



# Food and Lifestyle Interactions With Warfarin

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- Upon successful completion of this article, the pharmacist should be able to:
1. Identify the pharmacodynamics and/or pharmacokinetics and their relationship to certain food, dietary supplement or lifestyle interactions with warfarin.
  2. Recognize the level I causation, level II causation, and level III causation in regard to the risk of certain food or dietary supplement interactions with warfarin therapy.
  3. Identify at least three less commonly recognized foods that will increase the effects and efficacy of warfarin therapy.
  4. Identify at least six less commonly recognized foods or dietary supplements that will decrease the effects and efficacy of warfarin therapy.
  5. Identify at least five specific lifestyle interactions with warfarin therapy.
  6. Discuss dietary and lifestyle monitoring, modifications, and proper counseling for patients at risk for interactions with warfarin therapy.

Upon successful completion of this article, the pharmacy technician should be able to:

1. Identify food, dietary supplement, or lifestyle interactions with warfarin therapy.
2. Recognize potential interactions requiring review by the pharmacist.
3. Recognize potential signs of bleeding in patients on warfarin therapy requiring pharmacist attention.

4. Describe the potential for harm to the patient if goals of warfarin therapy are not met.

Warfarin is one of the most commonly prescribed drugs for anticoagulation in North America. Warfarin is an anticoagulant used to prevent and manage venous thromboembolism (VTE). It is also employed in the prevention of stroke and systemic embolism with cardiac valve replacement, atrial fibrillation, and coronary artery disease (CAD). Warfarin's mechanism of action involves inhibiting vitamin K-dependent clotting factors II, VII, IX, and X and the anticoagulant proteins C and S.

Despite its widespread use, warfarin is not without limitations. Due to a narrow therapeutic index, a somewhat unpredictable pharmacokinetic profile, and the potential to interact with a number of drugs, foods, dietary supplements, and certain lifestyles, routine laboratory monitoring is required for safe and effective use. The International Normalized Ratio (INR) is the laboratory test used to measure the efficacy and safety of warfarin. The therapeutic INR range for patients on warfarin is usually 2.0 to 3.0. The exception is for patients with mechanical heart valves for whom the range is 2.5 to 3.5. If the INR becomes elevated above the therapeutic range, the patient is at risk for bleeding. Higher INR values indicate the risk to the patient of bleeding events outweighs the benefit of warfarin therapy. Conversely, if a patient's INR falls below 2.0, the INR is considered sub-therapeutic and the patient is no longer protected from clotting events. It is also important to monitor drug plasma levels, clearance, and half-life when patients engage in certain lifestyles, such as smokeless tobacco and marijuana use, which will be discussed in more detail later. INR remains the most commonly used measure

to evaluate both the safety and efficacy of the drug and thus it is measured most frequently. INR fluctuations are somewhat common during the initiation of treatment as the clinician works to find the ideal dosing regimen for the patient. However, a large fluctuation in the INR after therapy has been stabilized is a cause for concern. These fluctuations could be indicative of a change in diet or lifestyle and it is important to know how to both manage this clinical situation and counsel the patient. Oral, subcutaneous, or intravenous vitamin K (phytonadione) can be administered if rapid correction of INR is warranted.

The purpose of this article is to provide the community pharmacist with the knowledge necessary to identify the potential food, dietary supplement and lifestyles that may interact with warfarin and provide recommendations for management. The article will focus on the level of causation with certain food interactions, proposed mechanism of specific food and lifestyle interactions, how these interactions interfere with warfarin therapy, and what can be done to counteract or eliminate the interaction. It will also provide patient counseling tips for pharmacists as they encounter patients receiving warfarin therapy who may experience food, dietary supplement, or lifestyle interactions.

The foods that will potentially cause notable interactions with warfarin are mango, grapefruit, cranberry, and those with high vitamin K content such as certain green leafy vegetables, oils, multi-vitamins, herbal supplements, edible seaweed, avocado, and soy milk. The lifestyle interactions that will potentially cause notable interactions with warfarin are chronic alcohol consumption, binge alcohol consumption, cigarette smoking, smokeless tobacco use, and marijuana use.

