Waikato Community Pharmacy Group

Warfarin Quick Reference Guide

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Waikato Community Pharmacy Group's position statement on warfarin management

The New Zealand Guidelines Group for the 'The Management of Atrial Fibrillation and Flutter' guideline recommend that all people with atrial fibrillation (AF) or atrial flutter (AFL) should have their thromboembolic risk assessed, irrespective of their current rhythm[1]. This can be done using the tool included in the guideline. The majority of people with AF or AFL will require anticoagulation to reduce their risk of stroke.

The following recommendations are made in the guideline:

- Antithrombotic treatment should be administered to all people with AF/AFL, except those with lone AF (people <60 years with no hypertension or heart disease), to reduce the risk of thromboembolic events.
- People with AF/AFL assessed as having a high or very high risk of stroke should receive long-term anticoagulant treatment with adjusted-dose warfarin, aiming for an INR between 2.0 and 3.0 (target 2.5), unless there are clear contraindications.
- People with AF/AFL assessed as having an intermediate risk of stroke should discuss their individual risks, the potential benefits and their preferences regarding anticoagulant or aspirin treatment, with their doctors.
- Anticoagulation should be started in every person with AF/AFL and ischaemic stroke or transient ischaemic attack (TIA) unless contraindicated, once intracranial haemorrhage (ICH) has been excluded. The optimal timing of anticoagulation is uncertain. Anticoagulation is usually started 14 days after a stroke. It may be started earlier in people with minor strokes if ICH has been excluded and if there is a high risk of early recurrent stroke.

The guidelines also note that warfarin treatment is more effective than aspirin treatment for reduction of the risk of stroke, but it increases the risk of bleeding. Community pharmacy plays a key role in reducing this risk of bleeding by ensuring the patients have a good understanding of their therapy, including, but not limited to, the indication for their warfarin therapy, the potential adverse effects and the signs and symptoms of these, any external factors that will effect their therapy, and the role of regular blood tests (INR).

The national guidelines recommend that any barriers that prevent access to medication and INR testing need to be addressed.[1]

Warfarin is also frequently associated with adverse events that result in hospital admissions.[2] While this is extremely undesirable for the patients it also results increased costs to the health system.

The Waikato Community Pharmacy Group fully supports the recommendations made in the Management of Atrial Fibrillation and Flutter guideline. The Waikato Community Pharmacy Group recognises that community pharmacy plays a vital role in assisting with reducing barriers to accessing medications and INR testing. As such they are supporting this through the development of a Warfarin Counselling Checklist, which will standardise the dispensing process to the same high level of quality service delivery across the membership. The Waikato Community Pharmacy Group members acknowledge the impact they can have through their direct contact with warfarin patients, and will continue to be the provider of high quality warfarin-related information. The Waikato Community Pharmacy Group members will continue to monitor the level of each patients understanding and supply the pertinent information when required.

[1] NZGG. New Zealand Guidelines Group for The Management of Atrial Fibrillation and Flutter guideline. May 2005

[2] M Pirmohamed, S James, S Meakin, *et al.* Scott Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329:15-19

Warfarin pharmacokinetics and pharmacodynamics

- Warfarin inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX and X.
- Half-life ranges from 20 to 60 hours, with a mean of about 40 hours.
- Warfarin is eliminated predominantly through metabolism in the liver ⇒ CYP 2C9.

Warfarin indication and durations of use

Indication	Duration of use
Distal Deep Vein Thrombosis (DVT)	3 months
Proximal DVT	6 months
Pulmonary embolus	6 months
Atrial fibrillation, unprovoked and/or recurrent DVT or PE	long-term
Antiphospholipid syndrome	life long
Annual review of warfarin therapy is advisable	

Notes:

- Once warfarin is stopped there is a small thrombosis recurrence rate irrespective of therapy duration.

Warfarin target INR values

Indication	INR range
Treatment of venous thromboembolism (DVT or PE)	2.0 - 3.0
Prevention of systemic embolism, caused by – Atrial fibrillation – Valvular heart disease – Following MI	2.0 - 3.0
Antiphospholipid syndrome	on Specialist advice
Mechanical and prosthetic heart valves[1]	on Specialist advice

Notes:

- A target INR should be 2.5 with an acceptable range from 2.0 to 3.0[3] (except in the setting of valvular heart disease). Aiming for a target value assists with ensuring the INR result actually remains within the target range.
- Asymptomatic super-therapeutic elevation of INR is a common and a clinically important problem.
- Strict INR control is advised in the first month of warfarin therapy due to a higher risk of thrombosis recurrence.

[3] NZGG. New Zealand Guidelines Group for the 'The Management of Atrial Fibrillation and Flutter guideline. May 2005

INR monitoring

Therapy initiation	Testing frequency	Duration
For patients initiated with low-dose protocols (warfarin initial dose 2 – 3mg		
Initially	**When INR <4** → weekly **When INR >4** → every 2-3 days	Until stable for 2 consecutive tests
Then	Fortnightly	Until stable for 2 consecutive tests
Maintenance	Most patients can be extended to 4-6 weekly testing however a minority may require more frequent testing	
For patients initiated with high doses		
Initially	Daily for at least 5 days	Until stable for 2 consecutive tests
Then	Every 3 to 5 days	Until stable for 2 consecutive tests
Then	Weekly	Until stable for 2-3 consecutive tests
Then	Fortnightly	Until stable for 2-3 consecutive tests
Maintenance	Most patients can be extended to 4-6 weekly testing however a minority may require more frequent testing	
Drug Interactions		
Interacting drug of < *5 days* duration	No change or omission of 1 complete dose can be considered	
Interacting drug of > *5 days* duration	Check INR after start of new drug and adjust warfarin on basis of results	

Taken from INR testing, Bpac[nz] October 2006

Dose Changes: a change in warfarin dose can take several days to influence the INR; so testing INR within 1 to 2 days of a dose change may not reflect the steady-state or true response to the change.

