



# Interactions with Warfarin



***Warfarin has the potential to interact with numerous drugs resulting in significant morbidity and potentially serious bleeds. Loss of anticoagulant control is one of the most frequent causes of drug related hospital admissions in New Zealand and in many cases the event is precipitated by an agent which alters the anticoagulant effect of warfarin.***

Mechanisms include inhibition or induction of warfarin metabolism, additive or synergistic antiplatelet effects (e.g. aspirin) and changing vitamin K status (e.g. dietary changes and antibiotics). Individual susceptibility may increase the risk of an interaction in some people. For many drugs the supporting evidence for an interaction is relatively weak and based on poor quality case reports. However, the consequences of an interaction are potentially severe so any change (starting or stopping) in drug therapy, diet or herbal/dietary supplement intake should be checked for the potential to alter anticoagulant control.

Rather than an extensive list of individual drugs we have focused on the major drug classes (plus some individual drugs which don't fit) to give some indication of the relative potential for interactions. Hopefully this will be easy to read and digest and prompt the need for further advice on management when necessary. As this 'list' is not totally comprehensive or inclusive our advice is to check any agents's potential to interact with warfarin, especially if you are unfamiliar with the combination.

## Acid regulating drugs

Cimetidine inhibits the metabolism of warfarin and increases its anticoagulant effect. Ranitidine appears not to interact but there have been isolated cases of bleeding.

There have been some reports of bleeding with proton pump inhibitors (PPIs) and warfarin but an interaction is relatively uncommon. An awareness of the slight possibility of bleeding along with the usual monitoring of the INR are required when PPIs are given with warfarin.

## Alcohol

Anticoagulant control can be affected by changes in alcohol consumption. Poor diet and liver damage in alcoholics may also be factors.

## Allopurinol

Most patients are not affected. Clinically important increases in INR are rarely reported.

Monitor the INR when allopurinol is first added.

## Antiarrhythmic Drugs

Amiodarone inhibits the metabolism of warfarin and this interaction occurs in most patients. The onset may be slow (about two weeks) and it may persist for weeks or even months after the amiodarone has been stopped. The anticoagulant effect of warfarin is possibly enhanced by quinidine.

## Analgesics

Most analgesics can increase the bleeding risk when given with warfarin but by different mechanisms. Aspirin and NSAIDs have antiplatelet effects so an increased risk of bleeding can occur without an increase in the INR. Warfarin can increase the severity of a GI bleed caused by aspirin, NSAIDs and COX-2 inhibitors. Other than occasional case reports there is little evidence that NSAIDs increase the INR in people taking warfarin. There is some evidence that the COX-2 inhibitors (e.g. celecoxib, etoricoxib) can cause a significant increase in the INR in some people on warfarin, especially the elderly. Consider monitoring the INR if a COX-2 inhibitor is added to warfarin.

Recent case reports indicate that tramadol can inhibit the metabolism of warfarin and increase its anticoagulant effect.

Regular use of paracetamol can increase the effect of warfarin in some patients. Occasional doses of paracetamol for two to three days are unlikely to have a significant effect, but regular use for a week or more may increase the INR in some patients. Monitor the INR in people starting or stopping regular use of paracetamol.

## Antibacterials

Most antibiotics have been reported to alter the anticoagulant effect of warfarin and the usual mechanism proposed is reduction of vitamin K synthesis by gut flora. Monitoring is recommended when an antibiotic is started or stopped. Clinically significant interactions appear to be more likely with ciprofloxacin, norfloxacin, macrolides (e.g. erythromycin) and metronidazole, where enzyme inhibition is also possibly involved.

Rifampicin is a potent enzyme inducer and can reduce the effect of warfarin.

## Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) have antiplatelet effects and as well as increasing the risk of bleeding *per se* they can enhance the risk of bleeding with warfarin without increasing the INR. There are also isolated case reports of SSRIs causing an increase in INR. Advise people to report signs of bleeding and consider monitoring the INR when an SSRI is added.

The effects of warfarin are occasionally increased by venlafaxine, sometimes with an increase in the INR.

With tricyclic antidepressants (TCAs) there are isolated reports of changes in the INR but the evidence for an interaction is poor and inconclusive. Monitor INR as normal.

St John's Wort can decrease the effect of warfarin in some people. The CSM in the UK advise against concurrent use.

## Antidiabetics

There are isolated reports of enhanced anticoagulant effect or hypoglycemia with sulphonylureas but evidence of a clinically significant interaction with warfarin is very weak and appears to be very unlikely.

## Antiepileptics

The metabolism of warfarin can be increased by carbamazepine, phenytoin and phenobarbitone (reduced anticoagulant effect). Enhanced anticoagulant effect has been reported with phenytoin and sodium valproate.