There are several food interactions that may occur with warfarin that have the potential to either potentiate or inhibit the effects of warfarin therapy in patients. Some health care providers will suggest that their patients avoid foods that are high in vitamin K content in order to possible interactions with warfarin. However, with proper monitoring and counseling, this is not necessary or practical. The key is "moderation," which will be covered more extensively throughout the article. However, it is important to keep in mind that the level of causation of the possible interaction with warfarin, the type of interaction, the mechanism of the interaction, recommendations for managing warfarin with concurrent use of the offending agent, and patient counseling tips should be clearly understood by both health care providers and patients to get the best results from warfarin therapy.

The level of causation that will be utilized in this article with each food interaction is supported by a previously completed "systematic overview of warfarin and its drug and food interactions" in which 642 citations were retrieved. In this overview, of the 642 articles, 181 eligible articles contained original reports on 120 drugs or foods, of which 86 percent were single case reports. To note, there were 31 incidents of clinically significant bleeding in case reports alone. This information is particularly important to express to the reader because the data contained in this current article is not based on several large, randomized trials. The information in this article is based mainly on many case reports and some small studies with the intention of bringing awareness to the possibilities of interactions that as pharmacist we don't always recognize.

For each food interaction, the probability of the proposed interaction was rated from level I (highly probable) to level IV (highly improbable). Definitive evidence of an interaction required a level I causation rating from both healthy volunteers and patient-based reports in which both described identical interaction direction and severity. Level designation was based on fulfillment of seven standard causation criteria. In this article, only foods rated with level I, level II, and level III causation will be discussed, primarily because the main purpose of this article is centered around patients at high risk for adverse events due to sub- or supratherapeutic warfarin treatment; patients identified with interactions within levels I, II, and III will require the most counseling contacts and assistance by pharmacists.

Foods were assigned a level III causation (possible interaction) if the following *standard criteria of causation* applied:

- 1) The timing was correct for an interaction to be pharmacologically plausible.

In addition to the standard criteria, any one *additional criteria* from the following list must be met for level III causation:

1. Laboratory tests such as INR or prothrombin, support the contention of an interaction.

2. Other potential factors affecting warfarin pharmacokinetics/pharmacodynamics were ruled out successfully.
3. The patient had a similar result with previous exposure to the same drug.
4. The alterations in the quantity of the implicated interacting food being consumed with warfarin correlated with subsequent changes in coagulation variables, inferring a dose-response relationship.
5. The patient was rechallenged and had a similar response occur.
6. Other objective evidence such as plasma levels of warfarin or coagulation factors were identified.

Foods were assigned a level II causation (probable interaction) if the standard criteria of causation was met, number 1 of the additional criteria was met plus any other of the additional criteria of causation was met. Foods were assigned a level I causation (highly probable interaction) if the standard criteria of causation was met, number 1 and 2 of the additional criteria of causation were met, plus any other of the additional criteria of causation was met. Other potential factors which must be ruled out in additional criteria 2 include diet, other interacting medications, and certain medical conditions (hepatic dysfunction and hyperthyroidism).

### **FOODS CAUSING POTENTIATION**

Foods that interact with warfarin by causing potentiation of the effects of warfarin will increase the risk of bleeding in patients. Usually, foods that potentiate the effects of warfarin do so by inhibiting the metabolism of warfarin, ultimately resulting in accumulation of warfarin in the body; however, other mechanisms may also exist. This will be expressed by an elevated INR and signs or symptoms of bleeding present in the patient.

#### **Mango**

Mangos are a tropical fruit originating from Southeast Asia. There are many different types of mangos, but most of the species consumed from the

United States are imported from Mexico and South America. Mangos are used in several recipes of Asian, Indian and South American origin. In these venues, mangos are used in drinks, salsas and stir-fry. Mango often accompanies sticky rice, a popular dessert. In many American venues, many chefs and bakers flavor muffins, cookies, and cakes with pureed mango, serve the fruit as a dessert such as a mango crisp or pair mango with meats like pork, chicken or shrimp. It is also slice or diced and eaten alone or placed in fruit salads, smoothies, or alcoholic beverages. Mango is classified a level I causation, which is highly probable of having an interaction if consumed in large amounts with warfarin.

