Warfarin: balancing the benefits and harms

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Summary

The benefits of warfarin therapy are substantial in the prevention of arterial and venous thrombosis, and in the primary and secondary prevention of stroke related to non-rheumatic atrial fibrillation. The major risk of warfarin is bleeding, which can cause significant morbidity or mortality. If the bleeding risk is high then alternatives to therapeutic doses of warfarin may be considered, although their efficacy may be suboptimal and may not eliminate the risk of bleeding. Constantly review the patient's circumstances in order to weigh up the benefits and harms of treatment with warfarin.

Key words: anticoagulation, haemorrhage, thromboembolism.

(Aust Prescr 2004;27:88–92)

Introduction

Anticoagulation with warfarin significantly reduces the morbidity and mortality related to arterial and venous thromboembolism. For many patients the benefit is clear and the risk of harm is acceptable, so anticoagulation is indicated.

Almost 1.9 million out-of-hospital prescriptions for warfarin were dispensed in 2001. The cost to the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) of warfarin for the same period was $8.3 million. From Health Insurance Commission statistics coagulation tests numbered 2.5 million in the same year at a cost of $29.4 million. Most of these tests are for routine monitoring of warfarin therapy. There are therefore many patients taking warfarin, but the decision to use the drug and accept the adverse effects requires constant review.

Before prescribing warfarin, the risk of bleeding should be evaluated and discussed with each patient

Indications for warfarin therapy

There are published recommendations, with supporting levels of evidence, for warfarin therapy.[1,2] The major indications are for prophylaxis and treatment of venous thromboembolism and its extension, for example pulmonary embolism. Warfarin is also indicated for the prophylaxis of non-rheumatic atrial fibrillation in association with risk factors, particularly previous thromboembolism (transient ischaemic attack or ischaemic stroke), diabetes and hypertension. Warfarin is not indicated in patients with lone atrial fibrillation who are less than 60 years of age with no risk factors.

One of the most frequent indications for anticoagulation is reducing the risk of stroke associated with non-rheumatic atrial fibrillation, particularly in the elderly. The prevalence of atrial fibrillation approximately doubles with each advancing decade of age. Non-rheumatic atrial fibrillation is found in approximately 15% of all stroke patients.[3,4] The average stroke rate among patients with atrial fibrillation is 5% per annum. With the ageing population stroke prevention in atrial fibrillation will continue to be a significant management issue.

Contraindications to warfarin therapy

Contraindications to warfarin are any localised or general physical condition or personal circumstance in which the hazard of haemorrhage might be greater than the potential clinical benefit of anticoagulation. These include:

- haemorrhagic tendencies and blood dyscrasias
- recent or contemplated surgery of the central nervous system or the eye
- traumatic surgery resulting in large open surfaces.

Warfarin is contraindicated if the patient is unwilling or unable to comply with monitoring due to cognitive impairment, alcoholism, psychosis or problems with accessing services.

In the major interventional trials studying the efficacy of warfarin for stroke reduction in atrial fibrillation, patients considered at excessive risk of bleeding were excluded (Table 1). These exclusion criteria resulted in the recruitment of a fit group with only a very small sub-group of very elderly people, so there are inherent problems in extrapolating the study results into everyday practice.

Pregnancy

Warfarin is contraindicated during pregnancy, particularly during organogenesis (weeks 6–12). The risk of fetal bleeding remains throughout pregnancy due to the immature fetal liver.[2] Warfarin is not normally prescribed at any stage during pregnancy in Australia.

