MOH CLINICAL PHARMACY PRACTICE GUIDELINES

ANTICOAGULATION - WARFARIN

Ministry of Health

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Anticoagulation
- Warfarin

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Statement of Intent

The contents of this publication are guidelines for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each healthcare professional is ultimately responsible for the management of his/her unique patient in the light of clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

Anticoagulation therapy is effective in preventing primary and secondary thromboembolic events. Warfarin, an oral anticoagulant, prevents the formation of blood clots, and if a blood clot has already occurred, it prevents further clot progression. Although Warfarin is an effective anticoagulant, due to its narrow therapeutic index and its interactions with many other drugs, both western and herbal, and food, patients on the drug have to be closely monitored to prevent any bleeding incidences.

These guidelines have been put together with the Asian population in mind. The workgroup has considered the smaller body weight of the Asian population when recommending the dosing of Warfarin and also included the possible Warfarin-herbal drug interactions. A section on frequently asked questions has also been incorporated.

I would like to congratulate the workgroup for coming up with these guidelines. I hope that all health professionals providing anticoagulation management service will find these guidelines useful in managing their patients on Warfarin therapy.

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DIRECTOR OF MEDICAL SERVICES

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1. INTRODUCTION

Oral anticoagulation therapy with warfarin is used for preventing and treating venous and arterial thrombosis and embolism. Whilst the benefits of treatment have been clearly documented, the high risk/benefit profile of oral anticoagulants is a major impediment to initiation of therapy.

Warfarin has a narrow therapeutic index, with bleeding as its most serious complication. Warfarin inhibits the enzyme vitamin K epoxide reductase, which is required for the carboxylation and activation of vitamin K dependent coagulation factors II, VII, IX and X.

The INR (International normalised ratio) measures the therapeutic effectiveness of warfarin and its bleeding risk. The target range for most clinical indications is kept at 2.0 to 3.0. However, this range should be adjusted according to the bleeding and thrombotic risks of each individual.

The INR is affected by patient's co-morbidities, diet and concurrent medications. Patient education and monitoring of INR are crucial to the optimisation of anticoagulation.

Despite the availability of published guidelines on anticoagulant management, there is a need to modify these guidelines for local practice. The recommendations draw on the proceedings of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy and are consistent with most other recently published guidelines such as the Scottish Intercollegiate Guidelines Network's (SIGN) Clinical Practice Guidelines and the Institute for Clinical Systems Improvement (ICSI) Health Care Guidelines for Anticoagulation Therapy. In view of the smaller body weight of Asian population and our tendency to consume herbal or traditional remedies, the workgroup has recommended a lower starting dose of warfarin when initiating therapy and emphasised on possible drug-herb / dietary interactions.

1.1 Who should use the Guideline?

In Singapore, patients on anticoagulation therapy are managed by the anticoagulation management service (AMS) comprising of pharmacists, nurse clinicians and doctors. This guideline is designed for the health professionals managing the AMS.

1.2 Objectives of the Guideline

1. To achieve effective anticoagulation within target INR range
2. To reduce complications of anticoagulation therapy
3. To improve patient understanding on the safe use of warfarin through patient education.

2. LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATION

Grade of Recommendation	Clarity of Risk/ Benefit	Methodological Strength of Support Evidence	Implications
1A	Clear	RCTs without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws)	Strong recommendation; likely to apply to most patients
1C+	Clear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under circumstances
2C+	Unclear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2C	Unclear	Observational studies	Very weak recommendations; other alternatives may be equally reasonable

3. INDICATIONS

3.1 Venous Thromboembolic (VTE) Disease [1,3,5,8,9,10]

Warfarin therapy should be continued for 6 weeks for patients with symptomatic calf vein thrombosis. Patients with proximal vein thrombosis with a precipitating cause such as surgery or immobilization should receive anticoagulation therapy for 3 to 6 months. Patients with idiopathic proximal vein thrombosis and or pulmonary embolism should receive anticoagulation therapy for at least 6 months **(Grade 1A)**.

Indefinite anticoagulant therapy is indicated for patients with more than one episode of idiopathic proximal vein thrombosis or for those with continuing pro-thrombotic risk factors **(Grade 1A)**.

3.2 Atrial Fibrillation [1,3,5,8,9,10]

Indefinite anticoagulation therapy is required for prevention of thromboembolic stroke and events **(Grade 1A)**. The benefits must be weighed against the risks. An alternative less effective option with lower risk is the use of anti-platelet drugs.