The result of consuming large amounts of mango during warfarin therapy is highly probable potentiation or enhancement the anti-coagulation effects of warfarin in patients. The exact interaction mechanism is unknown, but may be related to the vitamin A content, which may inhibit the metabolism of warfarin. In one small study, mango consumption was associated with an increased INR in 13 patients followed by a positive rechallenge in two of those patients. Patients were consuming one to six mangos a day for two to 30 days before the INR was tested. INR values decreased in all 13 patients after discontinuing mango ingestion. As previously stated, the mechanism for this interaction has been theorized to be related to the high amount of vitamin A in mangos. Human studies have shown that vitamin A (retinol) inhibits CYP 2C19 enzymes.

#### **Grapefruit Juice**

The grapefruit is a tart and tangy citrus fruit with an underlying sweetness. It is available for consumption throughout the year. However, it is primarily in season and best to eat from the winter months through early spring. Grapefruit comes in several varieties, with some containing seeds and others without, and in different colors such as pink or white in regards to the pulp of the fruit. Grapefruit is used in a variety of recipes such as leafy salads, citrus tarts, flavored and garnished cakes, flavored and garnished cheese-cakes, grapefruit sorbet, flavor and garnish for savory dishes and fruit salads. Grapefruit juice can be prepared fresh, or bought fresh or frozen. Candied grapefruit peel is a sweet snack and is seen alone dipped in chocolate or as a garnish in salads and desserts. Grapefruit can be eaten fresh from the tree by itself—raw or roasted. Grapefruit is classified as a level II causation which will probably cause an interaction if consumed with warfarin.

The result of consuming grapefruit during warfarin therapy will probably potentiate or enhance the anticoagulant effects of warfarin in patients. Grapefruit juice is a well-known inhibitor of cytochrome P450 (CYP) liver enzymes, primarily CYP3A4, CYP1A2 and CYP2A6. There are two proposed theories for an interaction with grapefruit juice and warfarin. The first is that the accumulation of the R-enantiomer of warfarin via inhibition of its metabolism by CYP3A4 and could result in a clinically significant increase in INR. This mechanism involves the flavonoids component of grapefruit juice, naringenin, which exerts an inhibitory effect on CYP 3A4. A second theory involves another component of grapefruit, bergamottin (furocoumarine) which inhibits CYP 2C9. The primary hepatic isozyme responsible for the metabolism of the warfarin S-enantiomer is CYP2C9. However, when considering this theory, there is evidence that only the CYP enzymes in the gastrointestinal wall are inhibited by grapefruit juice, which would mean only drugs with high first pass metabolism are affected. Warfarin does not undergo first pass metabolism, so its metabolism is not likely to be inhibited by this mechanism. Additionally, an observational study following 10 men found no significant changes in INR with ingestion of 1.5 liters of prepared frozen grapefruit juice from concentrate per day for eight days. The authors following that study commented that it is unknown whether or not grapefruit juice prepared from fresh fruit would have had a different effect than their prepared frozen grapefruit juice, because it is unclear if the flavonoids in grapefruit juice are stable when frozen.

However, in contrast, a case report of one man who began to drink 1.5 liters of grapefruit juice per day attributes a greater than twofold increase in INR to grapefruit juice. Fad diets that focus on grapefruit and grapefruit juice may put patients at risk for bleeding events. It is important to note that smaller quantities of grapefruit juice do not appear to create a problem or any significant changes with INR values.

