



# Therapeutic Brief

# 37

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## Topic 37: The oral anticoagulant dilemma

Warfarin, the most commonly used oral anticoagulant in Australia, is highly effective in a wide range of thromboembolic disorders, including prevention of stroke in patients with atrial fibrillation, thrombus formation in patients with prosthetic heart valves and prevention and treatment of venous thromboembolism (VTE).<sup>1,2</sup> Challenges associated with warfarin therapy have prompted the development of a number of novel oral anticoagulants (NOACs), of which dabigatran, apixaban and rivaroxaban are available in Australia and listed on the Pharmaceutical Benefits Scheme (PBS).<sup>3,4</sup>

This therapeutic brief provides information to help make an informed decision when considering which oral anticoagulant is most appropriate for your patient.

**Table 1: Comparison of novel oral anticoagulants and warfarin**

	<b>dabigatran (Pradaxa)<sup>4,5,8</sup></b>	<b>apixaban (Eliquis)<sup>4,6,8</sup></b>	<b>rivaroxaban (Xarelto)<sup>4,7,8</sup></b>	<b>warfarin (Coumadin, Marevan)<sup>8</sup></b>
<b>Actions</b>	Direct thrombin inhibitor	Direct and selective inhibitor of factor Xa	Direct and selective inhibitor of factor Xa	Inhibits synthesis of vitamin K-dependent clotting factors II, VII, IX, X and antithrombotic factors protein C and S
<b>Indications</b>	Prevention of: <ul style="list-style-type: none"> <li>VTE in total hip or knee replacement</li> <li>stroke and systemic embolism in non-valvular AF and at least one additional risk factor for stroke</li> </ul>	Prevention of: <ul style="list-style-type: none"> <li>VTE in total hip or knee replacement</li> <li>stroke and systemic embolism in non-valvular AF and at least one additional risk factor for stroke</li> </ul>	Prevention of: <ul style="list-style-type: none"> <li>VTE in total hip or knee replacement</li> <li>stroke and systemic embolism in non-valvular AF and at least one additional risk factor for stroke</li> <li>treatment of DVT/PE and for prevention of recurrent DVT/PE</li> </ul>	Prevention of: <ul style="list-style-type: none"> <li>VTE and treatment for VTE</li> <li>VTE in patients with prosthetic heart valves</li> <li>stroke and systemic embolism in AF</li> </ul>
<b>Onset of action/ Half-life</b>	Onset of action within 30 minutes. Half-life is 7-9 hours in young adults and 12-14 hours in elderly people. Half-life is prolonged in renal impairment	Onset of action within 30 minutes. Half-life is approximately 12 hours	Onset of action within 30 minutes. Half-life is approximately 5-9 hours in young adults and 11-13 hours in elderly people	Onset of action within 36-72 hours. Half-life is 20-60 hours
<b>Dosage</b>	Fixed according to clinical indication	Fixed according to clinical indication	Fixed according to clinical indication	Individualised and dose adjusted according to INR result

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### Key points

- > Adverse effects and interactions associated with novel oral anticoagulants remain largely unknown
- > Make an informed decision as to which is the most appropriate oral anticoagulant for your patient
- > Give careful consideration before switching your patient from warfarin to a novel oral anticoagulant.

We need to be careful that marketing promotion and familiarisation programs do not drive a needless trend to switch patients currently taking warfarin to the new agents for perceived ease of use or claims of superior safety or efficacy.<sup>9</sup> An informed decision and careful patient selection is recommended when considering treatment options as many patients may not benefit from switching to the new agents.



## Which of my patients may do better by continuing with warfarin?

While the novel oral anticoagulants offer an alternative to warfarin therapy for selected patients, like all anticoagulants, they are a class of medicines that can potentially cause severe or fatal bleeding.<sup>1,8</sup> Novel oral anticoagulants were studied for a median of 19-22 months in clinical trials and in select patient populations. **There is limited experience of their safety and efficacy in people with significant renal or liver impairment, the elderly and those with multiple comorbidities and concurrent medicines. Associated adverse effects, complications and interactions in these patient populations remain largely unknown.**<sup>5-7</sup>

Hence, careful consideration is advised before switching patients from warfarin to a novel oral anticoagulant as there is risk associated with changing medicines, especially in a population that is predominantly elderly with multiple comorbidities and concurrent medicines.<sup>10-12</sup> There is a familiarity, level of comfort and a wealth of experience associated with the use of warfarin because of its long term use, extensive experience in clinical trials and the ability to reverse its anticoagulant effects, if required.<sup>2,13</sup> It is likely patients will be asking about the novel oral anticoagulants.