3.3 Prosthetic Heart Valves [1,3,5,8,9,10]

Indefinite anticoagulation therapy is required for prevention of thromboembolic stroke and events **(Grade 1C+)**.

3.4 Tissue Heart Valves [1]

Patients with newly replaced tissue heart valves should receive anticoagulation therapy for 3 months **(Grade 1C)**.

Patients with bioprostheses and atrial fibrillation (AF), previous embolism or severe left ventricular (LV) dysfunction should receive anticoagulants indefinitely **(Grade 1C+)**.

3.5 Myocardial Infarction [1]

Lifelong anticoagulation therapy is indicated for:

(i) Post-MI patients in persistent AF, lifetime **(Grade 1A)**. The benefits must be weighed against the risks.

(ii) Patients with LV thrombus should receive warfarin for at least 3 months **(Grade 2A)**.

4. CONTRAINDICATIONS

Anticoagulation therapy is contraindicated in any medical condition or personal circumstance in which the risk of haemorrhage is greater than the potential clinical benefits of anticoagulation.

4.1 Haemorrhage

Warfarin is contraindicated for patients with active haemorrhage, cerebral vascular haemorrhage (confirmed or suspected) and those with active bleeding disorder and bleeding lesions of the gastrointestinal, respiratory and urinary tracts.

4.2 Pregnancy

Warfarin crosses the placenta and foetal exposure to warfarin is associated with a characteristic embryopathy, CNS abnormalities, foetal bleeding and increased foetal loss. The incidence of warfarin embryopathy is greatest at 6-12 weeks of gestation. Warfarin also increases the risk of serious perinatal bleeding during delivery.

Warfarin should be avoided throughout the entire pregnancy especially during the first and third trimester.

4.3 Breast-feeding

Warfarin does not induce an anticoagulant effect in the breast-fed infant and is therefore not contraindicated for the nursing mother.

4.4 Miscellaneous

4.4.1 Hypersensitivity to warfarin or any component
4.4.2 Severe uncontrolled hypertension
4.4.3 Severe vasculitis
4.4.4 Recent (2-3 weeks) trauma (especially to the central nervous system)
4.4.5 Neurosurgical procedures
4.4.6 Aneurysms (cerebral or dissecting)
4.4.7 Blood dyscrasias associated with haemorrhage or thrombocytopenia

Caution is to be exercised if there is debility of any cause, dysfunction from primary or secondary hepatic disorders, and conditions associated with vitamin K deficiency.

5. DOSING AND MONITORING

5.1 General Principles of Warfarin Dosing

5.1.1 Loading dose for rapid induction of warfarin should be avoided. Warfarin (irrespective of INR) is not fully effective in the first several days of therapy because of a delayed decrease in several circulating clotting factors. Loading doses can increase a patient's risk of supra-therapeutic INR and make it more difficult to determine a steady-state dose.

5.1.2 The target INR for most conditions is 2 to 3. However, this range should be adjusted according to the bleeding and thrombotic risks of each individual.

5.1.3 While there is a significant increase in thromboembolism as INR values decrease below 1.7, the bleeding risk increases substantially at INR above 5. Clinical risk and past medical history should be considered in all dosing decisions.

5.1.4 Prescription and over-the-counter medications can adversely affect the INR response to warfarin. Herbal or natural remedies can change the INR response to warfarin and/or increase a patient's risk of bleeding. In these instances, additional monitoring may be needed. Please refer to table 7.1 and 7.2 for the drug-drug and drug-herb interactions respectively.

5.1.5 Food that contains moderate amounts of Vitamin K can decrease the INR response to warfarin. Patients should maintain a consistent diet. Please refer to table 7.3 for the vitamin K content in common foods.

5.2 Initiation and Maintenance of Warfarin Therapy

5.2.1 For patients with ongoing thrombosis, warfarin should be started concomitantly with low molecular weight heparin or standard heparin. Patients without active thrombosis but require warfarin for prophylactic indications, e.g. atrial fibrillation, can be initiated on warfarin alone.

5.2.2 Patients receiving warfarin for the first time should begin with 2mg to 5mg daily.

5.2.3 Lower warfarin doses should be considered for patients with any of the following factors:

i) Age greater than 75 years
ii) Multiple co-morbid conditions
iii) Low albumin levels and poor nutritional status
iv) Impaired liver function, cardiac function and thyroid function.