Recommendation from the NZGG guideline on the Management of Atrial Fibrillation and Flutter guideline
The INR can be checked daily until a therapeutic range has been reached and sustained or 2 consecutive days, then 2 to 3 times weekly for 1 to 2 weeks, then less often, according to the stability of the results. If the INR response remains stable, the frequency of testing can be reduced to intervals as long as every 4 weeks, although there is growing evidence to suggest that more frequent testing will lead to greater time in the therapeutic range.

The optimal frequency of long-term INR monitoring is influenced by individual factors, such as compliance; fluctuations in co-morbid conditions; the addition, adjustment or discontinuation of other medications; changes in diet; the quality of dose-adjustment decisions and whether the person has demonstrated a stable dose response.

Risk factors for bleeding

- Bleeding risk factors are additive
- The risk of bleeding increases exponentially with INR results >5

Risk factors for bleeding complications of anticoagulant therapy	
Age	> 65 years
Cardiac	Uncontrolled hypertension (BP consistently ≥ 160/90 mm Hg)
GIT	History of gastrointestinal haemorrhage, active peptic ulcer, hepatic insufficiency
Haematological/ oncological	Thrombocytopenia (platelet count <50x10^9/L), platelet dysfunction, coagulation defect, underlying malignancy
Neurological	History of stroke, cognitive or psychological impairment
Renal	Renal insufficiency
Trauma	Recent trauma, history of falls (>3 per within previous treatment year, or recurrent, injurious falls), post surgery
Alcohol	Excessive alcohol intake
Medications	Aspirin (including anti-platelet therapy), NSAIDs, 'natural remedies' that interfere with haemostasis

Dental extractions and minor surgery

§ Anticoagulation does not need to be stopped for dental extraction for patients with an INR less than 3.0.

§ For minor surgical procedures the warfarin dose should be stopped or adjusted to achieve a target INR of approximately 2.0 on the day of the surgery.

§ For major surgery warfarin should be stopped at least three days prior to surgery. Further actions will depend on resulting INR levels and the thrombotic risk of the condition for which the patients is receiving anticoagulation.

Common warfarin-drug interactions.

Red – increase affect
Blue – decrease effect
Green – unpredictable effect (↑ or ↓)

