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Warfarin
Indications, risks and drug interactions

Background
Warfarin is a commonly used medication for the prevention and treatment of venous thromboembolism. It can be challenging for both the patient and the prescriber to manage at times.

Objective
To describe the mechanism of action of warfarin, and to discuss the indications for warfarinisation, the risks associated with warfarin use, and some of its drug interactions.

Discussion
The common indications for warfarinisation are atrial fibrillation, venous thromboembolism and prosthetic heart valves. Contraindications include absolute and relative contraindications, and an individualised risk-benefit analyses is required for each patient. There are many interactions with warfarin, including pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions can be monitored by using International Normalised Ratio levels. Pharmacodynamic interactions require knowledge by the prescriber to predict any interactions with warfarin, and International Normalised Ratio monitoring assists.

Keywords: warfarin; International Normalised Ratio; atrial fibrillation; venous thromboembolism; heart valve prosthesis

CPD

Warfarin is commonly used in general practice to treat and prevent thrombosis in a range of clinical settings. It acts by antagonising the action of vitamin K resulting in production of defective clotting proteins. It is cleared via the cytochrome P450 enzymes in the liver and is subject to interactions with a large number of drugs. It is extremely important to increase the frequency of International Normalised Ratio (INR) monitoring whenever a drug is started or stopped while a patient is on warfarin.

Mechanism of action and INR monitoring

Vitamin K is essential for the activation of certain clotting factors (II, VII, IX and X). In this process, vitamin K gets oxidised to vitamin K epoxide. There is a mechanism however, through which the vitamin K epoxide is recycled within the liver back to vitamin K. The enzyme involved is vitamin K epoxide reductase complex 1 (VKORC1) and this is the enzyme that is strongly inhibited by warfarin.[1] Administration of large doses of exogenous vitamin K will overcome the need to recycle vitamin K epoxide within the liver and will therefore reverse the effects of warfarin.

Following initiation of warfarin therapy, the liver produces defective clotting factors. However, the anticoagulant effect of warfarin will not be established until the pre-existing factors have been degraded through their natural metabolism. This process usually takes 5–7 days. In addition to interfering with the function of vitamin K dependent clotting factors, warfarin also interferes with the function of two important naturally occurring anticoagulant proteins (protein C and protein S). Because protein C and protein S have shorter half-lives than the clotting proteins during the initiation phase of warfarin treatment, it may have a procoagulant effect leading to clot extension. Patients with congenital deficiency in protein C or protein S are particularly vulnerable. For these two reasons it is important that until the full anticoagulant effect of warfarin is established, patients with pre-formed clots (for example pulmonary embolism or deep vein thrombosis) are covered with heparins.

Given the lack of predictability of an individual's INR in response to warfarin, it is recommended that the INR be monitored on a daily basis during the initiation phase. The frequency of monitoring can be

reduced to alternate days for a week upon achieving the therapeutic INR target. Once the INR is stabilised on a particular dose of warfarin, INR monitoring can be done on a monthly basis.

Indications for warfarinisation

The three most common indications for warfarin therapy are;
- atrial fibrillation (AF)
- venous thromboemolism (VTE), and
- prosthetic heart valves.

Atrial fibrillation

Atrial fibrillation is probably the most common indication for warfarin therapy in our community. There is a large body of evidence in the literature showing the high efficacy of warfarin in preventing ischaemic stroke in AF patients (60–70% relative risk reduction).[2,3] The target INR range is 2.0–3.0. It is important to realise that not all patients with AF need to be anticoagulated. A scoring system – the 'CHADS2' score – has been devised to help decision making regarding which patients with AF to warfarinise.[4] Patients score 1 point for having either of the following:
- **C**ardiac failure
- **H**ypertension
- **A**ge 75 years or more
- **D**iabetes mellitus
- and they score **2** points for prior history of **S**troke or transient ischaemic attack.

It is recommended that patients with a CHADS2 score of zero not be warfarinised. Patients with a score of 2 or more should be considered for warfarinisation if there are no contraindications (based on the risk-benefit ratio) and those with a score of 1 can either be treated with aspirin or warfarin.

Venous thromboembolism

The role of warfarin therapy in patients with deep venous thrombosis (DVT) or pulmonary embolism (PE) is twofold. In treating the current episode anticoagulation aims at limiting clot extension thus allowing the fibrinolytic system to resolve the clot, a process which may take up to 6 weeks. In this setting, parenteral heparins are used together with warfarin during warfarin initiation. The second aim of anticoagulation in venous thromboembolism is prevention of thrombus recurrence. For this reason, anticoagulation needs to continue for a period of time beyond what is needed to allow for clot resolution. Several factors need to be considered in order to decide on the appropriate length of anticoagulation (*Table 1*).

