

# How to manage warfarin therapy

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## Key words

anticoagulants, INR, point-  
of-care services, warfarin

*Aust Prescr* 2015;38:44–8

Corrected 29 February  
2016

Correction notice  
available at:

[http://dx.doi.org/10.18773/  
austprescr.2016.027](http://dx.doi.org/10.18773/austprescr.2016.027)



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continuing-professional-  
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## SUMMARY

Long-term treatment with warfarin is recommended for patients with atrial fibrillation at risk of stroke and those with recurrent venous thrombosis or prosthetic heart valves.

Patient education before commencing warfarin – regarding signs and symptoms of bleeding, the impact of diet, potential drug interactions and the actions to take if a dose is missed – is pivotal to successful use.

Scoring systems such as the CHADS<sub>2</sub> score are used to determine if patients with atrial fibrillation are suitable for warfarin treatment. To rapidly achieve stable anticoagulation, use an age-adjusted protocol for starting warfarin.

Regular monitoring of the anticoagulant effect is required. Evidence suggests that patients who self-monitor using point-of-care testing have better outcomes than other patients.

## Introduction

Warfarin is recommended for the prevention of systemic embolism, stroke associated with atrial fibrillation, and venous thromboembolism (Table 1).<sup>1</sup>

Its use is limited by several factors including a narrow therapeutic range, and drug–drug and drug–food interactions. Bleeding, particularly in the setting of over-anticoagulation, is a major concern.

The decision to start warfarin therapy requires an assessment of its harms and benefits for each patient. This assessment should take into account the patient's medical, social, dietary and drug history, level of education and adherence to previous therapy.<sup>2</sup> While the risk of falls plays a part in the harm–benefit assessment, published data indicate the propensity to fall is not an important factor in this decision.<sup>3</sup>

Educating the patient is essential before they start warfarin. This includes informing them about the signs and symptoms of bleeding, the impact of diet, potential drug interactions and actions to take if a dose is missed.

The safety and efficacy of warfarin is critically dependent on maintaining the INR within the target range. Patients must agree to undergo regular blood tests during treatment.

## Stroke prevention

In patients with non-valvular atrial fibrillation, the decision to start warfarin should be based on the CHADS<sub>2</sub> score. This assigns 1 point each for congestive heart failure, hypertension, age 75 years and older, and diabetes mellitus, and 2 points for previous ischaemic stroke or transient ischaemic attack.<sup>1</sup>

The CHADS<sub>2</sub> score reliably identifies patients at intermediate and high risk of stroke, but less reliably identifies those truly at low risk.<sup>4</sup> Anticoagulation with

warfarin is recommended if the CHADS<sub>2</sub> score is  $\geq 2$  and should be considered if the score is 1.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Table 2),<sup>5</sup> introduced by the European Society of Cardiology, provides a more comprehensive assessment of the risk factors for stroke. It is better at identifying 'truly low-risk' patients with atrial fibrillation, and is now preferred over CHADS<sub>2</sub>.

The HAS-BLED score (Table 2)<sup>5</sup> has been developed to determine the risk of bleeding. Scores range from 0 to 9. Scores  $\geq 3$  indicate a high risk of bleeding, the need for cautious management and regular review of the patient. It is not the intention to use HAS-BLED scores to exclude warfarin, but to allow the clinician to identify risk factors for bleeding and to correct those that are modifiable.<sup>6</sup>

## Optimising warfarin management

A patient's response to warfarin is driven primarily through genetic variance in the hepatic clearance, and vitamin K handling. Diet, age and dose also influence the anticoagulant effect. Assessing the response is complicated by a delay of 2–3 days before the INR reflects any changes in warfarin dose.

## Starting warfarin

When commencing warfarin it is important to measure the baseline INR. If this is 1.4 or above, without warfarin, liver function and nutrition status should be assessed and specialist advice sought regarding the patient's suitability for anticoagulation with warfarin.