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Alcohol (intermittent heavy use)	Liver enzyme inhibition.	Increases INR and increased risk of bleeding.	Patients should be advised to keep their alcohol consumption to a minimum or constant level.
Alcohol (chronic heavy use)	Liver enzyme induction.	Decreases INR and loss of therapeutic affect.	Patients should be advised to keep their alcohol consumption to a minimum or constant level.
Allopurinol	Inhibits metabolism in the liver. There is wide individual variability in the effects of allopurinol on drug metabolism in man so only a few individuals are affected.	Increased risk of bleeding.	Clinically important but very uncommon interaction. Monitor INR closely when allopurinol therapy initiated or discontinued or the dose changes.
Amiodarone	Liver enzyme inhibition	Increased serum levels of warfarin and increased anticoagulant effect. In patients stabilised on warfarin and amiodarone, the possibility of amiodarone-induced thyrotoxicosis should be considered if an abrupt increase in prothrombin time occurs.	Well documented, and an established and clinically important interaction and appears to occur in most patients. The dosage of warfarin should be reduced by 1/3 to 2/3. Average warfarin dose reductions of *(Stockley's):* – 25% for amiodarone 100 mg daily, – 30 to 35% for amiodarone 200 mg daily, – 35% for amiodarone 300 mg daily, – 40 to 50% for amiodarone 400 mg daily – 65% for amiodarone ≥600 mg daily The onset of this interaction may be slow, and may persist long after the amiodarone has been withdrawn. Amiodarone-induced thyrotoxicosis may affect the prothrombin time.
Antacids	Absorption of warfarin increased by magnesium trisilicate. Aluminium or magnesium hydroxide antacids will not affect warfarin absorption.	Increased serum levels of warfarin and increased anticoagulant effect.	There seems to be no direct clinical evidence of any important adverse interaction. No special precautions need be taken if aluminium or magnesium hydroxide antacids are given to patients on warfarin.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Aspirin	Antiplatelet activity of aspirin. The direct irritant effect on the stomach lining posing a risk for bleeding.	Increased risk of bleeding.	Low dose aspirin may be used in combination if benefits outweigh the risks. Analgesic doses should be avoided. Aspirin 500 mg daily increases the likelihood of bleeding 3 to 5 times in those taking anticoagulants, it damages the stomach wall, prolongs bleeding times and in daily doses of 2 to 4 g it can increase prothrombin times
Azathioprine (and mercaptopurine)	Not well understood. Mercaptopurine appears to increase the synthesis or activation of prothrombin.	Reduce anticoagulant effect.	No formal recommendations available, however it is postulated to be a clinically significant interaction so it would be prudent to monitor INR and warfarin dose requirements when azathioprine is started or discontinued.
Bezafibrate	Mechanism not known.	Reports of an increase and a decrease in anticoagulant effect.	Very little information available, but dosage reductions of ⅓ to ½ may be needed to avoid the risk of bleeding. Monitor the INR and adjust the dose accordingly.
Carbamazepine	Not entirely clear, but suspected to be increased metabolism in the liver through enzyme induction.	Reduced serum levels and anticoagulant effect.	Clinically significant. Recommend monitoring INR closely when carbamazepine therapy initiated, altered or discontinued. Warfarin dose may need to be increased by up to 50%.
Carbimazole	Hyperthyroid patients catabolism of the blood clotting factors (II, VII, IX and X) catabolism is increased.	Increased anticoagulant effect.	As patients return to euthyroid state a warfarin dose increase maybe required.
Cefaclor	Act as vitamin K antagonists to reduce the production of some blood clotting factors.	Cefaclor can cause bleeding on its own and worsen the risk of bleeding if given with anticoagulants.	Very rare and variable interaction.
Cholestyramine	Cholestyramine binds to bile acids and to coumarin anticoagulants in the gut so preventing absorption. The paradoxical increase in the effects of warfarin in the isolated case remains unexplained.	Reduced anticoagulant effect.	The magnitude and clinical importance is still uncertain. If concurrent use is thought necessary, INRs should be monitored and the dosage of the anticoagulant increased appropriately. Giving the cholestyramine 3 to 6 hours after the anticoagulant has been shown to minimise the effects of this interaction.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Cimetidine	Inhibits CYP450 enzymes in the liver.	Increases warfarin serum levels and consequent anticoagulant effect.	Avoid combination and use an alternative H_2 antagonist like ranitidine or famotidine which do not interact. The onset of the interaction appears rapid; effects have been seen within days, 2,7 and even as early as 24 hours
Ciprofloxacin	Mechanism is not clear.	Increased anticoagulant effect.	Reports of interactions are limited, however anecdotal reports indicate the interaction is responsible for a number of hospital admissions. Close INR monitoring is recommended or the combination avoided.
Clarithromycin	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	References suggest this interaction is unpredictable and that the combination need not be avoided but close monitoring of INR values should occur when erythromycin is started and stopped. However unofficial feedback suggests that macrolides are very common culprits in elevated INRs resulting in hospital admission.
Clopidogrel	Reduces clotting effect of platelets.	Increased risk of bleeding.	
Citalopram	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	Clinical significance unclear and interaction is unpredictable. Would be prudent to monitor INR closely on therapy initiation and discontinuation and adjust warfarin dose accordingly.
Colchicine	Colchicine alone may cause bone marrow depression or thrombocytopenia.	Possible increased risk of bleeding.	Avoid concurrent use, or monitor closely for signs of bleeding.
Co-trimoxazole (including Sulfamethoxazole) Also see trimethoprim	Not fully understood but thought to be combination of plasma protein binding displacement can occur, Sulfonamides can reduce the intestinal bacterial synthesis of vitamin K, but this is not normally an essential source of the vitamin unless dietary sources are exceptionally low and possibly metabolism of the anticoagulants is decreased.	Increased anticoagulant effect.	A well documented interaction. Close INR monitoring recommended or use an alternative antibiotic.
Cyclophosphamide	Mechanism is not clear as reports often included other antineoplastics drugs as well as cyclophosphamide.	Increased anticoagulant effect.	Close monitoring of INR when combination started. Interaction thought to be rare.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Danazol	Mechanism not well understood.	Increased anticoagulant effect.	Well documented, well established and clinically important interactions that develop rapidly, possibly within 2 to 3 days. Warfarin dose has been suggested to be reduced by 50% and increased by a similar amount when danazol discontinued.