(Please refer to table 7.4 for endogenous interactions with warfarin)

5.2.4 A baseline INR value should be drawn to rule out any underlying coagulopathy.

5.2.5 Monitoring of INR can be done at inpatient or outpatient settings.

5.2.6 During the first week, INR should be measured daily or every other day and warfarin dosage adjusted accordingly. It is then measured at increasing intervals, depending on the INR response.

5.2.7 Once the warfarin dose is stable, many patients can be well controlled with 4 to 8 weekly INR testing and warfarin dose adjustments. Steady-state INR values will not be realized for up to 3 weeks following a dose adjustment.

5.2.8 Patients with INR values outside target INR range should be considered for more frequent monitoring. Those with INR less than 1.5 or above 4 should have their INR repeated within seven days following dose adjustments.

5.2.9 Warfarin maintenance dose is usually in the range of 2-10mg orally once a day.

5.2.10 Warfarin dosing is affected by numerous factors. These are tabulated in table 7.5. An assessment of clinical variables known to affect the INR should be made with each dose adjustment.

6. REVERSING ANTICOAGULANT EFFECTS OF WARFARIN IN PATIENTS GOING FOR SURGERY

6.1 For elective procedures, warfarin should be stopped 3 to 5 days prior to surgery.

6.2 Patients with INRs of between 2 to 2.5 should achieve an INR of less than 1.5 after stopping warfarin for 3 days. Patients with INRs of between 2.5 to 3.5 generally require discontinuation of warfarin for 4 days before their INRs will drop to less than 1.5.

6.3 INR should be checked just before surgery to ensure adequate haemostatic function.

6.4 Warfarin may be restarted 24 hours after surgery if there is no bleeding risk.

6.5 The need to use heparin or low molecular weight heparin during the peri-operative period should be considered based on the bleeding risk from the surgery as well as the thrombotic risk arising from the surgery and the duration that the patient has to come off warfarin. This should be reviewed by the physician in charge.

7. INTERACTIONS OF WARFARIN

7.1 Drug Interactions

Table 7.1 - Drug interactions [7,8]

Drugs that Antagonise the Anticoagulant Effect of Warfarin		
Impairs absorption of warfarin	Cholestyramine* Colestipol	Sucralfate
Increase metabolic clearance of warfarin	Alcohol (chronic use) Barbiturates* Carbamazepine*	Griseofulvin* Rifampicin*
Increase synthesis of clotting factors	Oestrogen Propylthiouracil	Vitamin K
Mechanism unknown	Phenytoin* (biphasic with later inhibition)	
Drugs that Potentiate the Anticoagulant Effect of Warfarin		
Inhibit metabolic clearance of warfarin	Alcohol (acute ingestion) Allopurinol Amiodarone* Chloramphenicol Cimetidine* Clarithromycin Disulfiram* Erythromycin* Fluconazole Fluorouracil Itraconazole	Ketoconazole Metronidazole* Miconazole Omeprazole Phenylbutazone* SSRIs Tricyclic antidepressants Propefenone Trimethoprim-sulfamethoxazole* Voriconazole*
Increase catabolism of vitamin K clotting factors	Androgens (danazol*)	Thyroxine*
Decrease clotting factors synthesis	Cefazolin	Quinidine
Potentiate anticoagulant effect without affecting plasma levels of warfarin (pharmacodynamic)	Second and third generation cephalosporins	Clofibrate* Heparin
Displace warfarin from protein binding sites	Nalidixic acid*	Phenytoin* (initial phase)

Drugs that Potentiate the Anticoagulant Effect of Warfarin		
Mechanism not established	Anabolic steroids Ciprofloxacin Chloral hydrate (transient) Fenofibrate Gemfibrozil Glucagon Levofloxacin Lovastatin Norfloxacin Ofloxacin	Quinine Salicylates* Rosuvastatin Tamoxifen Testosterone Tetracycline Propafenone Vitamin A (megadose) Vitamin E (megadose)
Drugs that Potentiate the Antihaemostatic Effect of Warfarin		
Impair platelet function	Aspirin (GI ulceration*) Other NSAIDS Topical salicylates	

* Clinically significant.

