What You Should Know About Your Diet and Warfarin

What is warfarin?

Warfarin is a medication that helps "thin" your blood to decrease your body's chance of forming harmful clots. Unwanted blood clots may cause strokes, heart attacks, or other potentially harmful events such as clots in the legs (deep vein thrombosis) or lungs (pulmonary embolism).

How does warfarin work?

There are proteins in your blood to help form clots. These proteins are made by your liver with the help of vitamin K. Warfarin works by blocking the effects of vitamin K, making it harder for your body to form clots. In order to make sure the amount of warfarin you're taking is right for you, your healthcare professional will test your blood periodically. The blood test checks your protime (PT) or international normalized ratio (INR) to measure how long it takes for your blood to clot. If your PT/INR is outside your target range, your warfarin dose will need to be adjusted.

How does your diet affect warfarin?

Since vitamin K and warfarin work against each other, the amount of vitamin K in your diet can change warfarin's effects. It is important to keep your dietary intake of vitamin K consistent. Foods such as green leafy vegetables and certain oils have higher contents of vitamin K. (See the next page for a chart of vitamin K content in selected foods). If you DECREASE your intake of vitamin K (eat fewer foods containing vitamin K) your dose of warfarin may need to be lowered to prevent bleeding. If you INCREASE your intake of vitamin K, your dose of warfarin may need to be increased to prevent blood clots. A MAJOR change in your vitamin K intake can affect your PT/INR, but normal daily variation in the foods you eat is okay. You DON'T have to avoid foods that are high in vitamin K, just keep your diet consistent. You should let your healthcare professional know if there is going to be a major change in your diet, so your PT/INR can be closely monitored.

Many people are on special diets, such as the Atkin's or South Beach diets, to lose weight. These diets are high protein diets and can also affect the way warfarin works in your body. Once you take a dose of warfarin, some of it binds to protein in your bloodstream. While warfarin is attached to this protein, it has no effect on your body. It's thought that high protein diets can increase the amount of proteins in your body and cause more warfarin to be bound to protein. This causes a DECREASE in warfarin available to prevent clots, so your warfarin dose may need to be increased. Always check with your healthcare professional before starting any special diets, so your PT/INR can be closely monitored.

Certain foods can also affect how your liver clears warfarin from your body, causing warfarin levels to increase or decrease. Examples include alcohol, cranberry products (e.g., juice, supplements), and possibly grapefruit or grapefruit juice. Too much alcohol, cranberry products, or grapefruit products can INCREASE warfarin's effect and increase your risk of bleeding. Avoid or limit your intake of alcohol, cranberry products, and grapefruit or grapefruit juice. Make sure your healthcare professional knows if your diet contains any of these products, so your PT/INR can be closely monitored.

Other things to remember when taking warfarin

In addition to foods, many prescription and over-the-counter drugs, including vitamins and herbal supplements, can affect your warfarin level. You should not start, stop, or change doses of any drugs or supplements without first talking with your healthcare professional. Try to keep a healthy, well-balanced diet and keep your vitamin K intake consistent. Take your warfarin dose around the same time each day. If you miss a dose, take it as soon as you remember. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Don't double up doses without checking with your healthcare professional. Tell your healthcare professional immediately if you have unusual bleeding or bruising, black or bloody stools, blood in the urine, or stomach pain.

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Vitamin K Content of Selected Foods*

Note: This is <u>NOT</u> a list of foods to avoid. This list provides information on the vitamin K content of certain foods.

Vitamin K Content			
Foods	**Low**	**Moderate**	**High**
Vegetables			
	Green beans	Asparagus	Broccoli
	Carrots	Avocado	Brussels sprouts
	Cauliflower	Red Cabbage	Cabbage
	Celery	Green peas	Collard greens
	Corn		Endive (raw)
	Cucumber (peel removed)	Pickle (dill)	Kale (raw leaf)
	Eggplant	Lettuce (iceberg)	Lettuce (bib, red leaf)
	Mushrooms		Mustard greens (raw)
	Onions		Parsley
	Green pepper		Spinach
	Potato		Turnip greens (raw)
	Pumpkin		Watercress (raw)
	Sauerkraut (canned)		Swiss chard
	Tomato		
Fruits			
	Apple		
	Banana		
	Blueberries		
	Grapes		
	Orange		
Meats			
	Beef		
	Chicken		
	Pork		
	Tuna		
	Turkey		
Fats and Oils			
	Corn oil	Margarine	Mayonnaise
	Peanut oil	Olive oil	Canola oil
	Safflower oil		Soybean oil
	Sesame oil		
	Sunflower oil		
Dairy Products			
	Butter		
	Cheese (cheddar)		
	Eggs		
	Sour cream		
	Yogurt		
Beverages			
	Coffee		
	Cola		
	Fruit juices		
	Milk		
	Tea (black)		Tea (green)**

* Adapted with permission from Clotcare Online Resource at www.clotcare.com. (Accessed April 20, 2005).