Dextropropoxyphene	Mechanism not well understood. Possibly a result of enzyme inhibition.	Increased anticoagulant effect.	Difficult to predict in whom this interaction will occur. Concurrent use need not be avoided but recommend initially to monitor the INR when starting dextropropoxyphene and drugs containing it, because the occasional patient may show a marked response.
Dipyridamole	Reduces clotting effect of platelets.	Increased risk of bleeding.	Clinical significance unclear as information is limited.
Disulfiram	Mechanism not understood.	Increased anticoagulant effects.	An established interaction that will occur when combination used. If the combination is deemed to be necessary careful monitoring of INR and warfarin dose adjustment recommended.
Doxycycline	Mechanism not well understood. Can reduce prothrombin activity, hypoprothrombinaemia and bleeding so possibly an additive hypoprothrombinaemic effect.	Increased anticoagulant effect.	Given the wide spread use of tetracyclines and the limited number of interaction reports, the clinical significance is probably low. Prudent to remind patients to monitor for signs of bleeding when starting doxycycline.
Enteral Feeds	Some contain vitamin K which reduces the affect of warfarin.	Reduced therapeutic affect.	
Erythromycin	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	References suggest this interaction is unpredictable and that the combination need not be avoided but close monitoring of INR values should occur when erythromycin is started and stopped. Unofficial reports suggest that erythromycin is a very common culprit in elevated INRs resulting in hospital admission.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Fluconazole	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	Close monitoring of INR recommended with dose reduction considered. On the basis of pharmacokinetic studies it has been predicted that the warfarin dosage may need to be reduced by about 20% when using fluconazole 50 mg daily, ranging to a reduction of about 70% when using fluconazole 600 mg daily. However it should be remembered that there is considerable individual variation .
Fluoxetine	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	Clinical significance unclear and interaction is unpredictable. Would be prudent to monitor INR closely on therapy initiation and discontinuation and adjust warfarin dose accordingly.
Flutamide	Mechanism unclear.	Increased anticoagulant effect.	Monitor prothrombin times if flutamide is given to patients on warfarin, reducing the dosage when necessary.
Gemfibrozil	Mechanism not known.	Reports of an increase in anticoagulant effect.	Very little information available, but dosage reductions of ⅓ to ½ may be needed to avoid the risk of bleeding. Monitor the INR and adjust the dose accordingly.
Griseofulvin	Not understood. Suggested griseofulvin acts as a liver enzyme inducer, increasing warfarin metabolism.	Reduced anticoagulant effect.	This is an unpredictable interaction, so prudent to monitor INR when griseofulvin therapy started.
Itraconazole	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	Close monitoring of INR recommended with dose reduction considered. There is limited data on this interaction so recommendation is empirical.
Isoniazid (600mg/day)	Mechanism not known.		Reports of bleeding so caution with combination.
Ketoconazole	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	Its general importance and incidence is uncertain, however ketoconazole is a very strong enzyme inhibitor. INR should be monitored in any patient when first given both drugs, particularly the elderly, to ensure that excessive anticoagulation does not occur.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Lanzoprazole	Mechanism not entirely clear but suggested to be hepatic liver inhibition.	Increase anticoagulant effect.	Interaction is documented but there is considerable variation between individuals. Possibly prudent to monitor INR when a PPI is started and/or discontinued.
Levonorgestrel (ECP)	Mechanism not known.		Clinical importance not clear. Possibly prudent to recommend close monitoring on INR over the period of taking levonorgestrel.
Metronidazole	Inhibition CYP 450 enzymes responsible for the metabolism of the (S)-warfarin (but not the (R)-warfarin).	Leaves the more potent form of warfarin in the body, therefore increasing the anticoagulant effect.	Clinically important interaction. Close monitoring of INR on metronidazole initiation and discontinuation with warfarin dose adjustments of between ⅓ to ½ as required.
Methylphenidate	Decreased metabolism of warfarin	Increased risk of bleeding	This is a documented interaction, however it does not require any action.
Miconazole	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	The combination should be avoided. This also includes the oral gel formulation as quantities of this are swallowed and absorbed. If the combination is required, the INR should be monitored closely with any dose adjustments made. Close monitoring is required when miconazole is started and also when it is discontinued. There is some literature which also suggests an interaction may occur with intra-vaginal miconazole absorption. The risk is increased possibly in postmenopausal women with inflamed vaginal tissue
Norfloxacin	Mechanism is not clear.	Increased anticoagulant effect.	Reports of interactions are limited, however anecdotal reports indicate the interaction is responsible for a number of hospital admissions. Close INR monitoring is recommended or the combination avoided.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
NSAIDs	There does not appear to be a direct interaction between common NSAIDs and warfarin; however the concern is around the GIT irritant effect of NSAIDs and the potential for increased bleeding from a NSAID-induced ulceration. In addition there is the inherent antiplatelet effect of some NSAIDs which will increase the risk of bleeding		Combination should be used with caution in people at high risk for GIT irritation/ulceration. Monitor for signs of bleeding. Note: Risk factors for NSAID-associated adverse upper GI events include the use of NSAID (includes aspirin, and COX-2 inhibitors plus aspirin) plus the following: – aged 65 years and over – history of peptic ulcer – history of upper GI bleeding – concomitant disease, especially coronary heart disease – increased frailty such as substantial arthritis-related disorder (osteoarthritis is a milder disease than rheumatoid arthritis, requires lower doses of NSAIDs and use of oral prednisone is rare) – previous NSAID gastropathy – concomitant use of corticosteroids – concomitant use of anticoagulants – concomitant use of bisphosphonates – high doses of NSAID (includes NSAID + aspirin) – H. pylori infection. • Increased-risk patients are: – aged less than 65 years with 2 risk factors – aged 65 years and over with 1 risk factor.
Ofloxacin	Mechanism is not clear.	Increased anticoagulant effect.	Reports of interactions are limited, however anecdotal reports indicate the interaction is responsible for a number of hospital admissions. Close INR monitoring is recommended or the combination avoided.