### **Cranberry**

Cranberries are a major crop in certain areas in the United States and also in Canada. Most cranberries are processed into products such as juice, sauce, and dried cranberries. Cranberries are used in several recipes such as quick breads, cranberry sauces and relishes, cranberry vinaigrette, spreads, and pastries, to name a few. Cranberry juice is consumed on its own or in punches, cocktails and alcoholic beverages. Cranberries are classified as a level III

causation, which will possibly cause an interaction if taken with warfarin.

The result of consuming cranberry during warfarin therapy will possibly potentiate or enhance the anticoagulant effects of warfarin in patients. Several mechanisms of the interaction between cranberry juice and warfarin have been postulated. One potential mechanism involves salicylic acid, a common constituent of cranberries, which has an antiplatelet effect that can increase the risk of bleeding. A possible explanation for the INR increase may stem from the increased concentration of salicylic acid, which is highly protein bound and causes a displacement of warfarin from albumin binding sites. Salicylic acid is 50–80 percent bound to plasma proteins, and salicylate exhibits high protein binding (90 percent ) at low and therapeutic serum concentrations. However, toxic levels are associated with a lower percentage of protein binding (76 percent) and higher free levels. Therefore, the salicylic acid content in cranberry juice leads to low serum levels of salicylic acid and a high percentage of protein binding. Another possible explanation for the increase in INR in patients taking warfarin and drinking cranberry juice possibly involves the presence of flavonoids in cranberry extract, causing an effect on the CYP system similar to those mentioned with grapefruit juice. Although the exact mechanism for a cranberry and warfarin interaction is not well understood, case reports substantiate the likelihood that a clinically significant interaction can occur when patients taking warfarin drink large amounts of cranberry juice for prolonged periods of time.

There are at least three published case reports describing a potential cranberry juice and warfarin drug interaction. The first case involved a male patient in his seventies who suffered a fatal gastrointestinal and pericardial hemorrhage after coming to the hospital with an INR > 50. The patient had been drinking cranberry juice for six weeks preceding the incident, developed a chest infection for which he received cephalexin, and had a severely reduced appetite consisting primarily of cranberry juice. A second report consist-

ed of a 69-year-old male patient taking warfarin for atrial fibrillation and prosthetic mitral valve replacement. During his preoperative appointment for an elective bladder surgery, warfarin was discontinued and an INR was drawn. The patient had an unexpectedly elevated INR of 12, which required vitamin K administration. Warfarin was reinitiated postoperatively several days later and resulted in an INR of 11, followed by episodes of hematuria and bleeding from the stoma site. After further investigation, it was discovered that the patient had been drinking two liters a day of cranberry juice for two weeks prior to surgery to prevent recurrent urinary tract infections, and continued to consume cranberry juice after the surgery. After discontinuing the intake of cranberry juice, his INR stabilized at 3 and the patient fully recovered. A third case report describes an elderly male with hypertension and atrial fibrillation who had fluctuations in his INR (between 1 and 10) suspected to also be a result of cranberry juice intake.

### **FOODS CAUSING INHIBITION**

Foods that interact with warfarin and inhibit the effects of warfarin may increase the metabolism of drug. Most food interactions with warfarin overwhelm warfarin activity; these tend to be foods rich in vitamin K. The amount of circulating vitamin K will be elevated and the intended effects of the drug will be negligible. This will be expressed by a subtherapeutic INR, and signs or symptoms consistent with insufficient warfarin therapy which will be patient specific.

### **High Vitamin-K Containing Foods**

High Vitamin-K containing foods are classified a level I causation, which are highly probable of causing a lowered INR or clotting event when consumed with warfarin. Vitamin K is a fat-soluble vitamin and serves as a cofactor for the production of clotting factors. The primary sources of vitamin K-containing foods are dark green vegetables and cooking oils. Other sources of vitamin K, often overlooked, include processed foods and fast foods because of the oils used in the production of these items. To add, this group of foods

should include brussel sprouts and cabbage, which are high in vitamin K and can be overlooked by clinicians because they are not dark green vegetables. Foods rich in vitamin K, as well as unusual sources of vitamin K, will be discussed in detail later as potential sources of warfarin interactions.