7.2 Herbs/Supplements and Food Interactions

Table 7.2 - Herb and Food interactions [8,11,12]

Herbs/Supplements that May Reduce the Effect of Warfarin	
Increase metabolic clearance of warfarin	St John's Wort*
Similar structure to vitamin K	Coenzyme Q10*
Increased metabolism or reduced absorption	Avocado*
Mechanism unknown	Ginseng (Panax Ginseng)*

Herbs/Supplements/Food that May Enhance the Effect of Warfarin		
Impair platelet function	Capsaicin Clove oil Danshen (Salvia species)* Dong quai (Angelica sinensis)* Evening primrose oil Feverfew Fish oils (mega dose)	Garlic* Ginko (Ginko biloba)* Ginger (large amounts) Kava Licorice Rhubarb Saw palmetto
Contains coumarin derivative	Anise Celery Chamomile Red clover	
Contains salicylate	Meadowsweet	
Decrease production of clotting factors	Cinchona	
Mechanism unknown	Cranberry juice* Devil's claw Melatonin* Papain (in papaya extract)	

*Documented report.
This table is not all-inclusive.

7.3 Level of vitamin K-1 content in common foods

Table 7.3 - Level of vitamin K-1 content in common foods[13]

LEVEL OF VIT. K (mcg/100g)	0	1-10	11-50	51-100	101-200	201-500	OVER 500
BEVERAGES & SWEETENERS		Milk (cow)	Coffee (dry) Honey				Green tea (dry)
FATS, OILS	Cotton-seed Olive Peanut Safflower (linoleic)	Safflower (oleic) Palm Coconut		Corn			Soybean

LEVEL OF VIT. K (mcg/100g)	0	1-10	11-50	51-100	101-200	201-500	OVER 500
FRUITS		Apple Orange	Straw-berry				
GRAINS			Wheat flour Wheat germ	Oats Wheat bran			
MEATS (RAW), EGGS	Beef heart Beef kidney Lamb liver Pigeon liver Turkey liver	Ground Beef	Rabbit liver Veal liver Whole egg	Chicken liver Pork liver	Beef liver Egg yolk		
VEGETABLES (RAW)		Beet Corn Cucum-ber Mush-room	Aspa-ragus Carrot Green beans Natto Potato Tomato	Peas Sea-lettuce Water-cress	Broccoli Cabbage Cauliflower (green) Lettuce (iceberg) Mung beans Soybeans	Garbanzo beans (chickpea) Lentils Nettle leaves Seagrass Spinach	Brussel sprouts Seaweed (dulse) Seaweed (rockweed) Turnip greens

7.4 Endogenous Factors and Warfarin Therapy

Table 7.4 - Endogenous Factors and Warfarin Therapy [14,15]

a. Factors Associated with Decreased PT Response

<u>Decreased INR</u>

edema
hereditary coumarin resistance
hyperlipidemia
hypothyroidism

b. Factors Associated with Increased PT Response

Increased INR

Cancer
Collagen disease
Congestive heart failure
Diarrhea
Elevated temperature
Hepatic disorders (infectious hepatitis, jaundice)
Hyperthyroidism
Poor nutrition state
Steatorrhea
Vitamin K deficiency

7.5 Factors affecting Maintenance Dosing of Warfarin

Numerous factors should be considered with regards to warfarin dosing including:

(i) diagnosis
(ii) sensitivity to warfarin
(iii) age (especially if elderly)
(iv) patient compliance
(v) consumption of other medications (any interacting drugs)
(vi) body mass
(vii) alcohol consumption
(viii) nutritional status
(ix) diet/dietary changes
(x) activity level
(xi) smoking/no. of cigarettes per day
(xii) race
(xiii) accuracy of laboratory results

8. ADVERSE EFFECTS

8.1 Bleeding

The most common adverse effect of warfarin is bleeding with reported rates of major bleeding between 1.1% and 8.1 % during each year of long term warfarin treatment. Although the risk of bleeding for patients on warfarin increases substantially at INR values greater than 5, bleeding can occur at any INR value. The use of warfarin often unmasks bleeding potential e.g. a non bleeding peptic ulcer may bleed if the patient is put on warfarin.

The risk of bleeding is additive and related to the intensity of anticoagulation, use of concurrent medications and the patient's clinical condition.