Omeprazole	Mechanism not entirely clear but suggested to be hepatic liver inhibition.	Increase anticoagulant effect.	Interaction is documented but there is considerable variation between individuals. Possibly prudent to monitor INR when omeprazole is initiated and/or discontinued.
Orlistat	May reduce the absorption of water soluble vitamins including vitamin K, and changes to a lower fat diet associated with the use of orlistat may also contribute to changes in the balance between vitamin K and warfarin.	Increased INR	Clinical trials testing for an interaction found no change in warfarin pharmacokinetics. However, given that changes in diet are known to affect warfarin, it would be prudent to monitor the INR when orlistat is started and/or stopped. Four weeks has been suggested as an appropriate time to continue monitoring.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Oral Contraceptives & oestrogens	Mechanism not known.		Oral contraceptives are normally contraindicated in those with thromboembolic disorders but if they must be used, be alert for any changes in the anticoagulant response if an oral contraceptive is started or stopped.
Paracetamol (>2g/day for >1 week)	Mechanism not clearly established. Thought to be a result of CYP450 enzyme competition, however this is not the main metabolic pathway for paracetamol, however in older patients or patients who are hypoxic or hypertensive, hepatic metabolism may play a greater role in paracetamol clearance.	Increased anticoagulant effect.	There is evidence that if larger amounts are taken the risk of getting INRs above 6 steadily rises in a dose-dependent manner. Occasional small doses of paracetamol (no more than 2.5 to 3 g weekly) are unlikely to cause important INR rises.
Paroxetine	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	Clinical significance unclear and interaction is unpredictable. Would be prudent to monitor INR closely on therapy initiation and discontinuation and adjust warfarin dose accordingly.
Penicillins	Mechanism not well known.		Documented reports of interactions between oral anticoagulants and penicillins are relatively rare, bearing in mind how frequently these drugs are used, so that the broad picture is that no clinically relevant interaction normally occurs with most penicillins. Close monitoring possibly recommended.
Phenobarbitone	Potent liver enzyme inducing agents.	Increases the metabolism and clearance of the anticoagulants from the body and increases the risk of thromboembolism.	Stable anticoagulant control can be re-established in the presence of the barbiturate by increasing the anticoagulant dosage by about 30 to 60%. Care must be taken not to withdraw the barbiturate without also reducing the anticoagulant dosage, otherwise bleeding will occur. The reduction in the anticoagulant effects begins within a week, sometimes within 2 to 4 days, reaching a maximum after about 3 weeks, and it may still be evident up to 6 weeks after stopping the barbiturate.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Phenytoin	Mechanism is thought to be a result of phenytoin being an enzyme inducer so increasing warfarin metabolism and reducing its effect; however there have been reports of increased anticoagulant effects and phenytoin toxicity when used in combination.	Unpredictable effects.	Monitor INR closely when phenytoin therapy initiated in a patient already on warfarin. Monitor for signs of phenytoin toxicity when warfarin is started in a patient stabilised on phenytoin.
Primidone	Primidone is converted to phenobarbitone *in vivo* so expected to interact similarly.	Increases the metabolism and clearance of the anticoagulants from the body and increases the risk of thromboembolism.	No reported interactions but would be advisable to monitor INR when starting or stopping therapy.
Propylthiouracil	Hyperthyroid patients catabolism of the blood clotting factors (II, VII, IX and X) catabolism is increased.	Increased anticoagulant effect.	As patients return to euthyroid state a warfarin dose increase maybe required. Propylthiouracil in the absence of an anticoagulant has very occasionally been reported to cause hypoprothrombinaemia and bleeding.
Quinidine	Quinidine can depress the synthesis of the vitamin-K dependent blood clotting factors and has a direct hypoprothrombinaemic effect of its own. This however doesn't explain the potential to reduce warfarin effect.	Unpredictable.	Monitor INR closely when quinidine started and/or discontinued.
Quinine	Mechanism not clear but thought to be competitive inhibitor of vitamin K.	Increased anticoagulant effect.	Clinical significance is low. Concurrent use needn't be avoided, however the isolated cases have shown that very exceptionally, much larger changes and even bleeding can occur even with doses as small as 30 mg.
Rifampicin	Potent liver enzyme inducer.	Reduces the serum levels and increases the risk of thromboembolism.	A clinically significant interaction. Doses of warfarin will need to be doubled or tripled and then reduced by the same amount when rifampicin is discontinued. Close monitoring is recommended at all times.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Roxithromycin	Inhibits CYP450 enzymes in the liver.	Increased serum levels of warfarin so increased anticoagulant effect.	References suggest this interaction is unpredictable and that the combination need not be avoided but close monitoring of INR values should occur when erythromycin is started and stopped. Unofficial reports suggest that roxithromycin is a common culprit in elevated INRs resulting in hospital admission.
Simvastatin	Mechanism not clear.	Increased anticoagulant effect.	It would be prudent to remind the patient to monitor for signs of bleeding in the early stages of concurrent use in patients, or if the statin dose is altered, and being alert for the need to adjust the anticoagulant dosage. INR tests in every patient maybe being over cautious.
Sucralfate	Mechanism unclear. Suggested sucralfate may possibly adsorb the warfarin so that its bioavailability is reduced.	Reduced anticoagulant effect.	Combination does not need to be avoided, however monitoring INR recommended when sucralfate started or discontinued.
Tamoxifen	Mechanism unclear.	Increased anticoagulant effect.	A well established and clinical significant interaction. Monitor INR when tamoxifen therapy initiated. A dose reduction of between ½ and ⅔ may be required. The warfarin dose change will need to be reversed should tamoxifen therapy be discontinued.
Thyroid hormones	In hypothyroid patients the catabolism of the blood clotting factors (II, VII, IX and X) is low and this tends to cancel the effects of the anticoagulants. Conversely, in hyperthyroid patients the catabolism is increased, the net result is an increase in the effects of the anticoagulants.	Increased or decreased anticoagulant effect depending on thyroid state.	This is a clinically significant interaction. – Hypothyroid patients who are stabilised on warfarin will need a dose reduction when thyroid replacement therapy started. – Hypothyroid patients are relatively resistant to the effects of anticoagulants and need larger doses than hyperthyroid patients who are relatively sensitive. Drug-induced changes in thyroid status will alter the response to the oral anticoagulants.