Table 1

Exclusion criteria used in the major intervention trials of anticoagulation for patients with atrial fibrillation [13,19]

Bleeding disorder or abnormal coagulation at baseline
Recent stroke or transient ischaemic attack (previous two years)
Uncontrolled hypertension (> 180/100 mmHg)
Active bleeding
Haemorrhagic retinopathy
History of intracranial haemorrhage
Use of non-steroidal anti-inflammatory drugs
Chronic alcohol abuse
Risk of gastrointestinal bleeding (active peptic ulcer disease, positive faecal occult blood testing, known oesophageal varices)
Planned surgery or invasive procedure
Pregnancy or breastfeeding
Psychiatric disorder or dementia
Expected poor compliance
Limited life expectancy
Significant renal dysfunction (creatinine > 0.25 mmol/L)
Platelet count < 100 x 10^9/L

Patients were also excluded if they refused to participate or if their doctor considered the risk of anticoagulation was too great.

Harm:benefit analysis in prescribing warfarin (Fig. 1)

The risk of major bleeding in the atrial fibrillation intervention trials was 1–4% per year, with an intracranial bleeding rate of 0.2–0.5% per year. The fatality rate mirrored the intracranial bleeding rate.[5] In observational studies of ambulatory patients the risk of major bleeding is 4–9% per annum.[6,7]

Major determinants of warfarin-induced bleeding include the intensity of anticoagulation, patient characteristics, the concomitant use of drugs that interfere with haemostasis, and the length of therapy.[5] Before prescribing warfarin the risk of bleeding should be evaluated and discussed with each patient.[8]

Intensity of anticoagulation and duration of therapy

The risk of bleeding increases dramatically when the International Normalised Ratio (INR) exceeds 4.0.[9,10] An INR greater than 4.0 is probably the most important risk factor for intracranial haemorrhage, independent of the indication for warfarin.[5]

The risk of major bleeding is greatest in the first month of therapy (3%) and decreases with time to 0.8% per month for the remainder of the first year and to 0.3% per month thereafter.[7]

Patient characteristics

Age

Atrial fibrillation is an increasingly important cause of stroke as patients get older. In the Framingham study the incidence of stroke due to atrial fibrillation increased from 1.5% for those aged 50–59 years to 23.5% for those aged 80–89 years.[11] The prevalence of atrial fibrillation in those over 80 years old reaches approximately 10%.[12]

The results of studies conflict on whether age is an independent risk factor for bleeding. Advanced age is not itself a contraindication to warfarin. Studies in atrial fibrillation support the ongoing benefit of anticoagulation with increasing age. Warfarin therapy reduces the risk of ischaemic stroke in patients with non-rheumatic atrial fibrillation from 7.4% to 2.3% per year.[13]

Age is, however, a risk factor for more unstable prothrombin time results. For every 10-year increase in age there is a 15% increase in the risk of anticoagulation having to be suspended because of a raised INR.[14]

Comorbidities and medication

Conditions associated with an increased risk of bleeding during warfarin therapy include treated hypertension, cerebrovascular disease, serious heart disease, renal insufficiency and malignancy.[5] Over time a person's comorbidities and medications accumulate. These increase the potential for interactions with warfarin.

The INR becomes unstable with the introduction, change in dose or suspension of many common drugs such as antibiotics. Warfarin and aspirin combinations are associated with a high frequency of bleeding, even when combined with 'low intensity' warfarin therapy.[5]

