are usually all that is required. After cessation of a NOAC, restoration of haemostasis should be expected within 12 to 24 hours of the final dose, depending on its half-life (see Table 2).

**TABLE 5. POSTOPERATIVE RESUMPTION OF NOACS**

Postoperative bleeding risk	Dabigatran	Rivaroxaban	Apixaban
Low	Resume 24 hours after surgery		
High*	Resume 48 to 72 hours after surgery		

\*Interventions with a high bleeding risk include: complex left-sided ablation (pulmonary vein isolation, ventricular tachycardia ablation); spinal or epidural anaesthesia, lumbar diagnostic puncture; thoracic surgery; abdominal surgery; major orthopaedic surgery; liver biopsy; transurethral prostate resection; and kidney biopsy.

For more severe bleeding, reversal options should be considered. Dabigatran can be removed by dialysis, but the practicalities of instituting dialysis in the setting of severe bleeding may preclude its use.<sup>27</sup> Dialysis does not reverse factor Xa inhibitors because of their high protein binding. Oral activated charcoal may provide some benefit if administered within two hours of the last dose for all NOACs.

In the case of life-threatening bleeding, prohaemostatic agents should be administered. Prothrombin complex concentrates and activated prothrombin complex concentrates have been shown to have a reversal effect on NOACs (particularly factor Xa inhibitors) and should be administered in patients with life-threatening bleeding.<sup>28,29</sup> The current use and choice of agent depend on local experience and guidelines of the treatment centre. Fresh frozen plasma and vitamin K have no effect on reversal of anticoagulation and should not be used. There is no role for protamine in the reversal of NOACs.

In the case of a clinically significant bleed, haemostasis experts, emergency physicians or cardiologists should be consulted to determine a plan for bleeding management. Specific reversal agents are expected to be available in the near future.<sup>30</sup> *Outcome: Mr CR remains stable following initial resuscitation, commencement of a protein pump inhibitor infusion and blood transfusion. He undergoes endoscopy on the following day. As the half-life of rivaroxaban is short, and the patient is stable, it is decided not to use any haemostatic agents with the expectation that there will be no residual anticoagulant effect by the following day.*

#### Case 5. How do you switch patients from warfarin to NOACs?

*Mr IR is a 56-year-old man with nonvalvular AF who has been taking warfarin for three years. He has a past medical history of hypertension and gout. He presents to his GP wanting to switch over to one of the new anticoagulant agents that do not require monitoring, as he is sick of regular blood tests. How would you arrange this transition?*

When changing anticoagulants, the aim is to maintain therapeutic anticoagulation, without having significant periods of either over- or under-anticoagulation. This minimises the risk of bleeding and thrombosis.

#### Switching between anticoagulant regimens

##### Switching from one NOAC to another

The alternative NOAC can be initiated when the next NOAC dose is due, except in situations where higher than therapeutic plasma concentrations are expected, such as in patients with renal impairment.

##### Switching from warfarin to a NOAC

In patients switching from warfarin, the INR should be less than 2.5 before commencing a NOAC. The NOAC should be commenced on the next day at the appropriate dose for renal function.

##### Switching from a NOAC to warfarin

For patients who are unable to continue on rivaroxaban, apixaban or dabigatran and need to commence warfarin, a crossover period is required. This crossover period is important as clinical trials of the NOACs found an excess of strokes when a crossover period was not used. NOAC therapy should continue after initiation of warfarin until

**TABLE 6. RECOMMENDATIONS WHEN SWITCHING FROM A NOAC TO WARFARIN**

Calculated creatinine clearance (mL/min)	Time from warfarin initiation to stopping NOAC	
	Dabigatran	Rivaroxaban or apixaban
>50	Stop 3 days after starting warfarin	Stop 4 days after starting warfarin
31 to 50	Stop 2 days after starting warfarin	Stop 3 days after starting warfarin
15 to 30	Stop 1 day after starting warfarin	Stop 2 days after starting warfarin
<15	Consult with haematology service	Consult with haematology service

**TABLE 7. DOSE REDUCTION CRITERIA FOR NOACS**

	Dabigatran	Rivaroxaban	Apixaban
Usual dose*	150 mg twice daily	20 mg once daily	5 mg twice daily
Reduced dose	110 mg twice daily	15 mg once daily	2.5 mg twice daily
Criteria for dose reduction	Age $\geq$ 75 years, or creatinine clearance 30 to 50 mL/min	Creatinine clearance 30 to 49 mL/min	Presence of two of: • age $\geq$ 80 years • weight $\leq$ 60 kg • serum creatinine level $\geq$ 133 $\mu$ mol/L
Criteria for contraindication	Creatinine clearance <30 mL/min	Creatinine clearance <30 mL/min	Creatinine clearance <25 mL/min

\* For stroke prevention in patients with nonvalvular atrial fibrillation.

the INR has been above 2.0 for two days. It is necessary to take into account the expected time to onset of warfarin activity (approximately five days) as well as the half-life of the NOAC (Table 6).

*Outcome: Mr IR discontinued warfarin, and his INR was tested daily. When the INR fell below 2.0, dabigatran was commenced.*

### Case 6. How do you initiate a NOAC?

*Mrs GT is 78 years old and living independently. She is found to have AF on a routine check up. She has hypertension and type 2 diabetes mellitus. You recommend anticoagulation for stroke prevention. She says she does not want 'rat sack' and neither does she want many blood tests as she has a busy lifestyle. You suggest a NOAC. She weighs 79 kg and her serum creatinine level is 95  $\mu$ mol/L. What dose of NOAC should she receive and what follow up is required?*

All NOACs are renally excreted, albeit to varying extents, and all have a recommendation for dose reduction in patients

with reduced renal function. It is important to calculate the creatinine clearance, which may be lower than the estimated glomerular filtration rate, particularly in women and the elderly. Creatinine clearance calculators are readily available (e.g. Cockcroft and Gault). Additional factors that determine the need for dose reduction include age and weight. The criteria for dose reduction differ between NOACs (Table 7).<sup>31</sup>

As renal function declines with increasing age, regular monitoring of renal function is required to determine whether a dose reduction or even cessation of the NOAC is required. The recommended schedule of monitoring is:

- three to six monthly for patients with a creatinine clearance of 30 to 60 mL/min or those on dabigatran and aged over 75 years or frail<sup>27</sup>
- yearly if creatinine clearance is more than 60 mL/min.<sup>31</sup>

*Outcome: Mrs GT is suitable for NOAC therapy. Her calculated creatinine clearance is 54 mL/min, so she should receive*

*dabigatran 110 mg twice daily or rivaroxaban 20 mg once daily or apixaban 5 mg twice daily. She should return for repeat renal function testing after three months to ensure the chosen dose remains appropriate.*

### Conclusion

NOACs are at least as effective and safe as warfarin for the prevention and treatment of thrombotic disorders and offer many advantages including ease of use and fewer food and drug interactions. Their optimal use, however, requires knowledge of their pharmacokinetics and metabolism, as illustrated by the above cases. No specific reversal agents are available for NOACs, but this should not preclude their use as major bleeding is infrequent and bleeding management strategies are available. **MT**

### References

A list of references is included in the website version ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)) and the iPad app version of this article.

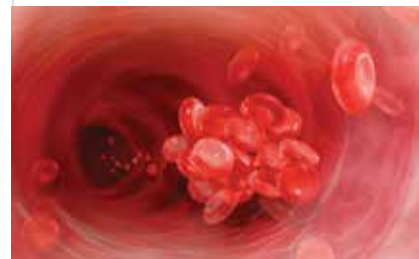
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This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

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