Warfarin-drug interactions	Mechanism of Interaction	Potential Outcome	Recommended Action or comments
Tramadol	Mechanism unknown. Evidence suggests the interaction may be associated with a variation in metabolism and only a sub-group of patients will be affected.	Increased INR and anticoagulant effect.	The incidence is not known as the interaction is unpredictable. The decrease in INR after tramadol is withdrawn may take several days. Where tramadol is prescribed with warfarin close monitoring of the INR is recommended, especially during the first week of treatment with tramadol.
Trimethoprim	Mechanism unclear.	Increased anticoagulant effect.	There are few clinical reports of a significant interaction, suggesting this interaction is of little clinical significance. The increased anticoagulation occurs when administered as co-trimoxazole.
Valproate sodium	There is certainly some in vitro evidence that the serum binding of warfarin is decreased by sodium valproate so that free warfarin levels rise.	Potentially increased anticoagulant effect.	Interaction appears not to be clinically significant. There is a report that suggests any change in INR is transient when the valproate is added, and the situation rapidly re-stablisies.

Common warfarin-herb interactions.

Warfarin-herb interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Arnica flower	Constituents of arnica can decrease platelet aggregation in vitro. The effect not proven in humans.	Increased risk of bleeding.	Combination should be used cautiously and with close INR monitoring on therapy initiation and cessation.
Celery seed oil	The herb is thought to be a coumarin constituent.	Increased risk of bleeding.	There are no known reports of an interaction and the interaction is theoretical. Prudent to warn patients of potential risks and recommend monitoring for signs of bruising/ bleeding.
Chamomile	The herb is thought to be a coumarin constituent.	Increased risk of bleeding.	Limited evidence available. Prudent to warn patients of potential risks and recommend monitoring for signs of bruising/ bleeding.
Cinchona/quinine	Effect thought to a result of the quinine content.	Increased risk of bleeding.	Combination should be used with caution and INR monitored when therapy initiated or discontinued.
Cranberry juice	Possible mechanism is that the constituents of cranberry juice (possibly flavonoids, which are known to inhibit cytochrome P450 activity) might inhibit warfarin metabolism.	Increases the anticoagulant effect.	The incidence and general clinical importance of this interaction is unknown. Recommendation is that patients on warfarin should limit (maintain consistent consumption) or avoid drinking cranberry juice.
Coenzyme Q10	Postulated to have a Vitamin K-like effect.	Reduced anticoagulant effect.	Some preliminary clinical research suggests coenzyme Q-10 might not significantly decrease the effects of warfarin in patients that have a stable INR. Closely monitor patients taking warfarin and coenzyme Q-10.
Danshen (Tan Seng)	Not clear. May be a result of inhibiting platelet aggregation.	Increased risk of bleeding.	There is enough evidence to suggest the combination should be avoided.
Dong Quai *	Mechanism not clear but dong quai is known to consist of natural coumarin derivatives.	Increased risk of bleeding	Prudent to avoid combination unless close INR monitoring can occur.
Devil's claw	Some evidence it may inhibit liver enzymes, no studies in humans have been conducted.	Increased risk of bleeding.	Devil's claw should be avoided or used cautiously in patients taking warfarin. Close INR monitoring recommended as dose adjustments may be necessary.

Warfarin-herb interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Echinacea	Postulated to be due to an enzyme inhibitory effect.		Interaction is theoretical. Close INR monitoring recommended on therapy initiation and cessation.
Fenugreek	Some of the constituents in fenugreek have antiplatelet effects, although these might not be present in concentrations that are clinically significant.	Increased risk of bleeding.	Clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Feverfew	Some evidence suggests that feverfew may inhibit platelet aggregation, however this has not been demonstrated in humans.	Increased risk of bleeding.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Garlic	Decreased platelet aggregation.	Increased anticoagulant effect.	Clinical significance unclear given the wide use of garlic and the few official reports of an interaction, however may be prudent to avoid combination unless close INR monitoring can occur
Ginger	Not clear but thought to be related to inhibition of platelet aggregation.	Increased anticoagulant effect.	There are no clinical reports of an interaction, despite widespread claims of an interaction. Caution with use of combination is prudent and close INR monitoring recommended.
Gingko biloba	Not clear.	Increased risk of bleeding.	Clinical reports of interaction limited but patients should be told to monitor for early signs of bruising or bleeding and seek informed professional advice if any bleeding problems arise.
Ginseng	Not clear, and there are reports of both an increase and decrease in INR. Panax ginseng has been found to contain antiplatelet components.	Increased anticoagulant effect or decreased INR results.	Prudent to use the combination cautiously, and avoid if bleeding risks are high.
Grape seed extract*	Due to the tocopherol content of grape seed oil (theoretical).	Increased risk of bleeding.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Green tea	Postulated to be due to Vitamin K_1 content of tea. Also contradictory evidence suggests that catechins and caffeine in green tea have antiplatelet activity.	Reduced anticoagulant effects or increased risk of bleeding.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.