Risk Factors for Bleeding during Warfarin Therapy

PATIENT-RELATED	
Age :	Above 65 years old
Cardiac:	Recent MI, AF, severe hypertension (diastolic pressure > 100mmHg, systolic pressure > 180mmHg)
GI:	Active peptic ulcer disease, history of GI bleeding, hepatic insufficiency
Hematologic / oncologic:	Anaemia, thrombocytopenia, platelet dysfunction, coagulation defect, malignancy
Neurologic:	History of stroke, dementia, cognitive or psychological impairment
Medications:	Use of other medications, such as NSAIDS, or "natural remedies" that interfere with haemostasis.
Others:	Recent trauma or surgery, excessive alcohol intake, intramuscular injection, potential bleeding sites (lumbar puncture, biopsy site, intra-arterial puncture)

8.2 Skin Necrosis

Skin necrosis is associated with thrombosis of venules and capillaries within subcutaneous fat, and usually occurs within the 3rd to 8th day of treatment. It presents as painful localised skin lesions and is usually associated with protein C or S deficiency. Skin necrosis may occur with large loading doses of warfarin and may be circumvented by initiating therapy at low doses while continuing heparin to avoid an abrupt fall in protein C levels before coagulation factor levels are reduced.

8.3 Purple Toe Syndrome

Purple toe syndrome is characterized as a dark cutaneous lesion with blue discoloration of the feet and lower leg. It is caused by peripheral emboli and usually occurs 3-10 weeks after initiation of therapy.

8.4 Less Serious Adverse Effects

Adverse effects that are less serious include alopecia, osteoporosis, rash and gastrointestinal discomfort.

9. MANAGING BLEEDING AND EXCESSIVE ANTICOAGULATION

9.1 The Risk of Bleeding and INR

Bleeding risk increases significantly when INR exceeds 5. An INR above 5 requires close monitoring. Intervention is required based on the INR reading, the presence of bleeding and the patient's underlying condition, as outlined.

9.2 The Recommendation for Management if there is No Significant Bleeding and Patient has Low Bleeding Risks

INR	RECOMMENDATION
4.0 to 5.0	Reduce dose or omit 1 to 2 doses. Monitor INR more frequently and resume therapy at a lower dose when INR is within therapeutic range.
5.0 to 9.0	Check for bleeding / headache / anaemia. Admit if any suspicion of bleeding or if patient is unwell. If not for admission, advise patient of risk of bleeding and to go to A & E if there is any suspicion of bleeding or if patient is unwell. Omit 2 to 3 doses. Monitor INR more frequently and resume therapy at a lower dose when INR is within therapeutic range. Alternatively, omit 1 dose and administer 1-3mg of oral vitamin K. Check INR in 24 hours. If INR remains high, administer additional 1-2mg of oral vitamin K. Resume therapy at a lower dose when INR is within therapeutic range.
Above 9.0	Admit. Check for bleeding / headache / anaemia. Omit warfarin and administer 3-5mg of oral vitamin K. Check INR in 24 hours. Administer additional vitamin K if necessary. Resume therapy at a lower dose when INR is within therapeutic range.

9.3 The Recommendation for Management if there is Serious Bleeding and INR is Elevated

Hold warfarin therapy and administer 10mg vitamin K by slow IV infusion, supplemented with fresh plasma or prothrombin complex concentrate 50IU/kg, depending on the urgency of the situation. Vitamin K administration can be repeated every 12 hours.

For life-threatening bleed, hold warfarin therapy and administer prothrombin complex concentrate 50IU/kg, supplemented with 10mg vitamin K by slow IV infusion. Check INR every 6 hours and repeat the procedure if necessary, depending on the INR.

*Oral Vitamin K is given for outpatients. The oral preparation is prepared from KONAKION MM ® preparation. IV Konakion ® has oral bioavailability of 50% (Roche company data).

9.4 Considerations for Vitamin K

The dose of vitamin K used to reverse over-anticoagulation depends on the INR. Ideally, vitamin K should be administered in a dose that will quickly lower INR into a safe but not sub-therapeutic range. For most patients, 1 to 3 mg of vitamin K is sufficient in the absence of bleeding. These small doses are obtained by dilutions from a 10 mg vial of injectable vitamin K and this is administered via oral or parental route.

High doses of vitamin K (10mg) are very effective but will lower the INR to sub-therapeutic range and lead to warfarin resistance for up to a week.

Due to near complete absorption, oral vitamin K has shown to be convenient and effective.

Intravenous injection produces a rapid response but anaphylactic reaction is a rare complication. This is reserved for patients who require very rapid reversal of anticoagulation; and can be administered by slow intravenous infusion (10mg over 30 minutes in 50ml dextrose 5%).