For an individual with a VTE episode, balancing the risk of VTE recurrence versus the risk of haemorrhage when deciding on how long to anticoagulate for can be difficult. In part, the difficulties arise from uncertainties in the literature regarding evidence based recommendations. Although there are recommendations within sources such as the Australian Medicines Handbook and Therapeutic Guidelines, these are simply guidelines, and there needs to be

Table 1. Pretreatment factors determining risk of VTE recurrence and duration of anticoagulation
Is the current episode a first event or a recurrence?
Is the VTE episode idiopathic or precipitated?
Does the VTE episode represent pulmonary embolism or deep vein thrombosis?
If deep vein thrombosis, is the thrombus limited to the calf veins or does it involve the proximal veins?
Are there detectable acquired or genetic thrombophilic disorders?

consideration of the risk and benefit for each individual patient.[5,6] *Table 2* gives an example of guidelines adopted by the American College of Chest Physicians (ACCP).[7]

In an attempt to further quantify the risk of recurrence for an individual following cessation of anticoagulation, markers such as the presence of residual venous thrombus and an elevated D-dimer level have been shown to provide additional value when weighing the risks and benefits of continuing long term anticoagulation versus cessation of therapy.[8,9]

Prosthetic heart valves

In the presence of a prosthetic heart valve, the aim of anticoagulation is prevention of valve thrombosis and systemic embolisation. The risk of major embolism without antithrombotic therapy has been shown to be around 4 per 100 patient years, and this risk is reduced to about 1 per 100 patient years with oral anticoagulation.[10] Therefore, patients with prosthetic heart valves need to be anticoagulated indefinitely. The target INR is 2.0–3.0 for aortic valve replacement in the absence of other risk factors for thrombosis (AF, previous embolism and low left ventricular ejection fraction). For prosthetic mitral valves or prosthetic aortic valves with risk factors the recommended target INR is 2.5–3.5.[11]

Table 2. The ACCP guidelines regarding duration of anticoagulation following VTE	
Clinical condition	**Recommended duration of anticoagulation**
First episode of DVT secondary to transient risk factors	3 months
First episode of idiopathic DVT	At least 6–12 months – consider indefinite anticoagulation
First episode of PE secondary to transient risk factors	At least 6 months
First episode of idiopathic PE	At least 6–12 months – consider indefinite anticoagulation
VTE in the presence of irreversible risk factors	At least 6–12 months – consider indefinite anticoagulation

In cases of life threatening bleeding (eg. intracranial haemorrhage) withholding anticoagulation is mandatory. Even in the highest risk patients, it is recommended that warfarin therapy be interrupted for up to 1–2 weeks following a major haemorrhage.[12,13] The decision concerning when to restart anticoagulation following such an event should be made on the basis of the likelihood of further bleeding compared to the risk of embolism should anticoagulation be stopped.

Contraindications to warfarinisation

The most obvious contraindication to warfarin therapy is recent haemorrhage. Bleeding tendencies due to congenital or acquired disorders of the clotting system are also important. The presence of severe liver disease may predispose to bleeding when warfarin is prescribed via a number of mechanisms including:

- the liver's inability to synthesise clotting proteins
- reduced clearance of warfarin
- the presence of concomitant thrombocytopenia due to portal hypertension
- the presence of oesophageal varices.

Traditionally, the risk of falls was perceived as a strong contraindication to warfarin treatment and this has been the basis on which many elderly patients were denied therapy. The history of a fall *per se* does not predict future falls, and many factors should be taken into account before withholding therapy, such as the patient's gait, degree of frailty and the presence of other risk factors for future falls. Whether to prescribe warfarin or not in a patient who has a history of falls should be made on an individual basis taking into account the risk-benefit ratio. Some literature suggests that the risk of falls does not outweigh the warfarin benefits.[14] Clearly, strategies which reduce the risk of falls (such as modification of the environment and stopping drugs which may precipitate falls) play a particularly important role.

Less obvious contraindications to warfarin are the inability to have INR determination, and difficulties with hearing, vision, and numeracy for patients who have to listen to alterations in dosage recommendations, and carry these out themselves without the support of carers or others.

Warfarin is teratogenic and should be avoided during pregnancy. This should be discussed with all women of childbearing potential. Heparins (both unfractionated and low molecular weight) can be prescribed during pregnancy and provide a safe alternative.