The evidence for clinically significant drug interactions is strongest with carbamazepine and phenobarbitone (reduced anticoagulant effect) but consider monitoring all patients started on concurrent therapy.

## Antifungals

Fluconazole inhibits the metabolism of warfarin and a clinically significant interaction occurs in most patients. A reduction in the dose of warfarin (20–70%) is usually required. Miconazole also inhibits the metabolism of warfarin and potentially serious bleeds have been reported when miconazole preparations (including oral gel and vaginal preparations) have been given in combination with warfarin. Miconazole or fluconazole should not be co-administered with warfarin unless the INR can be very closely monitored.

Apart from isolated case reports, there is very little evidence that itraconazole or ketoconazole interact in the same way.

## Antivirals

The anticoagulant effect of warfarin can be enhanced or reduced by ritonavir and nevirapine.

## Clopidogrel

The anticoagulant effect of warfarin is enhanced due to antiplatelet action.

## Corticosteroids

The anticoagulant effect of warfarin may be enhanced or reduced by low to moderate oral doses of corticosteroids (e.g. prednisone, methylprednisolone, dexamethasone), although the supporting evidence is weak and a clinically significant interaction does not usually occur. High doses of corticosteroids appear to be more likely to cause a significant effect (increased INR).

## Cytotoxics

Anticoagulant effect possibly enhanced by etoposide, fluorouracil and ifosfamide and reduced by azathioprine and mercaptopurine.

## Dipyridamole

Increased bleeding risk due to antiplatelets effects.

## Disulfiram

Disulfiram enhances the anticoagulant effects of warfarin and an interaction (increased INR) probably occurs in most people.

## Enteral Foods

These are often high in vitamin K which may reduce the effect of warfarin.

## Foods and Juices

A change in diet, especially changing intake of vegetables, fruits and juices high in vitamin K can affect anticoagulant control. The range of possible foods that interact ranges from avocados to ice cream. Generally only significant or sustained dietary changes are likely to have an effect so people should be advised to discuss planned dietary changes with their GP or pharmacist. Patient information leaflets provide further advice.

Cranberry juice seems to have a different effect and compounds in the juice may inhibit the metabolism of warfarin. There have been several reports of bleeding and although information is limited the Committee on Safety of Medicines (CSM) in the UK advise against drinking cranberry juice whilst taking warfarin.



## Herbals and supplements

All people taking warfarin should check with their GP or pharmacist before taking herbal preparations or dietary supplements.

Fenugreek, dong quai, ginkgo biloba and garlic are amongst those reported to increase bleeding risk, without a change in INR (i.e. due to antiplatelet effect). Ginseng has been reported to decrease the INR.

St John's Wort can decrease the effect of warfarin in some people. The CSM in the UK advises against concurrent use.

## Hormone Antagonists

Anticoagulant effect can be enhanced by danazol (inhibits metabolism of warfarin), flutamide and tamoxifen. All these interactions are established and clinically important and concurrent therapy requires close monitoring of the INR. Tamoxifen and warfarin is the commonest combination seen in practice and dose reductions of warfarin of 30–50 % or more are sometimes required.

## Leflunomide

Anticoagulant effect of warfarin possibly enhanced. In case reports an increased INR has occurred after just two or three doses.

## Lipid lowering drugs

Simvastatin can cause small increases in the INR in some people taking warfarin but a dose reduction of the latter is not usually required. Atorvastatin does not appear to interact with warfarin. The interaction with fluvastatin and lovastatin may be more significant.

Cholestyramine has been reported to enhance or reduce the effect of warfarin.

Bezafibrate has been occasionally reported to increase the INR in people taking warfarin.

## Oestrogens and progestogens

Anticoagulant effect is antagonised

## Orlistat (Xenical)

Pharmacokinetic studies indicate no interaction but fluctuations in anticoagulant control may occur in practice. Consider monitoring the INR if orlistat is added to warfarin treatment.

## Thyroid Hormones (thyroxine)

A well documented and clinically important interaction. In people with hypothyroidism who are also taking warfarin, the addition of thyroxine usually results in an increased anticoagulant effect and a reduction in the dose of warfarin is necessary. The change in anticoagulant effect may be gradual as the dose of thyroxine is titrated. The addition of an antithyroid drug (e.g. carbimazole) may necessitate an increase in the warfarin dose.

## Sibutramine (Reductil)

There is an increased risk of bleeding when sibutramine given with warfarin.

## Vitamin preparations

Vitamin K containing preparation can antagonise the effects of warfarin. Check the vitamin K content of multivitamin preparations and dietary supplements.

## Bibliography

*This information is based on;*

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British National Formulary (BNF). BMJ Publishing Group and Royal Pharmaceutical Society of GB

Bachmann KA (Ed). Drug Interactions Handbook. Lexicomp, Ohio.