10. FREQUENTLY ASKED QUESTIONS DURING WARFARIN COUNSELLING

What is Warfarin?

Warfarin is an anticoagulant, sometimes called a 'blood thinner'. It works by blocking the action of Vitamin K in the liver, which is necessary in the formation of 'clotting factors', thereby preventing clot formation. Warfarin helps prevent harmful blood clots that may form in the blood vessels and lodge within the brain, heart, lungs or legs that can result in life-threatening strokes or heart attacks. Warfarin does not dissolve clots that have already formed but may prevent the clots from getting bigger, while letting the body's natural processes dissolve the clots.

Why am I taking Warfarin?

Those with deep vein thrombosis, pulmonary embolism, irregular heart beat, artificial heart valves or other conditions that tend to promote harmful clotting events e.g. Antiphospholipid Syndrome, may benefit from warfarin therapy. The duration of treatment may vary from 3-6 months to long term.

How do I recognise my tablets?

Warfarin comes in tablet form with 3 strengths and is available in different brands. The brand Marevan® is used in restructured hospitals. Do not switch brands because different brands may have slightly different effectiveness. Recognize the strength of the tablets by identifying the colour: pink (5mg), blue (3mg), brown (1mg).

What dose of Warfarin should I take?

The dose of warfarin to be taken varies among individuals. It normally depends on the results of a blood test (the International Normalized Ratio or INR) which measures how long your blood takes to clot. Your doctor will set a target INR for you. An INR below the target means that the blood may not be adequately "thin" and hence, clotting may occur. An INR above the target means that the blood may be too "thin" and hence, more prone to bleeding. When you have just started taking warfarin or when there is a change in dosage, you may need to go for blood tests more frequently so that the dose can be adjusted according to your response to the medication. Your doctor or pharmacist will instruct on the dose to take after each blood test. Do not change the dose of warfarin on your own.

When should I take Warfarin?

It is best that you can take warfarin at the same time each day. A missed dose should be taken as soon as you remember. If more than 8 hours have passed or it is nearing the time for the next dose, do not take that dose. Just continue to take your warfarin at the usual time the next day. Do not double the dose in order to 'catch up' but continue with your usual regime. Doubling the dose may cause excessive bleeding. Record any missed doses and inform your doctor or pharmacist at the next appointment.

Can Warfarin be taken with other medications?

Many different medicines can affect the way warfarin works in your body. It is very important that you check with your doctor or pharmacist before you start or stop taking any other medicine, or change the amount you are taking. This includes:

- prescription drugs including other blood thinners, antibiotics, medicines (e.g. pain-killers and fever/flu pills)
- over-the-counter medicines (e.g. pain-killers and fever/flu pills)
- nutritional supplements (e.g. vitamins)
- traditional remedies (e.g. ginseng)

With the addition or removal of medicine from your usual regimen, more frequent measurement of INR may be required.

Do I need to change my diet?

The effect of warfarin depends on the amount of Vitamin K in your body and most of it comes from the food you take. Hence it is important to be consistent with your dietary intake of Vitamin K and keep to your normal balanced diet. It is not necessary to avoid food rich in Vitamin K as some of them contribute to a healthy diet. Maintain your diet and avoid drastic changes, especially to foods like soybean products, green tea, brussel sprouts, spinach, chickpeas, broccoli, cauliflower, cabbage. Inform your doctor or pharmacist if you intend to make major changes to your diet (e.g. becoming a vegetarian).

Moderate amounts of alcohol e.g. 1 to 2 glasses of beer or sherry or a glass of wine occasionally should not unduly interfere with your treatment. Larger amounts of alcohol or stronger alcoholic drinks e.g. whisky, brandy, gin should be avoided.

Check with your doctor if you are unable to eat for several days or if you have continuing stomach upset, diarrhoea or fever. This could decrease the amount of Vitamin K that gets into your body.

What are the important side effects of Warfarin?

The side effects of warfarin are related mainly to its action of delaying blood clotting.