Warfarin-herb interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Guarana	Thought to be related to the antiplatelet effects of the caffeine present in guarana (not proven in humans).	Increased risk of bleeding.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Horse chestnut	May be related to antiplatelet effects.	Increased risk of bleeding.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Liquorice	Liquorice may act as a liver enzyme inhibitor or inducer. In animal studies it appears to be an inducer.	Reduced anticoagulant effect.	Patients should be advised to consume a consistent amount of liquorice daily or avoid it completely to ensure stable INR levels.
Milk Thistle	Possibly inhibits liver enzymes, however evidence is conflicting.	Increases the anticoagulant effect.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Papain/Papaya extract	Mechanism not known.	INR results increased.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Red clover	Mechanism not clear. Red clover contains coumarins and is also a liver enzyme inhibitor.	Increased risk of bleeding.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
St John's wort	Mechanism not confirmed but suggested to be due to liver enzyme induction.	Reduces the anticoagulant effects.	Concurrent use should be discussed with doctor as the interaction is of moderate clinical significance. There is not absolute contraindication, however close monitoring of INR required when therapy started, dose changed or therapy discontinued.
Sweet clover	Mechanism not known.	Theoretical increase in risk of bleeding.	Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.
Sweet woodruff	Mechanism not known.		Theoretical risk and clinical significance is unclear. Close INR monitoring recommended on therapy initiation and cessation.

Warfarin-herb interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Vitamin E >400iu/day	Possibly inhibition of platelet aggregation and antagonism the effects of vitamin K-dependent clotting factors.	Increased risk of bleeding.	Effect appears to be dose-dependent, and probably only likely to be clinically significant with 800 units/day or more. Advise patients to avoid high doses of vitamin E, especially in people with low vitamin K intake or other risk factors for bleeding.

Common warfarin-nutritional supplement interactions.

Warfarin-nutritional supplement interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Carnitine	Mechanism not known.	May increase the risk of bleeding.	Reports pertain to acenocoumarol, a shorter acting anticoagulant drug similar to warfarin. An interaction with warfarin is not clear. Patient should be advised to monitor for signs of bruising/bleeding and have an INR done when therapy initiated and/or discontinued.
Cranberry juice	Contains flavonoids which may inhibit warfarin metabolism in the liver and salicylic acid which has antiplatelet effect.	Increased risk of bleeding.	It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks. Increased medical supervision and INR monitoring should be considered for any patient taking warfarin and a regular intake of cranberry juice. It is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin, therefore similar caution should be observed with these products.
Chondroitin	Chondroitin is a small component of a heparinoid and might have weak anticoagulant activity.	May increase the anticoagulant effects.	There is concern that high-dose chondroitin sulfate (2400 mg per day) combined with high-dose glucosamine (3000 mg per day) may enhance the effects of warfarin. There are no reports of an interaction that can confidently be attributed to chondritin. Patient should be advised to monitor for signs of bruising/bleeding and have an INR done when therapy initiated and/or discontinued.
Evening Primrose Oil (EPO)	EPO contains gamma-linolenic acid (GLA), which is postulated to have anticoagulant effects.	May increase risk of bleeding.	Patient should be advised to monitor for signs of bruising/bleeding and have an INR done when therapy initiated and/or discontinued

Warfarin-nutritional supplement interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Fish Oil	Fish oils have antiplatelet effects.	May increase the risk of bleeding.	Conflicting research suggests that 3-6 grams of fish oils per day do not significantly affect INR when used in patients taking warfarin. Patients should be advised to monitor for signs of bruising/bleeding and have an INR done when therapy initiated and/or discontinued.
Flaxseed oil	There is some evidence that flaxseed oil can decrease platelet aggregation .	May increase the risk of bleeding.	Interaction is theoretical. Patient should be advised to monitor for signs of bruising/bleeding and have an INR done when therapy initiated and/or discontinued.
Methylsulphonylmethane (MSM)	Mechanism not known.	May increase the risk of bleeding.	Patient should be advised to monitor for signs of bruising/bleeding and have an INR done when therapy initiated and/or discontinued.

Common warfarin-disease state interactions.

Warfarin-disease state interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Acute diarrhoea/vomiting	Potential for vitamin K deficiency.	Increased warfarin sensitivity.	Close monitoring of INR.
Fever	Increases the rate of degradation of clotting factors.	Increased warfarin sensitivity.	Close monitoring of INR.
Changes in thyroid function	In hypothyroid patients the catabolism of the blood clotting factors (II, VII, IX and X) is low and this tends to cancel out the effects of the anticoagulants.	Decreased INR results and reduced anti-thrombotic effect.	Hypothyroid patients who are stabilised on warfarin will need a dose reduction when thyroid replacement therapy started. Hypothyroid patients are relatively resistant to the effects of anticoagulants and need larger doses than hyperthyroid patients who are relatively sensitive. Drug-induced changes in thyroid status will alter the response to the oral anticoagulants.
	In thyrotoxicosis and hyperthyroid patients the metabolic clearance of some of coagulation factors is increased.	Increased anticoagulant effects.	Less warfarin would be required to prolong the prothrombin time.
Increased age	Evidence indicates that age affects warfarin dose requirements and people are more sensitive to affects of warfarin.	Increased risk of bruising/bleeding.	Closer monitoring for signs of bruising/bleeding and adjust warfarin dose when and as required.
Uncontrolled congestive heart failure (CHF)	Lead to hepatic congestion and reduced metabolism of warfarin and reduced production of clotting factors.	Increased risk of bleeding.	This is a theorised risk and clinical data regarding the clinical significance of impact is lacking. Can be troublesome during exacerbations of heart failure.
Hypoalbuminaemia (albumin <30g/L)	Warfarin is extensively protein bound. A reduction in plasma proteins increases the free fraction of warfarin.	Increase anticoagulant effect.	Closer monitoring on INR.
Smoking cessation	Alters hepatic enzyme function as smoking induces CYP450 enzymes.	Reduced anticoagulant effect.	INR should be monitored and warfarin dose may need adjusting when a long-term smoking quits smoking.