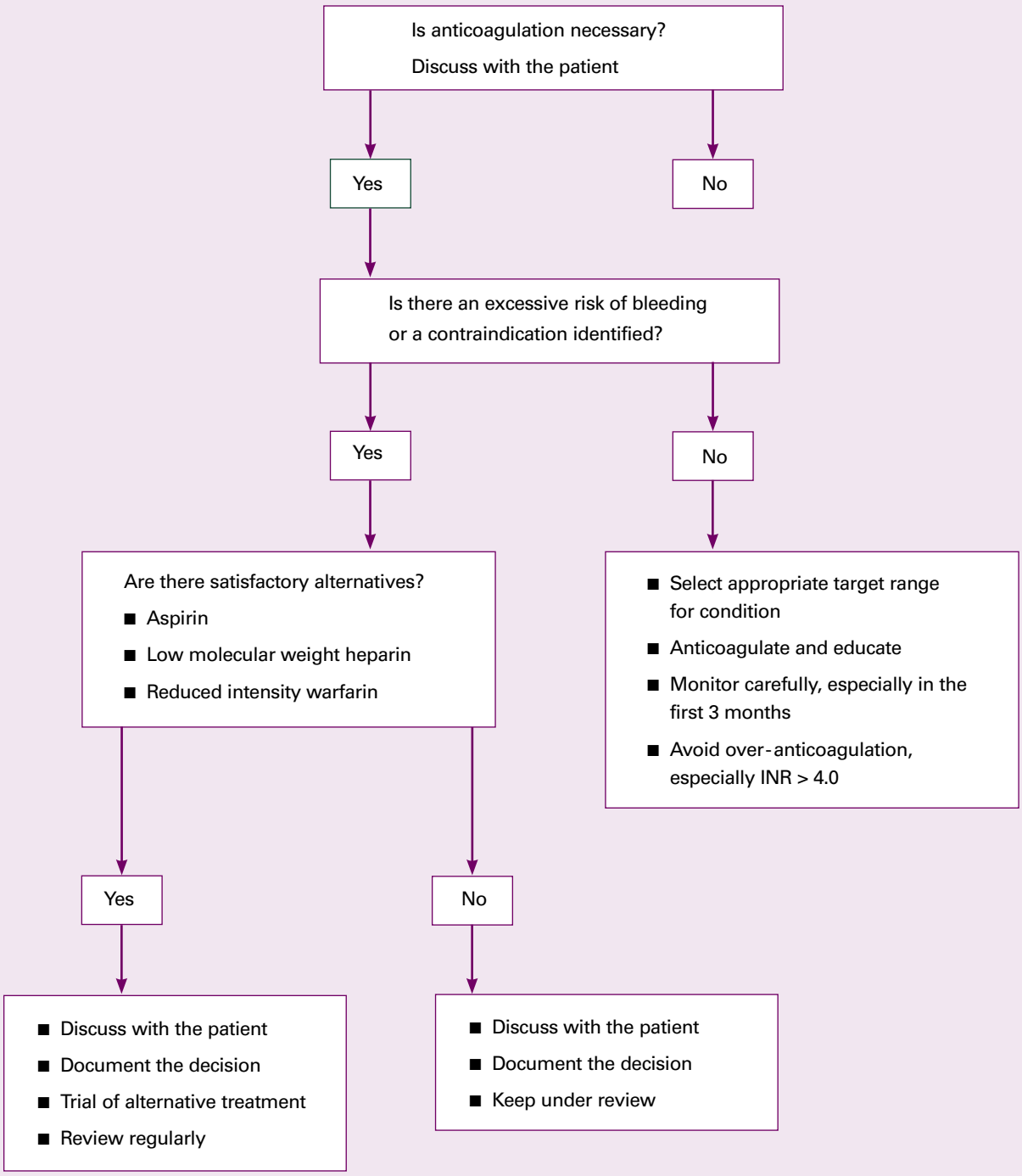
Some herbal preparations and large quantities of vitamin K-rich foods can also interfere with warfarin.[15] Many such interactions are unpredictable so the INR should be checked within a few days of any change. Poor nutrition results in a relative deficiency of vitamin K and increased sensitivity to warfarin. A temporary dose reduction and increased monitoring are essential during an acute illness.

Falls

Patients should be assessed for their risk of falls and possible causes. Where a cause is identified and reversible, for example postural hypotension, and can be ameliorated by a change in medication, anticoagulation can be maintained although careful monitoring of the patient is essential. If the falls continue then the patient should be reviewed and alternatives to warfarin considered.

Fig. 1

Defining the indication for anticoagulation therapy



A decision analysis model of the risks of central nervous system bleeding found that the propensity to fall is not a contraindication to the use of antithrombotic drugs (especially warfarin) in the elderly person with atrial fibrillation.[16] However, approximately 1 in 10 falls causes major injury, including fractures, and people who fall are much more likely to suffer other serious morbidity. There is insufficient evidence to know whether those who fracture a bone while on warfarin suffer greater morbidity and mortality.