Warfarin is usually started with loading doses. The Fennerty warfarin loading protocol published in 1984 was efficient in the relatively young population tested, but it was subsequently shown to cause significant over-anticoagulation in the elderly.<sup>7,8</sup> Another protocol,

Table 1 Indications, goals and duration of warfarin therapy <sup>1</sup>

Indication	Target INR (range)	Duration of therapy
Deep vein thrombosis of the leg or pulmonary embolism	2.5 (2.0–3.0)	At least 3 months
<b>Atrial fibrillation or flutter</b>		
Intermediate to high risk of stroke	2.5 (2.0–3.0)	Indefinite
Elective cardioversion	2.5 (2.0–3.0)	3 weeks before scheduled cardioversion and for 4 weeks after successful cardioconversion
Mitral stenosis	2.5 (2.0–3.0)	Indefinite
After stent placement and high risk of stroke	2.5 (2.0–3.0)	Bare-metal stent (1 month) and drug-eluting stent (3–6 months) as triple therapy with clopidogrel and aspirin After initial triple therapy, continue warfarin and a single antiplatelet drug until 12 months after stent placement After 12 months, use warfarin alone
<b>Valvular heart disease</b>		
Rheumatic mitral valve disease	2.5 (2.0–3.0)	Long term
Mechanical prosthetic heart valves	Bileaflet or tilting-disk valves: 2.5 (2.0–3.0) in the aortic position and 3.0 (2.5–3.5) in the mitral position	Long term Recommended to use aspirin in addition, 50–100 mg daily, if low bleeding risk
Bioprosthetic valves in the mitral position	2.5 (2.0–3.0)	3 months after insertion

Table 2 Scoring systems for assessing the risk of stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc) and bleeding (HAS-BLED) in patients with atrial fibrillation <sup>5</sup>

CHA <sub>2</sub> DS <sub>2</sub> -VASc	Score	HAS-BLED	Score
Congestive heart failure	1	Hypertension (systolic blood pressure >160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function (1 point each)	1 or 2
Age ≥75 years old	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency/predisposition	1
Stroke/transient ischaemic attack/thromboembolism	2	Labile INRs (if on warfarin)	1
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1	Elderly (e.g. age >65 years old)	1
Age 65–74 years old	1	Drugs or alcohol (1 point each)	1 or 2
Sex category (i.e. female sex)	1		
Maximum score	9	Maximum score	9

based on the Fennerty protocol, decreased the loading dose with increasing age. This age-adjusted protocol (Table 3\*)<sup>9</sup> recommends a 10 mg starting

dose for patients aged 50 years and under, decreasing to 6 mg for patients over 80 years old.

The age-adjusted protocol was superior to the Fennerty protocol and to empirical prescribing.<sup>8</sup>

Patients more rapidly achieved a stable INR, had fewer results above 4.0 during the initiation phase and fewer doses withheld due to rapidly rising INRs.<sup>8,9</sup>

\* Table 3: Age-adjusted protocol for starting warfarin. See online with this article at [www.australianprescriber.com/magazine/38/2/44/8](http://www.australianprescriber.com/magazine/38/2/44/8)

Warfarin can be safely started in the community setting, but a recognised initiation protocol should be used. Even purportedly 'safe' starting doses of 5 mg represent a large loading dose for a patient who requires a maintenance dose of only 1–2 mg, and can lead to marked over-anticoagulation in a few days if INRs are not monitored. There is generally a significant movement in INR on the third or fourth day after starting warfarin, regardless of whether an initiation protocol is adhered to, or a 'safe' dose of 5 mg is used.

When possible, a single strength warfarin tablet should preferably be prescribed so that doses are multiples of one tablet.<sup>10</sup> Patients should take their warfarin once a day at the same time in the evening, with INR testing in the morning. The INR should be measured daily for the first five days.

### Maintenance therapy

Once the patient has had two consecutive INRs in the target range, the INR can be measured at increasing intervals depending on its stability. Once the dose and INR are stable, patients can usually be well controlled with 4–6-weekly testing, but some patients will require more frequent testing. Dose adjustment is not required for minor INR fluctuations, if the result remains within the patient's target range.