** There is some controversy as to whether brewing green tea alters the vitamin K content and/or whether green tea may alter the effect of warfarin by some other mechanism.

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Detail-Document #210507

–This Detail-Document accompanies the related article published in–

PHARMACIST'S LETTER / PRESCRIBER'S LETTER

May 2005 ~ Volume 21 ~ Number 210507

Warfarin-Food Interactions

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Background

The interaction between warfarin and vitamin K-containing foods is well documented. Patients on warfarin therapy are instructed to report any significant changes in their dietary vitamin K intake in order to maintain a therapeutic international normalized ratio (INR). However, possible interactions between warfarin and high protein diets, foods with antiplatelet effects, or foods that affect the cytochrome P450 enzyme system are not as well documented.

Warfarin is a racemic mixture of R-warfarin and S-warfarin enantiomers.[1] Warfarin is predominately metabolized by the cytochrome P450 enzyme system.[1] The two warfarin enantiomers have different therapeutic potency and are metabolized by different CYP450 isoenzymes. S-warfarin is the most potent of the two enatiomers.[1,2] S-warfarin is primarily a substrate for CYP2C9 and secondarily CYP3A4.[2] R-warfarin is primarily a substrate for CYP1A2, secondarily CYP3A4, and slightly CYP2C19.[2] Foods that induce these isoenzymes can decrease warfarin effect and foods that inhibit these isoenzymes can potentiate warfarin effect.[2] The significance of the interaction will depend on which isoenzyme(s) the food affects and how much of the implicated food is consumed.

Theoretically, foods such as cranberry juice, grapefruit juice, mango fruit, charbroiled foods, alcohol, and caffeine can affect warfarin metabolism via the CYP450 enzyme system and potentially alter warfarin effects.

High Protein Diets

In the last few years, the popularity of high protein, low carbohydrate diets, such as the Atkins diet and South Beach diet has soared in the U.S. Patients get on these diets in hopes of shedding extra pounds. The diets instruct patients to increase dietary intake of protein and decrease intake of carbohydrate-containing foods. Both diets have an induction phase, where patients are to eliminate almost all carbohydrates from their diet for at least two weeks.[3,4] Anticoagulation clinicians are seeing more INR fluctuations in patients who are on high-protein, low-carbohydrate diets. There are two case reports of decreased INR after initiation of high-protein, low-carbohydrate diets, requiring warfarin dosage to be increased by 20% to 30% to achieve therapeutic INR.[5]

Warfarin is a medication that is highly protein bound.[1] The decreased INR in patients following initiation of a high-protein, low-carbohydrate diet may be related to the effect of protein intake on albumin level.[5] An increase in albumin level appears to occur within ten days of initiating a high-protein, low-carbohydrate diet.[5] The increase in albumin level causes an increase in warfarin binding to albumin, making less free warfarin available for anticoagulant effect.[5] Some experts suggest that a high-protein, low-carbohydrate diet may also have an affect on warfarin's metabolism via the cytochrome P450 system.

Because of the potentially significant decrease in INR level, patients are at high risk of developing thromboembolism shortly after starting the diet. Advise patients to consult their anticoagulation clinician prior to starting a high-protein, low-carbohydrate diet in order to ensure close monitoring of INR level [Evidence level D; Anecdotal evidence].[5]

Cranberry Juice

In 2003, the England-based Committee on Safety of Medicine (CSM) issued a warning about the possible interaction between cranberry juice and warfarin based on five case reports of such interactions.[6] The potential interaction is suspected to be due to flavonoids found in cranberry. It is theorized that the flavonoids in cranberry might inhibit CYP2C9 metabolism of warfarin, and therefore, increase INR.[7,8] Another

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theoretical mechanism of interaction is the antiplatelet effect of the cranberry constituent, salicylic acid.[8] Cranberry juice contains approximately 7 mg of salicylic acid per liter. Drinking three 250 mL servings of cranberry juice daily for two weeks increases serum salicylate levels.[8] Theoretically, the salicylic acid in cranberry could potentiate warfarin's anticoagulant effect. It is not known how different cranberry products affect warfarin metabolism or if this interaction can be avoided by separating doses or limiting cranberry product consumption. For now, advise warfarin patients to avoid or limit cranberry product consumption. Closely monitor warfarin patients who are consuming cranberry products concurrently [Evidence level D; Anecdotal evidence].[9]

