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Therapeutic brief 17

The S.A.F.E approach to warfarin therapy

Warfarin is effective in preventing thrombo-embolism in a range of conditions, including stroke associated with atrial fibrillation (AF).[1] During 2006-2007, five percent of veterans were prescribed warfarin.[2] Warfarin therapy presents several challenges arising from its bleeding risk and other complex issues. This therapeutic brief aims to optimise warfarin therapy, by considering;

- (S) Selection of patients for warfarin therapy by assessing individual risk/benefit.
- (A) Awareness of factors influencing warfarin effect.
- (F) Frequent monitoring of international normalised ratio (INR).
- (E) Education for patients - essential for safe and effective warfarin therapy.

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Key points

- Warfarin is recommended in patients with AF at moderate to high risk of ischaemic stroke, unless contraindicated. Target INR is usually 2 to 3.
- Age alone is not a contraindication to warfarin but older patients often require lower doses to achieve a therapeutic level of anticoagulation, and more frequent monitoring of INR.
- Older patients, especially those over 75 years, are at increased risk of AF and related stroke, but at the same time are at increased risk of warfarin-associated bleeding. Individual risk/benefit must be considered.
- Starting, stopping or changing the dose of many other medicines, changing diet, and the effects of acute or chronic illness necessitate more frequent INR testing.
- The need for anticoagulation should be re-evaluated regularly, as individual risk factors change over time.
- Patients need systematic education about the risks and benefits, adverse effects and monitoring requirements.

(S)election of patients

Patient selection for warfarin therapy must assess the risks of a thromboembolic event, such as stroke, and of major bleeding.[3] Factors such as relative and absolute contraindications to warfarin, patient preference and ability to comply with treatment and monitoring should also be taken into account.

Assessing stroke risk in AF

One of the most frequent indications for anticoagulation is reducing the risk of stroke related to non-valvular AF. In this setting, warfarin has been shown to confer a relative risk reduction of 64% compared with control. Without anticoagulation, the overall risk of stroke in this setting is about 5% per year, but is also influenced by increasing age and accumulates with the presence of additional risk factors.[3,4] Stroke risk in patients with AF should be regularly reassessed to guide appropriate therapy.

Warfarin should be considered for the primary and secondary prevention of ischaemic stroke in patients with AF at moderate to high risk of thromboembolic stroke[3,4]. Aspirin is an alternative in those with contraindications to warfarin or a high bleeding risk, but is less effective (relative risk reduction of 22%).[1] For patients at low risk of stroke, aspirin alone is recommended.[3,4]

Recommendations for antithrombotic therapy in patients with AF are summarised in Figure 1.

Figure 1: Recommended antithrombotic therapy for patients with atrial fibrillation [4]

Risk factors	Recommended therapy
AF with no risk factors	aspirin (100 - 300mg/day)*
AF with one of the following moderate-risk factors: • Age ≥ 75 years • Hypertension • Heart Failure • Congestive Heart Failure (ejection fraction ≤ 35%) • Diabetes mellitus	aspirin (100 - 300mg/day)* **or** warfarin (INR 2 to 3)
AF with any of the following high-risk factors: • Previous stroke, TIA or embolism • Mitral stenosis • Prosthetic heart valve **or** **AF with more than one of the following moderate-risk factors:** • Age ≥ 75 years • Hypertension • Heart Failure • Congestive Heart Failure (ejection fraction ≤ 35%) • Diabetes mellitus	warfarin (INR 2 to 3)

* Aspirin is available on the PBS in strengths of 100mg and 300mg.

Assessing bleeding risk on warfarin

Major bleeding rates on warfarin vary according to the indication and trial setting, but range between 1-4% in younger patients and up to 13.1 per 100 person-years in patients ≥ 80 years of age.[5] Predictors of major bleeding include high INR levels, increasing age, poorly controlled hypertension, serious concomitant disease, and previous cerebral ischaemia.[6-8] Polypharmacy, co-prescribing of warfarin with aspirin or NSAIDs, and social factors (dementia, tendency to fall) also contribute.[9,10] Various models have been developed to help predict those at higher bleeding risk, such as the Outpatient Bleeding Risk Index (Figure 2).[11-13] Using this model, the rate of major bleeding in AF has been reported at 2.2% (95% CI, 1.0-4.0) per patient-year of warfarin in the intermediate-risk group, and 12.3% (95% CI, 5.3-24.3) in the high-risk group.[12]

Figure 2: The Outpatient Bleeding Risk Index[11-13]

Bleeding risk factors	Points assigned
☐ Age ≥ 65 years	1
☐ History of stroke	1
☐ History of GI bleed	1
☐ Recent myocardial infarction ☐ Haematocrit < 30% ☐ Serum creatinine > 133 micromol/L (1.5 mg/dL) ☐ Diabetes mellitus	1 point maximum if any are checked
Bleeding risk group	**Total points assigned**
Low	0
Intermediate	1 to 2
High	3 to 4

Awareness of factors influencing warfarin effect

Many factors change the effect and safety of warfarin.