### What to discuss with your patient asking about novel oral anticoagulants<sup>10,13,14</sup>

- The risks and benefits of treatment options
- Safety issues involved with switching medicines
- The importance of continued clinical monitoring no matter what anticoagulant is prescribed
- Blood tests are a good way to monitor safety, e.g. renal function
- The importance of strict adherence
- Reporting of any unexpected adverse effects
- There is no benefit in switching for most patients who are well controlled taking warfarin.

### The stable patient

Although the risk of intracranial haemorrhage is less with the novel oral anticoagulants, this alone does not warrant switching your patient from warfarin.<sup>10,13</sup> Stable patients taking warfarin whose international normalised ratios (INRs) are largely within the targeted therapeutic range and in whom INR testing does not present a problem, may not benefit from switching.<sup>13</sup> In stable well controlled patients taking warfarin, there is evidence that the benefits of the novel oral anticoagulants, particularly dabigatran, decrease as time in the therapeutic range (TTR) increases.<sup>14,15</sup> The importance of frequent patient contact that is inherent with regular INR monitoring cannot be over emphasised. As well as measuring anticoagulant response and assessing patient adherence, regular contact offers an opportunity to clinically monitor the patient and reinforce key aspects of treatment.<sup>14,15</sup>

If your patient does not have INR results within the therapeutic range most of the time and you are considering switching to a novel oral anticoagulant, first assess correctable causes for INR variation. (See Box 1).

### The non-adherent patient

Patients taking warfarin who have difficulty in maintaining correct dosing regimens should not be switched to a novel oral anticoagulant. Because of the shorter half-life of the novel oral anticoagulants, a missed dose is more likely to cause a significant or complete loss of antithrombotic effect.<sup>13,14</sup> Likewise, taking additional doses is likely to increase the risk of a bleed.<sup>11</sup> Dabigatran and apixaban in particular, should not be considered alternatives to warfarin in poorly adherent patients as they need to be taken twice daily.<sup>5,6,13</sup> Because there is no validated laboratory method to measure the anticoagulant response of the novel oral anticoagulants, the first sign of poor compliance may be seen as a stroke or other embolic event or as a bleed.<sup>5-7,14</sup> Therefore, strict adherence is essential for adequate anticoagulant protection with novel oral anticoagulants.<sup>10</sup>

### Box 1: Common factors that influence INR results<sup>1,16</sup>

- Acute illness
- Chronic comorbidities
- Warfarin-medicine interactions, including herbal and over-the-counter medicines
- Diet
- Alcohol intake
- Poor adherence

### The multimorbid patient

The prevalence of multimorbidity increases with age, with those over 40 years ten times more likely to take four or more prescribed medicines each day, potentially putting them at a high risk of medicine-related adverse effects.<sup>17</sup> The extent and clinical significance of interactions between many medicines and novel oral anticoagulants are currently unknown. The detection of these interactions may be difficult due to the lack of a validated measure of anticoagulant response. Caution is recommended when starting, stopping or adjusting the dose of any medicine or anything that may increase the bleeding risk.<sup>2</sup> As with warfarin, there is an increased risk of major bleeding when novel oral anticoagulants are taken in combination with any antiplatelet therapy, non-steroidal anti-inflammatory drugs (NSAIDs), fish oil, selective serotonin reuptake inhibitors (SSRIs) or other anticoagulants.<sup>1,5-7,18-20</sup> The risk increases significantly with the addition of a single antiplatelet with a novel oral anticoagulant. This suggests caution when considering combining these medicines with any oral anticoagulant.<sup>18</sup>

Practical points relating to medicine and food and alcohol interactions with novel oral anticoagulants can be found on the NPS MedicineWise website at: [www.nps.org.au/newer-anticoagulant-drug-interactions](http://www.nps.org.au/newer-anticoagulant-drug-interactions)

## Contraindications and cautions with novel oral anticoagulants

### Contraindications

- All novel oral anticoagulants are contraindicated in patients:
  - with a known hypersensitivity or condition/s associated with a significant increased risk of bleeding<sup>5-7</sup>
  - with valvular atrial fibrillation, (including rheumatic valvular disease or a prosthetic heart valve)<sup>8</sup>
  - with significant hepatic disease<sup>5-7</sup>
  - undergoing dialysis.<sup>6,7,11</sup>
- dabigatran is contraindicated in patients with a creatinine clearance less than 30mL/minute.<sup>5</sup>
- rivaroxaban is contraindicated in patients with a creatinine clearance less than 30mL/minute for 15mg and 20mg tablets and in patients with a creatinine clearance less than 15mL/minute for 10mg tablets.<sup>7</sup>
- apixaban is contraindicated in patients with a creatinine clearance less than 25mL/minute.<sup>6</sup>