When adjusting maintenance doses for high or low INR values, it is important to think in terms of adjusting the dose as a percentage-based change. There is a reasonable linear relationship between dose and INR response during maintenance dosing, so a 10% dose increase will result in an increase of approximately 10% in the INR.<sup>11</sup> A 1 mg increment is a major adjustment for a patient normally receiving 2 mg daily (50% adjustment), and would result in a major INR change, but not for a patient receiving 10 mg daily (10% adjustment). Table 4 gives an example of the dose changes that may be needed to maintain the INR within a target range of 2–3.

For INR  $\geq 5$  follow the Australian consensus guidelines.<sup>12</sup> In all cases of out-of-range INRs, possible causes for altered INR should be considered to

determine if they are reversible. For example, if the INR has been elevated by antibiotics it can be expected to fall when the course is finished. This can be factored into the dosing and monitoring requirements.

Warfarin is subject to multiple interactions including:

- diet – for example beetroot, liver, green leafy vegetables (decreased INR)
- drugs that may increase INR – macrolide antibiotics, imidazole antifungals, sulfamethoxazole/trimethoprim, amiodarone, statins, some non-steroidal anti-inflammatory drugs
- weight loss or weight gain
- excess alcohol.

The risk of bleeding is minimised by regularly monitoring the INR, and ensuring the patient understands the action of warfarin and how to recognise the signs of bleeding. Patients should have their INR checked after any dose changes, the addition of any potentially interacting drugs, or dietary changes.

To prevent INRs outside of target range:

- consider potential warfarin–drug interactions
- wait at least 48 hours before testing INR after any change of dose, as earlier testing will not reflect the full response to the dose adjustment
- if INR drifts below the target, avoid excessive increases in dose
- provide ongoing patient education.

Although bleeding can occur in the target range, the risk increases with a rising INR. Elevated INRs between 4.5 and 10, and not associated with bleeding or a high risk of bleeding, can be safely managed by withholding warfarin and carefully monitoring the INR. Vitamin K<sub>1</sub> can be given orally or intravenously to reverse the effect of warfarin in patients with INRs above 10 or those with bleeding or a high risk of bleeding. In patients who are not actively bleeding, it is important to avoid overtreatment as this will make it difficult to re-establish control of the INR. The initial intravenous dose of vitamin K should

Table 4 Suggested dose changes for maintaining INR within a target range of 2–3

INR	Dose change
<1.5	Increase by 20%
1.6–1.9	Increase by 10%
3.1–3.4	Decrease by 10%, adjustment may not be necessary
3.5–3.9	Decrease by 20%, consider holding one dose
4.0–4.9	Hold dose until INR returns to range then decrease by 20–30%

probably not exceed 0.5–1 mg. If immediate reversal is required, prothrombin complex is preferred to fresh frozen plasma.<sup>12</sup>

### Warfarin management strategies

Approaches for managing patients taking warfarin include:

- usual care by the GP
- patient self-monitoring
- laboratory care program.

Anticoagulation clinics coordinate and optimise the delivery of anticoagulant therapy by providing specialised monitoring and management. Patients treated in anticoagulation clinics spend more time in the therapeutic range (50.4% vs 35%). They also experience less significant bleeding (8.1% vs 35%), major or fatal bleeding (1.6% vs 3.9%) or thromboembolic events (3.3% vs 11.8%).<sup>13</sup> In general practice it should be possible to have patients within the therapeutic range 60% of the time.

Some centres use computer-assisted warfarin dosing.<sup>14</sup> This assists in achieving a stable state of anticoagulation faster, and increases the overall percentage of time in the target range, potentially reducing the frequency of testing. It also reduces the risk of bleeding and thromboembolic events and is more cost-effective than manual dosing using clinical assessment.<sup>15</sup>

### Point-of-care testing

Point-of-care testing of the INR can be done in general practice, in other locations such as pharmacies, or by the patients themselves (known as self-monitoring). These approaches are more convenient for patients than visits to an anticoagulation clinic in a pathology practice or in a hospital.