Age and warfarin dose

The elderly (especially those who are frail, have a low body weight, abnormal liver function tests or cardiac function, and other co-morbidities) are at risk of an unstable response to warfarin and may require lower initial doses.[14]

Drug-drug interactions

A comprehensive list of drug interactions with warfarin is available in the Australian Medicines Handbook.[15] Interactions with warfarin may be unpredictable and sporadic and generally involve either inhibition or induction of warfarin metabolism. Bleeding can also be mediated via potentiation of the antiplatelet effect of aspirin and NSAIDs. If possible, avoid drugs that have well-known interactions with warfarin. If another drug cannot be substituted, monitor INR more frequently.[16] A detailed description of these is beyond the scope of this brief, but several of these drugs encountered in general practice are noteworthy;

- **Most antibiotics**, but in particular co-trimoxazole, macrolides, metronidazole and quinolones, can increase the risk of bleeding.[15]
- **Selective serotonin reuptake inhibitors (SSRIs)** can increase risk of bleeding although INR may not be raised.[15,16]
- **Azole antifungals** may interact with warfarin. This includes a potential and often unrecognised interaction with miconazole oral gel.[17]
- **Amiodarone**, which inhibits the metabolism of warfarin and increases INR, has a very long half-life that may result in a delayed onset of the interaction and a very slow off-set of effect after it has been stopped.[16, 18]
- **Aspirin or NSAIDs**, which have been shown to increase the risk of GI bleeding when co-prescribed with warfarin[9] but do not increase INR.[5] Antiplatelet agents should generally not be combined with warfarin, except in some patients at very high risk of thromboembolism.[15]
- A number of **complementary and alternative medicines** may also have interactions with warfarin.[15]
- **Alcohol** in small to moderate amounts probably has little effect on warfarin, although heavy drinking can increase the risk of GI bleeding and falls.[16, 19]

Changes to diet. A balanced and consistent diet helps avoid fluctuation in vitamin K intake.

Intercurrent illness can affect INR levels, particularly conditions which affect liver function (including acute exacerbations of heart failure or COPD), thyrotoxicosis and infections. Vomiting or diarrhoea can affect absorption of dietary vitamin K. More frequent monitoring of INR is recommended until the patient's condition has stabilised.[15]

Frequent INR monitoring

Frequent monitoring is essential to ensure that the INR is within therapeutic range as often as possible and to guide warfarin dosing (Figure 3). A therapeutic range of 2.0 - 3.0 is recommended for most indications, including AF (but higher in patients with some artificial heart valves).[14] Major bleeding risk increases substantially when the INR is ≥ 4 and the risk of ischaemic stroke increases when the INR falls below 2. Optimal warfarin management requires accurate measurement of INR. The clinical value of Point of Care Testing in Australian general practice is currently being evaluated.[20]

Figure 3: Tips for INR testing

- ✓ Avoid warfarin if the patient is likely to be noncompliant with monitoring.
- ✓ Check INR (and platelet count and LFTs) before initiating warfarin and then check INR daily or second daily after initiation, adjusting the dose according to the INR.[14,15]
- ✓ Once INR is in the therapeutic range for 2 consecutive days, re-check every 3 to 5 days. When INR and warfarin dose have been stable for 1 week, check INR weekly. If stable for an additional 2 to 3 weeks, extend the testing interval to every 4 weeks.[21]
- ✓ Ensure a consistent time interval between dosing and taking blood for INR.
- ✓ Whether laboratory or Point of Care Testing is used, the method should be consistent.
- ✓ The effect of a change in warfarin dose may not be apparent for several days due to the relatively long half-life of warfarin. Therefore it is important not to change the dose too often.
- ✓ Monitor INR more frequently after any dose changes, stopping or starting other drugs, or intercurrent illness. Re-check INR 48-72 hours after the change in therapy.
- ✓ If consistent increases or decreases in the INR are noted, assess for possible causes and adjust the dosage. Increase the frequency of INR monitoring until the response is stable.
- ✓ Have a process in place for reviewing results and documenting and acting on any changes in dosing, in a timely manner.[22]
- ✓ An INR above 5.0 needs urgent intervention, especially in people with a high bleeding risk. Vitamin K may be required to reverse the effect of warfarin if INR is ≥ 5, or if there is major bleeding. Seek expert advice. Recommendations for the reversal of high INR values are available at https://www.mja.com.au/journal/2004/181/9/warfarin-reversal-consensus-guidelines[23]

4 Educating patients

Successful warfarin therapy requires patient participation in the initial decision making, as well as day-to-day management. Ideally, education should be systematic and ongoing. Messages about any dose changes should include **clear verbal and written instructions**.[22] Consider referring a patient for an Home Medicines Review (HMR) to aid education early in the course of warfarin treatment.

For more information, including interactions and contraindications, refer to the Australian Medicines Handbook 2008 and approved Product Information.

Veterans may be eligible for a subsidised Safety Alert Bracelet/Pendant (item no. AS16). The eligible person's doctor, specialist or registered nurse may organise the provision of the item by forwarding a completed D992 Direct Order Form to DVA. Direct Order Form available at: http://www.dva.gov.au/health-and-wellbeing/home-and-care/rehabilitation-appliances-program-rap

Points to discuss with your patient

- Explain how warfarin works and how it prevents clot formation and strokes.
- Explain why their dose of warfarin may change.
- Explain how the INR works and the need for frequent INR monitoring.
- Describe the common signs and symptoms of bleeding (and of thrombotic events).
- Stress the importance of notifying all their health care providers (doctors, pharmacists, dentists) that they are taking warfarin. Discuss the importance of wearing a Safety Alert Bracelet.
- Stress the importance of talking to their doctor or pharmacist before they start any other medicines (complementary and alternative medicines).
- Explain why it is important not to change the brand of warfarin.
- Specify when to take warfarin and what to do if a dose is missed.
- Discuss the need to limit alcohol consumption.
- Discuss the potential duration of therapy.

Adapted from Jaffer 2003[24]

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