Grapefruit Juice

Grapefruit juice contains flavonoids that can inhibit CYP3A4, CYP2C9, CYP2C19, and CYP1A2 isoenzymes.[2,10] The effect of grapefruit juice on drugs is difficult to predict because the amount of flavonoids may vary from product to product and the uptake of these flavonoids may also vary among individuals.[10] Theoretically, grapefruit juice and the fruit itself might increase warfarin effect by competing with both R-warfarin and S-warfarin metabolism. There is one case report of significantly increased INR associated with consumption of 50 ounces of grapefruit juice daily.[10] But a small clinical trial found that consumption of 24 ounces of grapefruit juice daily for one week had no effect on INR in a group of men on warfarin therapy.[10] Given the inconsistent findings and lack of clinical research, the best advice now is to advise warfarin patients to avoid or limit grapefruit juice consumption to 24 ounces or less a day [Evidence level D; Anecdotal evidence].[10] Monitor INR closely if a large amount of grapefruit juice or grapefruit consumption and warfarin use occur concomitantly [Evidence level D; Anecdotal evidence].[10]

Alcohol

Interactions between alcohol and warfarin have been reported. There are two possible mechanisms of interaction with alcohol: alteration of protein binding and inhibition or induction of CYP2C9 isoenzyme.[11] An increase in blood alcohol levels competes for protein binding sites, making more active warfarin available for clinical activity.[12] Acute alcohol consumption can decrease warfarin metabolism and increase warfarin effect, whereas chronic alcohol consumption can induce warfarin metabolism and decrease warfarin effect.[12] Due to the increased risk of bleeding with acute alcohol consumption, patients should be advised to avoid or limit alcohol consumption while on warfarin [Evidence level D; Anecdotal evidence].[12]

Mango Fruit

There are at least thirteen cases of increased INR associated with mango fruit consumption reported.[13] The subjects ingested anywhere from one to six mangos daily for two days to a month. The average increase in INR was 38%. It is theorized that mango fruit inhibits CYP2C19; therefore, inhibit R-warfarin metabolism and increase INR.[13] Advise patients to limit consumption of mangos while on warfarin therapy [Evidence level D; Anecdotal evidence].[13]

Caffeine and Charbroiled Foods

Caffeine and charbroiled foods both have an effect on the CYP450 enzyme system and theoretically can affect warfarin metabolism; however, there are no case reports or evidence to support such interactions. Caffeine is a substrate for CYP1A2 and theoretically may compete with R-warfarin for metabolism.[2] The hydrocarbons of charbroiled food can induce CYP1A2, therefore can theoretically increase R-warfarin metabolism and decrease warfarin effect.[2] Due to the lack of evidence of these interactions, the best advice right now is to tell warfarin patients to keep their caffeine consumption consistent and limit consumption of charbroiled foods [Evidence D, Anecdotal evidence].[2]

Garlic

Garlic can inhibit platelet aggregation and theoretically can potentiate the effects of warfarin.[14] There are case reports of excessive garlic or garlic supplement consumption associated with altered platelet aggregation and prolonged bleeding.[15] In addition, there are two anecdotal reports of increased INR in patients previously stabilized on warfarin when they took garlic products.[15] Patients taking warfarin should

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be advised to avoid garlic supplements [Evidence level D; Anecdotal evidence].[15] They should also be advised that regular consumption of foods containing small amounts of garlic is unlikely to have an effect on warfarin efficacy [Evidence level D, Anecdotal evidence].[15] Monitor INR closely if excessive garlic consumption and warfarin occurs concomitantly [Evidence level D, Anecdotal evidence].[15]

Ginger

Ginger is thought to inhibit thromboxane synthetase and decrease platelet aggregation.[16] Theoretically, excessive consumption of ginger might increase the risk of bleeding. There is a case report of increased INR when ginger supplements were used concomitantly with phenprocoumon, a coumarin derivative.[17] Regular consumption of food containing ginger is unlikely to pose a problem in patients taking warfarin. However, ginger supplements contain much more ginger than regularly found in food and might have the potential of increasing bleeding risk in patients taking warfarin. Patients taking warfarin and ginger supplements concomitantly should be advised to watch for symptoms of unusual bleeding or bruising and their INR should be monitored closely [Evidence level D; Anecdotal evidence].[15]