The convenience of self-monitoring can be extended further to a model of self-management. Patients use algorithms to determine any necessary dose adjustments following INR measurement.<sup>16</sup> Evidence supports the practice of self-monitoring, with or without self-management, but an essential prerequisite is the ability of the patient to correctly, competently and safely use the testing devices.<sup>17</sup>

A number of randomised controlled trials of both self-monitoring and self-management have been included in systematic reviews and meta-analyses.<sup>16,18–20</sup> In three systematic reviews, self-monitoring and self-management had similar results to routine care in a hospital clinic. Patients undertaking self-monitoring had significant reductions in thromboembolic events and death, with more time in the target range, compared to those who did not self-monitor.<sup>18–20</sup> A further systematic review of 22 randomised controlled trials showed similar results including a 26% reduction in death.<sup>21</sup> A recent meta-analysis also found that patients who self-monitored had a reduced risk of thromboembolic events.<sup>16</sup>

Few studies have compared INR point-of-care testing by GPs with laboratory testing. A systematic review included three studies, but none showed improvements in the proportion of patients within the target range.<sup>22</sup>

An Australian trial of point-of-care testing in general practice included INR testing as well as other tests. While it showed improvements in glycated haemoglobin (HbA1c) and some lipid profiles, there was no such improvement for anticoagulated patients.<sup>23</sup>

There is evidence of a poor understanding of INR testing, including therapeutic guidelines, among physicians and GPs in several countries, including Australia.<sup>24</sup> The possibility remains that the improved outcomes achieved by self-management may be because patients more consistently follow therapeutic guidelines, especially if they manage their doses using software algorithms.

### Conclusion

Warfarin can be a challenging drug to manage, but if used appropriately it can be effective for the prevention of systemic embolism, stroke associated with atrial fibrillation, and venous thromboembolism. Regular monitoring and good patient education are important for successful treatment. ◀

*Conflict of interest: none declared*

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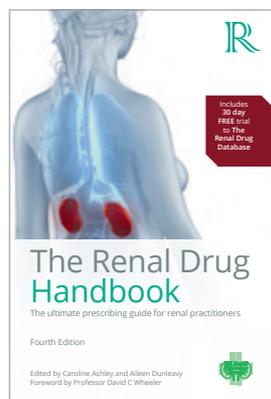
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## Book review

### The Renal Drug Handbook. 4th ed.

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Ashley C, Dunleavy A  
London: Radcliffe Publishing; 2014.  
1016 pages  
Also available in online database format  
[www.renaldrugdatabase.com](http://www.renaldrugdatabase.com)

This handbook provides detailed drug information to assist healthcare professionals to safely dose medications in patients with kidney disease. It is also available online which I suspect will extend the readership from predominantly renal pharmacists to other groups.

The Preface outlines how to use the monographs and basic drug dosing advice including valuable information on the use of estimated glomerular filtration rate (eGFR).

Over 800 drug monographs are arranged in alphabetical order, making navigation easy. Each monograph has a standard format, which includes information about the drug's clinical use, its dose in normal renal function, and its pharmacokinetics and metabolism. If a dose reduction is required in renal impairment, the dose is given either in milligrams with

the appropriate frequency, or as a percentage of the normal dose. Dosing for patients undergoing renal replacement therapies is also included. If relevant, other useful information about drug interactions, administration, adverse effects more commonly seen in patients with kidney impairment and monitoring is also included.

The section on pharmacokinetics is particularly useful as it gives the prescriber access to information so that first principles can be applied. Although I would like to have seen more referencing within the individual monographs, a list of texts and websites is included in the Preface.

One limitation is that the handbook is a UK publication so some of the drugs and dosing recommendations are not relevant to the Australian situation. Perhaps a consideration for future editions might be to include some general comments on the use of various drug classes in patients with renal disease.

Overall I applaud the authors for updating this publication, which is an extremely useful resource for guiding prescribing in patients with kidney impairment.