Side effect	Warning signs	To reduce this side effect
Obvious bleeding	• Bleeding from gums when brushing teeth • Unexplained nose bleeds • Prolonged bleeding from cuts • Unexpected or unusual vaginal bleeding	Check with your doctor if the bleeding does not stop within minutes or if you feel unwell. For women, increased menstrual flow is common but check with your doctor if you feel unwell.
Internal bleeding	• Black, sticky or bloody stools • Coughing up blood or coffee ground-like material • Unexplained large bruising or purplish areas on skin • Blood in the urine • Sudden severe headache with nausea or loss of consciousness • Sudden abdominal pain or swelling • Sudden severe backache or joint pain or weakness • Shortness of breath	Check with your doctor immediately or admit yourself to the Accident and Emergency Department.
Nausea, vomiting, loss of appetite or diarrhoea (uncommon)		Improves as you get used to the medicine.

Do I need to make any lifestyle changes?

Avoid sports and activities that may cause you to be injured. Report to your doctor any falls, blows to your head or body or other injuries since serious bleeding (especially internally) may occur without your knowing it.

Avoid cutting yourself. Be extra cautious when handling razors or other sharp objects. This includes taking special care in brushing your teeth and in shaving. Use a soft toothbrush and floss gently. Also it is best to use an electric shaver rather than a blade.

Special Precautions

1. Notify all doctors/dentists you visit that you are taking warfarin. This will avoid prescription of drugs that may interfere with warfarin and the performance of surgical procedures without reversing the anticoagulation.

2. Carry some form of identification with you stating that you are taking warfarin, e.g. your anticoagulation booklet. This will ensure that others will know your condition and administer appropriate treatment in case you are involved in an accident and taken to hospital.

Blood clots may still form while on warfarin therapy. The signs and symptoms depend on the site where it is found. Recognise these signs and contact your doctor immediately if any of these occur.

Legs (or deep vein thrombosis)	Swelling, redness, pain, warmth
Lungs (or pulmonary embolism)	Chest pain, breathlessness, coughing up blood
Brain (or stroke)	Muscle weakness, blackouts, giddiness, slurred speech, visual disturbances
Heart (or heart attack)	Chest pain, fainting, shortness of breath, irregular heart beat

3. Pregnancy and breastfeeding: warfarin can cause birth defects. As with all medicines, inform your doctor if you intend to conceive or breastfeed while taking this medicine.

How should I keep my medicines?

Keep warfarin in a cool, dry and dark place, out of children's reach. Do not keep in the bathroom or refrigerator. Store at room temperature and protect from light.

11. REFERENCES

1. Seventh American College of Chest Physicians Antithrombotic Consensus Conference on Antithrombotic Therapy. Chest. 2004. 126(3):204S-233S.

2. Genton EE. Warfarin. In:Messerli FH (ed). Cardiovascular Drug Therapy. W.B. Saunders Company 1996; 2nd ed: 1517-1521.

3. Institute for Clinical Systems Improvement Health Care Guideline: Anticoagulation Therapy Supplement. Third edition. Nov 2003.

4. Thomas M. Hyers. Antithrombotic Therapy, 4th edition.

5. Wittkowsky AK. Thrombosis. In: Young LY, Koda-Kimble MA (ed). Applied therapeutics: the clinical use of drugs. Applied Therapeutics, Inc, Vancouver, 1995 (6th ed):12-1-12-25.

6. LaCalamita S. Warfarin. Hospital Pharmacy 1997; 32(3):414-420.

7. Hansten PD, Horn JR, Koda-Kimble MA, Young LY, editors. Drug interactions analysis and management. Applied Therapeutics, Inc, Vancouver 1997.

8. Warfarin [drug evaluation monograph]. In: Micromedex Inc 1974-1977; Vol 122: Exp 31.12.04.

9. Hirsch et al. American Heart Association/ American College of Cardiology Foundation Guide to Warfarin Therapy. Circulation. 2003. 107:1692-1711.

10. Guidelines on oral anticoagulation: third edition. British Journal of Haematology. 1998. 101:374-387.

11. Lambrecht JE, Hamilton W, Rabinovich A. A Review of Herb-Drug Interactions : Documented and Theoretical. US Pharmacist 2000; 25(8). http://www.uspharmacist.com/ .

12. The Natural Pharmacist: TNP Encyclopedia: Warfarin. Sep 21 2001. http://www.tnp.com/encyclopedia/interaction/486/ .

13. Vitamin K-1 content of foods. In: micromedex Inc 1974-1996 Vol90. Exp 31.12.04.

14. Handbook of Antithrombotic Therapy, 4th Edition. Thomas M Hyers.

15. C.A.R.E. Clinical Research Handbook@CareInternet.com.

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1. Pharmaceutical Society of Singapore

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