Green Tea

There are constituents in green tea that seem to have antiplatelet effects and theoretically might increase the effect of warfarin.[18] However, there are no reports of green tea increasing the effect of warfarin in patients to date. Excessive consumption of green tea has been reported to antagonize the effects of warfarin in a patient previously stable on warfarin therapy.[19] The interaction has been attributed to the vitamin K1 content or possibly other constituents in green tea.[18,19] The amount of vitamin K1 content or other constituents vary greatly among different green tea products depending on their sources and processing; therefore, it's difficult to determine how much green tea consumption would have an effect on warfarin. Patients should be advised that excessive consumption of green tea might decrease the effectiveness of warfarin. Close monitoring is warranted if concomitant use of large amounts of green tea and warfarin is expected [Evidence level D; Anecdotal evidence].[19]

Soy

Soybeans contain vitamin K and may also inhibit platelet aggregation.[20] Different soy preparations have varying amounts of vitamin K content. There is a case report where a patient's INR decreased significantly after consuming soy milk daily for four weeks.[20] However, the vitamin K content of soy milk is so low that there are probably other mechanisms for the interaction between warfarin and soy milk. It's been theorized that soy can also decrease the absorption of warfarin, but the exact mechanism of interaction is unknown.[20,21] Advise patients to limit consumption of soy products and monitor INR closely if consumption of soy products and warfarin occurs concurrently [Evidence level D; Anecdotal evidence].[21]

Conclusion

Most of the available information on these potential drug-food interactions is based on *in vitro* data or case reports. Without well-designed clinical trials, it is difficult to prove a definitive cause and effect relationship between these foods and warfarin.

Drug-food interactions with warfarin can potentially lead to hemorrhage or thromboembolism. Therefore, it is important that healthcare professionals are aware of the potential implications of these drug-food interactions with warfarin. Patients should be aware that changes in dietary habits can sometimes affect warfarin efficacy and should be advised to consult their healthcare professional prior to making major changes in their diet.

In addition to foods, a number of dietary supplements may also affect warfarin's efficacy. (See the chart on the next page for a list of selected dietary supplements that may increase or decrease warfarin effectiveness). For more details on interactions between warfarin and dietary supplements, please refer to *Natural Medicines Comprehensive Database* at http://www.naturaldatabase.com. If you see a possible interaction between certain foods/supplements and warfarin, use the online reporting form at https://www.accessdata.fda.gov/scripts/medwatch/ to submit a report to the FDA.

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Potential Interactions of Dietary Supplements with Warfarin[a]

Potential Increase in Risk of Bleeding		
Acetyl-L-carnitine	Fish oil	Mate
Arnica	Flaxseed, Flaxseed oil	Melatonin
Alcohol, acute use	Fo-ti	Mesoglycan
Bishop's weed	Forskolin	Milk thistle
Black tea	Forsythia	N-acetyl glucosamine
Bladderwrack	Gamma-linolenic acid	Nattokinase
Boldo	Garlic	Oolong tea
Borage seed oil	Ginger	Pantethine
Burdock	Ginkgo	Papaya
Caffeine	Ginseng, Siberian	Peppermint oil
Chondroitin sulfate	Glucosamine	Propionyl-L-carnitine
Cod liver oil	Grapefruit, Grapefruit juice	Red clover
Coltsfoot	Guarana	Reishi mushroom
Cranberry, cranberry juice	Guggul	Resveratrol
Danshen	Holy basil	Saw palmetto
Devil's claw	Honeysuckle	Sea buckthorn
Dong quai	Horse chestnut	Tiratricol
Epimedium	Ipriflavone	Turmeric
Eucalyptus oil	Jiaogulan	Vinpocetine
Evening primrose oil	Kava	Vitamin A
Fenugreek	L-carnitine	Vitamin E
Feverfew	Lycium	Willow bark
		Wintergreen
Possible Decrease in Warfarin's Effects		
Acerola		
Alcohol, chronic use		
Alfalfa		
Cherokee rosehip		
Chlorella		
Coenzyme Q10		
Corn silk		
EDTA		
Ginseng, American		
Ginseng, Panax		
Green tea		
Limonene		
Rose hip		
Smartweed		
Soy		
Spinach		
St. John's wort		
Stinging nettle		
Vitamin C		
Vitamin K		
Watercress		

[a]Adapted from *Natural Medicines Comprehensive Database* at www.naturaldatabase.com. (Accessed 4/21/05).

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Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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Cite this Detail-Document as follows: Warfarin-food interactions. Pharmacist's Letter/Prescriber's Letter 2005;21(5):210507.

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