**NOTE:** for further details on contraindications, see Product Information for each novel oral anticoagulant.

### Cautions

#### The renally impaired and elderly patient

- Exercise caution in patients with mild to moderate renal impairment especially if considering the use of dabigatran as it is predominantly excreted via the kidneys.<sup>5,10,20</sup>
- Careful consideration in the elderly is advised as renal function commonly declines with increasing age and the risk of incurring a major bleed increases in those people 75 years of age and over.<sup>5-8,20</sup>
- Consider a reduced dose if your patient has moderate renal impairment (creatinine clearance 30-50mL/minute), is 75 years or older or has a potentially higher risk of major bleeding.<sup>5-7</sup>

#### The low body weight patient

- Patients with low body weight may be at an increased risk of bleeding.<sup>21</sup>

#### The patient with a history of GI bleeding

- Bleeding in the lower gastrointestinal tract, gastritis and dyspepsia are all more common in patients receiving dabigatran or rivaroxaban, compared with warfarin, especially in people over the age of 75 years.<sup>5,7,20</sup>
- Older people who have a history of lower gastrointestinal disease or bleeding may be at an increased risk of harm with the use of dabigatran or rivaroxaban.<sup>14</sup>

#### The patient with mild to moderate hepatic disease

- Caution is advised in patients taking apixaban with mild to moderate hepatic dysfunction.<sup>6</sup>
- Use rivaroxaban with caution in cirrhotic patients with moderate hepatic dysfunction.<sup>7</sup>

#### No reversal agent

- It is difficult to manage bleeding associated with the novel oral anticoagulants. As there is no specific pharmacological antidote currently available for any of the new agents, their actions are not able to be effectively and rapidly reversed. Thus management is largely supportive.<sup>5-7,14</sup>
- This is particularly hazardous in patients experiencing an overdose, major bleeding such as intracranial/extracranial or gastrointestinal bleeding, and during emergency invasive procedures.<sup>2,14</sup>

#### Increased risk of myocardial infarction

- There is evidence to link the use of dabigatran with a small increased risk of myocardial infarction or acute coronary syndrome.<sup>22</sup>

See the 'Australian Medicines Handbook' for information on how to safely switch your patient from warfarin to a novel oral anticoagulant.<sup>8</sup>

## Which of my patients would I consider switching to a novel oral anticoagulant?

When determining whether your patient currently taking warfarin would benefit from switching to a novel oral anticoagulant, give careful consideration to the clinical profile of the patient, the specific aspects of the new medicine and the risks and benefits and safety issues associated with switching medicines.<sup>11,13,14</sup> Discuss treatment options with your patient and ensure they are aware of the advantages and disadvantages, including the importance of regular monitoring, strict adherence and bleeding risks.

Patients currently taking warfarin most likely to benefit from continuing with warfarin

- Well controlled in whom INR testing is not a problem
- May miss a dose
- Valvular atrial fibrillation or prosthetic heart valve (NOACs are contraindicated)
- Significant renal impairment
- Significant hepatic impairment
- Over 75 years with multimorbidities
- Lower gastrointestinal disease or history of bleeding

Patients who may benefit from switching to a novel oral anticoagulant<sup>23</sup>

- Poorly controlled
- Unable to access INR testing
- Unable to tolerate warfarin
- Unwilling to take warfarin

## Managing patients taking novel oral anticoagulants

If you have made the decision to initiate a novel oral anticoagulant, make sure it is the most appropriate oral anticoagulant for your patient and that any medicines that increase the bleeding risk, such as low molecular weight heparin, antiplatelet therapy, aspirin or NSAIDs have been ceased or their continuation has been carefully considered.<sup>5-7, 18-20</sup>

If you have made the decision to switch your patient from warfarin to a novel oral anticoagulant, monitoring of the patient remains crucial. Although routine laboratory monitoring is not suitable for dose adjustment, the importance of regular clinical monitoring of the patient cannot be over emphasized.<sup>10,23</sup> This is of particular importance during the early stages of treatment as patients may differ from those included in trial

populations and adverse effects may be unpredictable.<sup>3</sup> Regular clinical review with the patient will enable opportunities to closely reassess for bleeding risk, reinforce key aspects of treatment such as adherence and assess tolerability.<sup>11</sup>