In 2005, the United States Department of Agriculture (USDA) revised the food pyramid to make specific recommendations about each food group, which consequently resulted in an increase in dietary vitamin K. There are several benefits to increasing the daily intake of vitamin K, such as bone and cartilage metabolism. However, this can also pose a problem for patients taking a vitamin K antagonist and who adhere strictly to the meeting the daily requirements. To ensure a stable INR, it is important to keep track of the quantity of foods rich in vitamin K eaten on a weekly basis. Therefore, if a patient increases vitamin K intake, warfarin doses can be adjusted accordingly. Education should focus on keeping a consistent amount of vitamin K from week to week.

### **Cooking Oils**

Cooking oils are not only a significant source of vitamin K, but they may also increase the absorption of vitamin K in foods. Cooking oils are classified as a level II causation, which makes a lowered INR or clotting event interaction *probable*. Cooking oils that are highest in vitamin K content include rapeseed (canola), soybean, and olive oil. Olive oil can have as much as 60  $\mu\text{g}$  of vitamin K per 100 g. It is not likely that 100 g of olive oil, equivalent to about seven tablespoons, is eaten in a single meal, but it is possible that intake of this volume may occur over the course of the day or week. Because vitamin K is a fat-soluble vitamin, the bioavailability is maximized in meals containing > 35 g of fat. For this reason, large consumption of these oils should be recognized as potential food interactions with warfarin.

Patients who consume greater amounts of fat on a high-protein diet, such as the Atkins diet, may experience enhanced absorption of vitamin K. Because high protein diets limit carbohydrates, more vegetables are consumed, resulting in an increase intake of vitamin K that can ultimately alter warfarin dose requirements.

### **Pre-formulated Enteral Nutritional Supplements**

Pre-formulated enteral nutritional products can also contain significant amounts of vitamin K. Supplements are usually given when nutritional status is compromised, and they

are often utilized as a substitute for meals that are missed or when overall dietary intake is inadequate to meet daily demands. Although an 8-ounce can of a given product contains 15-30  $\mu\text{g}$  of vitamin K, well under the recommended intake, it is an extra source of vitamin K and can decrease INR if a significant amount is consumed. It is important to specifically ask patients on warfarin if they drink any supplemental nutrition throughout the week. Table 1 lists several products and the vitamin K content of numerous nutritional supplements.

**Table 1: Nutritional Supplements and Vitamin K Content Per 8 Ounce**

Product	Vitamin K ( $\mu\text{g}$ )
Advera	24
Boost	30
Carnation Instant Breakfast	20
Ensure	25
Glucerna	14

Meal replacement or energy bars and shakes can also be additional sources of vitamin K in a patient's diet. Many patients utilize energy bars or shakes as meal replacements, or they consume them as snacks in between meals. They can be potential causes for INR fluctuations in an otherwise stable patient who is taking warfarin for various reasons. (See Table 2.)

**Table 2: Vitamin K Content in Energy Bars and Supplemental Bars**

Product	Weight (g)	Vitamin K content ( $\mu\text{g}$ )
Balance Bar	50	20
Clif Bar	68	20
Glucerna Meal Bar	58	28
Luna Bar	48	8
MetRx Bar	85	0
Pria Bar	28	12
Pria Complete Nutrition Bar	45	12
Power Bar	65	0
Slim Fast Breakfast Bar	44	20
Slim Fast Meal Options Bar	56	20

Tables 1 and 2 adopted from: Dailey JH: Dietary considerations in *Managing Oral Anticoagulation Therapy. Clinical and Operational Guidelines*, Ansell JE, Oertel LB, Wittkowsky AK, (Eds.), Aspen publishers, Gaithersburg, MD. (2003):36.1-36.9.

### Edible Seaweed

Sushi has been reported in the literature to decrease the INR because of its seaweed content. A patient on a stable warfarin dose had a drop in the INR after consuming 12 pieces of sushi in one day and an unknown amount a few days later. It was estimated that the patient consumed approximately 45  $\mu\text{g}$  of vitamin K from 12 pieces of sushi. The type of seaweed used in sushi is known as asakusa-nori, which contains between 11.4  $\mu\text{g}$  per 100 g to 18.8  $\mu\text{g}$  per 100 g of vitamin K.