There are factors that contribute to the risk of falls that may also have an impact on the ability to adhere to warfarin therapy and monitoring. These include cognitive and sensory impairment as well as poor mobility due to gait, balance and foot problems. Often the general practitioner will be aware of other problems in addition to falls that preclude the safe and reliable use of anticoagulation.

Change in patient status

Each new diagnosis, treatment or major change in the patient's condition, particularly with concomitant poor diet, requires a further assessment of the risks and benefits of oral anticoagulation. The goals of therapy need constant review and possible revision, particularly when anticoagulation is used for long-term prophylaxis as, for example, in atrial fibrillation. An emphasis on 'perfect' primary prevention may be inappropriate when the patient only has a limited life expectancy.

Gastrointestinal bleeding

A similar analytical model has also been used to balance the risk of stroke and gastrointestinal bleeding in older patients with atrial fibrillation.[17] For those with a significant risk of upper gastrointestinal bleeding or lower risks of stroke, warfarin is not clearly the optimal antithrombotic therapy. An 80-year-old with a baseline risk of stroke of 4.3% per year, who is concurrently taking a non-steroidal anti-inflammatory drug, has no difference in predicted outcomes with warfarin, aspirin or no treatment (quality-adjusted life-years of 7.44 for warfarin, 7.39 for aspirin and 7.21 for no treatment).[17]

What are the alternatives to oral anticoagulation?

If the target INR carries too high a risk of bleeding with the usual doses of warfarin, consider if the patient will benefit from other strategies.

Aspirin

When warfarin is contraindicated in patients with atrial fibrillation, aspirin should be given as it confers a 42% risk reduction compared to placebo.[13] This is inferior to warfarin and still increases the risk of bleeding (major bleeding rate of 1.4% per year[13]).

Reduced intensity regimens

Moderately sub-therapeutic levels of anticoagulation (INR 1.6–1.9) may still reduce the risk of stroke in patients with non-rheumatic atrial fibrillation[18] although a minimum INR of 2.0 is required if there is a history of prior stroke or recent transient ischaemic attack.[19] However, there is conflicting evidence about the efficacy and safety of reduced intensity regimens.

Previous studies of fixed low doses of warfarin showed low rates of major bleeding.[5] A more recent study of long-term, low intensity treatment with warfarin (INR target 1.5–2.0) for the prevention of recurrent thromboembolism also found low rates of major haemorrhage[6], while other research reported no difference in bleeding risk.[20] Another study has found that reduced intensity regimens result in more frequent strokes, that are more severe and lead to greater mortality, than regimens which aim for an INR greater than 2.0. This study found the stroke rate was no better than with aspirin and the bleeding complications were greater.[21] These findings suggest that the target INR should be at least 2.0.

Low molecular weight heparin

An alternative to warfarin is the extended use of low molecular weight heparin for venous thromboembolism. If there are problems with compliance or with recurrent wild fluctuations in the INR, low molecular weight heparin can be administered under supervision. It is important to measure renal function as accumulation occurs with renal impairment, particularly when the creatinine clearance falls below 30 mL/min.

Discontinuation of warfarin

Warfarin therapy should be discontinued when the risk of bleeding outweighs the potential benefit. Any decision to discontinue warfarin should only be made after discussion with the patient or carer. Once the decision is made the relevant clinical carers should be informed, and the reasoning and the harm:benefit analysis should be clearly identified and documented. This decision should be subsequently reviewed if clinical or social circumstances alter.

Future directions

New oral anticoagulants, particularly the oral direct thrombin inhibitors, appear promising. They are currently being evaluated for a variety of thrombotic disorders including atrial fibrillation.

Note

Two case studies accompany the electronic version of this article on the *Australian Prescriber* web site www.australianprescriber.com

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 105)

3. Old age is a contraindication to warfarin therapy.
4. The risk of bleeding increases dramatically with INR values above 4.0.