**When prescribing dabigatran, consider if patients have cognition/dexterity problems, as it should be dispensed and stored in the manufacturer's original packaging until taken. It should not be repackaged into any dosage administration aids, including pill boxes. The capsules must not be opened, broken or chewed as this may increase the risk of bleeding and should be swallowed whole with a full glass of water.<sup>5,24</sup>**

All novel oral anticoagulants require dose reduction depending on renal function.<sup>10,11</sup> Assess renal function at initiation of treatment and at least annually thereafter. Assess renal function more often in patients receiving dabigatran or in patients potentially at risk of declining renal function, such as frail or elderly people or where a decline in renal function may be suspected.<sup>11</sup> Assess current liver function as a baseline prior to commencing any of the novel oral anticoagulants, especially if there is suspicion of hepatic dysfunction, as it is not recommended to commence patients with significant liver disease on any of the novel oral anticoagulants.<sup>5-7</sup>



## Educating patients taking oral anticoagulants

Evidence suggests patients who have a poor understanding of their anticoagulant therapy are at an increased risk of bleeding complications and poor anticoagulant control. Educating patients to include fundamental aspects of their treatment such as recognising signs and symptoms of bleeding and when to report them, and the importance of adherence to dosing and regular monitoring may reduce bleeding complications.<sup>25</sup> Encourage your patient to carry details of their anticoagulant therapy with them at all times.<sup>11</sup>

No matter what oral anticoagulant you choose for your patient, the importance of regular monitoring and frequent reviews in managing a potentially complex patient population cannot be over emphasised.

To report a medicine-related adverse event go to: <http://www.tga.gov.au/hp/problem.htm>

For further information regarding dose adjustment of novel oral anticoagulants, see the 'Australian Medicines Handbook'.<sup>8</sup>

**Consider a Medicines Review\* by an accredited pharmacist for your patient receiving oral anticoagulants.**

HMRs have been shown to significantly reduce the likelihood of hospitalisation due to bleeding in patients taking warfarin. High risk patients taking any anticoagulant will benefit from a HMR.<sup>26</sup>

**To get the best out of a Medicines Review, include all relevant clinical information and clearly state the purpose and specific medicine-related problem/s you wish to be addressed in your referral (see insert).**

\*Home Medicines Review (HMR) or Residential Medication Management Review (RMMR)



Full reference list available on the MATES website at: [www.veteransmates.net.au](http://www.veteransmates.net.au)



# Medicines Review for patients prescribed anticoagulants

Over the next few months, accredited pharmacists may receive Medicines Review referrals\* as a result of the latest release of Veterans' MATES. The therapeutic brief provides detailed information about warfarin and the recent extension of PBS listing for novel oral anticoagulants (NOACs), and highlights important considerations for use of these medicines.

With the recent expanded availability of the novel oral anticoagulants, GPs may be reviewing their patients who are prescribed warfarin. Regardless of anticoagulant type, patient education is vital in maximising the benefits of therapy while minimising the risk of bleeding. For patients prescribed warfarin, having a Home Medicines Review (HMR) can delay the time to next hospitalisation for bleeding.<sup>1</sup> Therefore, in the latest Veterans' MATES we have highlighted to GPs their patients who are prescribed anticoagulants and asked them to consider a medicines review for these patients.

If you do receive such a referral, consider the points below as part as your review process. It is likely that the patient's GP will value concise feedback that includes any education provided to the patient, and your assessment of whether the patient is stable on current therapy, or is experiencing any difficulty with adherence so may benefit from further support.

If no problems are identified through the review, this is important information that should also be outlined in your feedback to the GP.

The patient will have received a veteran brochure, highlighting what they need to know about new medicines (such as the risks and benefits of treatment) as well as vital information about anticoagulant medicines in particular.

The therapeutic brief, veteran brochure and this document is available on the Veterans' MATES website.

[www.veteransmates.net.au](http://www.veteransmates.net.au)

HMRs can improve health outcomes for members of the veteran community.<sup>2</sup> Thank you for your work with veterans, we hope this information helps you respond to a GP's medicine review referral for patients prescribed an anticoagulant.