### Avocado

Large amounts of avocado will result in decreased levels of circulating warfarin and elevated levels of circulating vitamin K. Typically fruits do not usually contain large amounts of vitamin K. However, there are at least two case reports of patients consuming large amounts of avocado in which the INR was decreased. A decrease in INR was observed when 100 g of avocado were consumed daily and when 400 g were consumed over two days in two patients with previously stable INRs. One proposed mechanism is that avocado induces liver enzymes and, therefore, individuals would require larger doses of warfarin. Although it is believed that avocado may decrease absorption of warfarin from the gut, it is important to note that one avocado has approximately 30 g of fat, which can increase the bioavailability of vitamin K when other foods are eaten concomitantly.

### Soy Milk

Unlike the previously mentioned foods discussed which contain significant amounts of vitamin K and are classified as level I causations, soy milk is classified as a level II causation which will probably cause an interaction if consumed with warfarin and will result in a lowered INR. One case report in a 70-year-old man on warfarin for atrial fibrillation for seven months noted a lowered INR after drinking 480 ml (two 8-ounce glasses) per day of soy milk. His INR 10 days prior to starting the soy milk was 2.5, and five days after starting the soy milk, his INR was 2.3.

He continued taking his usual warfarin dose of 3 mg per day and after four weeks of continuing to drink the soy milk, his INR dropped to 1.6. At that point, he stopped drinking the soy milk, continued his usual warfarin dose at 3 mg per day and returned one week later with an INR of 1.9. For the next two months, the patient remained within therapeutic range of 2.0 to 3.0 on warfarin 3 mg per day. The mechanism for an interaction with soy and warfarin is uncertain. Although soybeans are found to have high amounts of vitamin K, soy protein in the form of soy milk contains only trace amounts of vitamin K and would not be expected to alter warfarin metabolism. Theoretical mechanisms include changes in warfarin absorption or metabolism resulting from alterations in the P-glycoprotein efflux system or organic anion-transporting polypeptides. Soy may also inhibit platelet aggregation. Although the evidence does not suggest that soy milk should be avoided in patients taking warfarin, it may be sensible to monitor INR closely whenever initiation or discontinuation of soy protein occurs.

### **Alcohol Consumption**

Alcohol interference with warfarin anticoagulation therapy is an important factor to consider when initiating or adjusting warfarin doses. Consistent, moderate alcohol consumption seems to have very little effect on warfarin therapy in men as indicated by no significant changes in the INR. Three other studies that investigated the effect of moderate consumption of wine in men and women also showed that this level of consumption had very little effect on warfarin therapy. It has also been demonstrated that chronic alcohol abuse results in the induction of the enzymes that metabolize warfarin, and that binge drinking has the opposite effect.

Warfarin has two enantiomers which are metabolized differently. The R-enantiomer is metabolized by the CYP1A2 and CYP3A4 enzymes, while the more potent S-enantiomer is metabolized by the CYP2C9 enzyme. It is also important to note that warfarin is highly bound to albumin. The mechanism of alcohol metabolism can vary

according to the amount consumed as well as from person to person. Alcohol is metabolized primarily by CYP2E1, but CYP3A4 and CYP1A2 also contribute to the metabolism. CYP2E1 metabolism is most prevalent when there is heavy alcohol consumption, whereas there is more CYP3A4 and CYP1A2 alcohol metabolism with low to moderate consumption. Concurrent warfarin and alcohol consumption can result in a few different outcomes. Chronic alcohol use generally results in decreased availability of warfarin in the blood, which consequently decreases the protection from blood clots. This is due to the increased activity of the CYP2E1 enzyme in alcohol metabolism and the resulting decreased activity of the CYP3A4 and CYP1A2 enzymes in alcohol metabolism. This allows for the increased metabolism of warfarin. Binge drinking, or acute alcohol consumption, has the opposite effect. This type of alcohol consumption increases the availability of warfarin, thus elevating the INR and creating a high risk for excessive bleeding. The mechanism in this scenario is the limited availability of CYP3A4 and CYP1A2 enzymes which are occupied metabolizing alcohol. In addition, alcohol can also displace warfarin from albumin creating higher levels of warfarin in the blood.