Drug interactions

Warfarin can potentially interact with a large number of drugs (approximately 250 according to MIM[15]). The interactions generally fall under two categories: pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions are those that involve the way the body handles warfarin, whereas dynamic interactions add to the 'blood thinning' effect of warfarin via a different mechanism (such as an antiplatelet effect). Importantly, pharmacokinetic interactions result in a change in the INR and are therefore easily monitored. This is unlike the situation with pharmacodynamic interactions where a patient may suffer from bleeding with no significant change in the INR. In this case, monitoring of the INR is not a useful predictor of bleeding and one has to therefore anticipate that such an interaction may occur based on knowledge of pharmacology. Many examples exist of drugs which were shown to lack an interaction with warfarin in a formal drug interaction studies in healthy volunteers, yet have been reported to produce an interaction in patients (eg. roxithromycin).[16,17]

Pharmacokinetic interactions

Warfarin is a racemic mixture of S and R isomers. The S isomer is five times more potent than the R isomer. It is important to realise that those two isomers are metabolised via two different pathways and that drug interactions affecting the S isomer are more important clinically because of its high potency. The S isomer is metabolised via the cytochrome P450 (CYP) 2C9 enzyme whereas the R isomer is metabolised via CYP 3A4. Knowledge of the effects of co-prescribed drugs on the activity of the CYP enzyme enables reasonable predictions on subsequent changes in the INR as follows:

- inhibitors of CYP2C9 (eg. metronidazole) may result in significant rise in the INR
- drugs which interfere with clearance of the R isomer (eg. dilitazem) may have a modest effect only on the INR
- drugs which interfere with the clearance of both isomers (eg. amiodarone) may profoundly increase the INR
- hepatic enzyme inducers (eg. some of the antiepileptics) may result in reduction in the INR if co-prescribed with warfarin.

The interaction between warfarin and antibiotics is commonly encountered in clinical practice, often resulting in an increase in the INR. There are a number of mechanisms for this interaction:

- some antibiotics may directly interfere with the clearance of warfarin as mentioned above
- antibiotics my affect the bacterial flora in the intestine thereby reducing the amount of vitamin K produced by the intestinal bacteria
- many patients who are prescribed antibiotics for infections have dietary changes that result in reduction of vitamin K intake
- the underlying condition for which the antibiotic is prescribed (eg. pneumonia) may alter the clearance of warfarin, increasing the INR.

In cases where there is a change in concurrent medications, the frequency of INR monitoring should be increased in order to pick up any changes in the INR early enough to enable dose adjustment before the development of an adverse event. We recommend measuring the INR within 3–7 days following changes in pre-existing medications. Subsequent monitoring must then be individualised taking into account a number of factors such as:

- trend in the INR change
- age of the patient
- nutritional status of the patient
- presence of comorbidities which may affect the INR (eg. liver disease)
- nature of the drug prescribed/stopped (eg. CYP enzyme inhibitors or inducers).

Pharmacodynamic interactions

Many drugs with an antiplatelet effect add to the 'blood thinning' effects of warfarin and can result in significant bleeding. Obvious examples of such drugs are aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDS). The problem with NSAIDS is further worsened by their tendency to cause peptic ulceration, thus creating a substrate for haemorrhage. Less obvious examples are drugs with anti-platelet effects that are prescribed for other indications such as selective serotonin reuptake inhibitors (SSRIs). Alternatively, drugs associated with falls in the elderly (eg. long acting benzodiazepines) can also increase the risk of bleeding with warfarin. Knowledge of such additional side effects of a drug is paramount in predicting interactions with warfarin.

Aids to discussion with patients

Discussing the issues of the risks and benefits of warfarinisation for conditions such as AF are complex. The clinician needs to keep in mind not only the evidence for benefit and risk, but also the impact of warfarin on the patient's lifestyle, compliance issues, ability to monitor INR and to report haemorrhage if it occurs. All of these are then impacted by the patient's own previous experiences, their health literacy, and sociocultural understandings. The patient's general practitioner is ideally placed to take these factors into account and individualise the explanation of risk and benefit. Decision tools[18,19] have been created and tested to simply advise regarding the risks and benefits of treatment, but have not received widespread adoption, and do not address the other complex issues in adopting the lifestyle change, which warfarinisation involves.

Key practice points

- In a patient with a pre-formed clot (eg. DVT or PE) parenteral anticoagulation should be co-prescribed with warfarin during the initiation phase treatment.
- Given the potential interaction between warfarin and a large number of other medications, it is important to increase the frequency of INR monitoring whenever there is a change in concurrent medications in a patient who is already stabilised on warfarin.
- Pharmacodynamic interactions do not lead to change in the INR.
- In patients with AF, the risk of thromboembolism can be assessed using the CHADS2 score. Patients with a score of 2 or more should be considered for anticoagulation.
- The duration of anticoagulation following a VTE episode should be determined on the basis of the likelihood of future VTE recurrence and the risk of haemorrhage with long term anticoagulation.

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