\*Either Home Medicines Review (HMR) or Residential Medication Management Review (RMMR)

## Points to consider when conducting a Medicines Review for a patient prescribed an anticoagulant:

- Patients' understanding of the need for the anticoagulant, how the anticoagulant works, risks and benefits of treatment, duration of treatment and nature of monitoring needed
- Highlight the importance of being aware of the signs and symptoms of bleeding, how to manage minor bleeds, and when to call the doctor or seek emergency care – mention steps that the patient can take to minimise risk of physical trauma such as reducing the risk of falls
- The patient's adherence – highlight the importance of adherence with therapy, what to do if a dose is missed, the possible effects of poor control of anticoagulation (this can be catastrophic in some situations e.g. after a PE or valve replacement), and emphasise the need for continuity of supply of the anticoagulant
- Look for potential interactions with other prescribed, complementary or over-the-counter medicines – highlight the importance of asking their GP before starting any new medicine
- Highlight the importance of telling all health professionals about anticoagulant use and ensure the patient understands the need to seek advice about anticoagulation use in the period leading up to elective surgery or procedures, including before dental work
- Suggest keeping identification that states anticoagulant use in case of an accident or an emergency – reinforce importance of keeping an up-to-date medicines list
- Explain the importance of minimising alcohol consumption
- Special considerations – what to do in the event of illnesses such as episodes of diarrhoea or vomiting, or when making travel plans etc.





## If the patient is prescribed warfarin:

- Explain the international normalised ratio (INR), ensure the patient is aware of their target INR and reinforce the need for regular testing
- Discuss an INR diary and the importance of noting missed doses
- If inconsistent INR results are noted, discuss possible correctable causes including concurrent medicines, poor adherence, alcohol consumption, inconsistent diet, concurrent illness; report to the patient's GP where these causes may be corrected
- Outline the role of vitamin K and the importance of consistency in diet.

Following media coverage about the release of the novel oral anticoagulants (NOACs), patients may ask you about these medicines. Reinforce, if necessary, that if they are stable on warfarin, it may still be the best treatment for them and that the new medicines may not be suitable for a variety of reasons.

*Refer to the therapeutic brief and veteran brochure.*

## If the patient is prescribed a novel oral anticoagulant:

- Reinforce that although they do not require INR tests, it is recommended that they still have regular check-ups with their GP, and that they need to have their kidney and liver function tested every 12 months
- Explain that as these are new medicines, some side effects and interactions with other medicines may yet to be discovered; reinforce the need to report any unusual symptoms to their GP
- Highlight that there is no specific antidote for these medicines but treatment is available in the case of bleeding
- Reinforce the importance of being vigilant to the early signs and symptoms of bleeding
- Highlight the importance of adherence, as these medicines are shorter acting
- Reinforce special instructions for use of each medicine; identify whether the patient may have trouble following these instructions due to visual, physical or cognitive impairment
- If the patient is prescribed dabigatran (Pradaxa) – highlight the effects of exposure to air and thus special storage requirements, not crushing or breaking tablets, and the importance of not removing from the original blister pack or bottle for use in dose administration aids or pill boxes.

## Further information

- NPS consumer information on warfarin and anticoagulants [www.nps.org.au/medical-info/consumer-info/warfarin-apixaban-eliquis-dabigatran-pradaxa-and-rivaroxaban-xarelto-anticoagulants-and-how-to-take-them](http://www.nps.org.au/medical-info/consumer-info/warfarin-apixaban-eliquis-dabigatran-pradaxa-and-rivaroxaban-xarelto-anticoagulants-and-how-to-take-them)
- NPS MedicineWise Medicines List [www.nps.org.au/medical-info/consumer-info/keeping-a-medicines-list](http://www.nps.org.au/medical-info/consumer-info/keeping-a-medicines-list)
- NPS consumer information on warfarin [www.nps.org.au/medical-info/consumer-info/warfarin](http://www.nps.org.au/medical-info/consumer-info/warfarin)
- The Warfarin Patient Information booklet (copies can be either downloaded or ordered) [www.aspenpharma.com.au/resources/index/warfarin](http://www.aspenpharma.com.au/resources/index/warfarin)
- Home Medicines Review <http://www.5cpa.com.au/initiatives-programs/medication-management/home-medicines-review>

## References

1. Roughead EE, Barratt JD, et al. Collaborative home medicines review delays time to next hospitalization for warfarin associated bleeding in Australian war veterans. *Journal of Clinical Pharmacy and Therapeutics* 2011; 36: 27-32.
2. Roughead EE, Barratt JD, et al. The effectiveness of collaborative medicine reviews in delaying time to next hospitalisation for heart failure patients in the practice setting: results of a cohort study. *Circulation: Heart Failure* 2009; 2(5): 424-8.