Warfarin-disease state interactions	Mechanism of Interaction	Potential outcome	Recommended Action
Malignancy/shock/sepsis	Increased consumption of coagulation factors and platelets. In some cancers there are subsets of patients who have thrombi and are warfarin resistant.	Increased risk of bleeding.	Increased frequency of INR monitoring required.
Hepatic disease and cirrhosis	Decreased coagulation factor synthesis, thrombocytopaenia and reduced metabolism of warfarin.	Increased INR results and risk of bleeding.	Increased monitoring of INR and monitor for signs of bruising/bleeding.
Renal disease	Acquired platelet dysfunction.	Increased risk of bleeding.	Increased monitoring of INR and monitor for signs of bruising/bleeding.
Weight gain or loss	Mechanism is not clear but postulated to be a result of altered vitamin K absorption through changes in fat content of diet.	Increased or decreased INR.	Monitor INR if large weight gain/loss occurring.

Warfarin and food

- Dietary advice should include:
    - mixing the colours of vegetables at each meal
    - a stable amount of green vegetables daily
    - never having only green vegetables at one meal.
- Foods containing high levels of vitamin K need not be avoided completely, but can be eaten in small, regular amounts.
- The daily variation in consumption of Vitamin K foods should not be greater than 250-500 mcg/day
- Changes in dietary fat content will affect INR as vitamin K is fat soluble so will have greater absorption with a diet high in fat. This will need to be considered if someone is loosing weight and changing the fat content of their diet.

Þ **A constant intake of vitamin K to match the dose of warfarin is the key to good control.**



Sample dishes using a mix of green and other coloured vegetables
(curtsey of Teaching Patients about Warfarin: College of Pharmacists Audioconference. May 2006.

Food	General content	Approx household measure = 100 grams	Micrograms of vitamin K in 100 gram
Tea leaves (green)	High	100 grams	1428
Alfalfa	-	¾ punnet	425-850
Coriander	-	100 grams cooked	1510
Spinach	High	3 cups raw	400
Broccoli	High	2 stems & floret cooked	270
Spring onions	-	100 grams	207
Lettuce (red leaf)	High	2 large head leaves	200
Lettuce (iceberg)	Moderate	-	-
Soya bean	-	3 tablespoons	190
Canola oil	High	-	-
Soybean oil	High	-	-
Mayonnaise	High	-	-
Parsley	High	-	-
Silverbeet	High	-	-
Watercress	High	-	-
Avocado	Moderate	100 grams raw	40
Anlene® milk products	-	200ml milk or 150g yoghurt	40
Wheat germ	-	1 cup	37
Cheese	Low	100 grams	35
Butter	Low	5 tablespoons	30
Dill pickles	Moderate	100 grams	26

Pork liver	-	100 grams	25
Kiwifruit	-	100 grams	25
Asparagus	Moderate	7 spears	21
Potatoes	Low	1 medium	20
Oats	Low	¾ cup	20
Green peas	Moderate	½ cup	19
Ham	Low	3 slices	15
Carrots	Low	¾ cup raw	15
Green beans	Low	¾ cup sliced raw	14
Strawberries	Low	12-14 medium	13
Whole eggs	Low	100 grams	11
Minced beef	Low	100 grams	7
Chicken liver	-	100 grams	7
Tomato	Low	1 medium	5
Cow's milk	Low	100 mls	5
Most seafood (except paua)	Low	100 grams	5
Apple, banana, orange	Low	1 medium piece	<5
Skim milk	Low	100 mls	4
Wheat flour	Low	¾ cup	4
Bread	Low	3-4 slices	4
Cauliflower	Low	-	-
Celery	Low	-	-
Egg plant	Low	-	-
Mushrooms	Low	-	-
Green pepper	Low	-	-
Pumpkin	Low	-	-
Corn	Low	-	-
Oranges/lemons/grapefruit	Low	-	-
Peaches	Low	-	-

Warfarin and alcohol

- See warfarin-drug interactions
- Acute binge drinking is associated with inhibition of cytochrome P450 enzyme (CYP2E1) and an increased INR
- Chronic heavy alcohol intake induces the activity of CYP2E1, resulting in reduced INR.

Þ Abstain from alcohol or a maximum of 2 standard drinks a day.

A standard drink is equal to 10g alcohol which is equal to:

- 300ml beer (ordinary strength)
- 60ml fortified wine (sherry, port, martini)
- 30ml spirits (whiskey, gin, vodka)
- 100ml table wine

Disclaimer

The Waikato Community Pharmacy Group has taken every care to compile accurate up-to-date information however they cannot guarantee its correctness and completeness. Waikato Community Pharmacy Group does not accept responsibility for any errors or omissions nor loss, damage or expense resulting from the use of this information.

Waikato Community Pharmacy Group does not intend for the information provided in this document to be relied upon when making, or refraining from making, any decision. The information is not a substitute for exercising professional clinical judgement.

Members of the public must consult their doctor or pharmacist before undertaking any course of action resulting from information that they have read in this document.

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