Management of warfarin therapy in patients who use alcohol can prove difficult depending on the type of use. In chronic alcoholism, since there is reduced availability of warfarin in the blood, the dose should be increased. Moderate but consistent alcohol consumption should have little effect on the dosing. Binge drinking should be avoided, as it will put the patient at risk for bleeding events and may require reversal of anticoagulant effects. For all these circumstances, the dosing will be highly individualized and unfortunately, there is no universal algorithm that can be used. When counseling patients regarding warfarin use, it is imperative that the importance of consistency be stressed. Both consistent chronic and consistent moderate alcohol consumption can be accounted for with dose adjustments and careful PT and INR monitoring. However, binge drinking cannot be compensated for with dose adjustments, as there is no consistency. Therefore, patients should be counseled in such a way that they are aware of the large risk associated with binge drinking and the importance of avoiding this type of alcohol consumption.

### **Tobacco and Marijuana**

Concurrent tobacco and warfarin usage presents the potential for a few different interactions that may result in

adverse events. Smokeless tobacco and cigarette smoking differ in their effects on warfarin levels, although both do have potential serious adverse effects.

Cigarette smoking has always had a theoretical interaction with warfarin and has been investigated in a number of studies. Results thus far have been inconclusive as to the exact consequences across a large population of smokers who are concurrently using warfarin, but there is evidence that confirms there is an interaction. Smoking theoretically interferes with warfarin because of the induction of CYP1A2 by one or more of the many chemicals identified in tobacco. The CYP1A2 enzyme is one of the enzymes involved in the minor pathway of warfarin metabolism. Two studies looked at the interaction between smoking and warfarin. Bachmann et al conducted a small study that investigated the impact of smoking on warfarin therapy in nine chronic smokers. The study was conducted by administering a two-week course of warfarin while the subjects smoked, and then another two-week course administered during which the subjects did not smoke. The second two-week course was given after one month of not smoking. The study concluded that there were 13 percent, 23 percent, and 11 percent increases in steady state warfarin levels, warfarin half life, and volume of distribution, respectively. Additionally it was reported that smoking cessation caused a 13 percent decrease in clearance. Mungall et al conducted a similar study and had similar results. The study results showed that smoking increased warfarin clearance by 10 percent.

From the results of this study it follows that tobacco smokers will require a slightly higher warfarin dose than non-smokers, and that smoking cessation will raise the steady state levels of warfarin, putting the patient at risk for significant bleeding. Patients should be cautioned against sudden changes in smoking habits due to the risk of increased bleeding.

Smokeless tobacco has somewhat of a different effect as evidenced by a few studies conducted. Chewing tobacco contains a high level of vitamin k, specifically phyloquinone, which accounts for approximately 10 to 30 times more vitamin k that is found in normal sources, such as green leafy vegetables. The level of vitamin K will build up with chronic smokeless tobacco usage, which can potentially interact with the anticoagulation effects of warfarin. Because of this, it is logical to conclude that users of smokeless tobacco will require a slightly higher dose of warfarin to attain a therapeutic INR. Patients should again be cautioned against sudden

changes in smokeless tobacco usage as sudden stoppage could cause a large increase in INR and create a substantial risk for bleeding.

There has been limited research on the effect of marijuana use on warfarin levels, but a preliminary report shows that there is a probable interaction between the two. Marijuana is thought to inhibit the metabolism of warfarin and displace it from plasma proteins. This would in turn increase the anticoagulation effects of warfarin. Therefore, a lower dose may be needed in patients who chronically use marijuana. It is best to advise patients to abstain from marijuana use while taking warfarin because there is not enough clinical data to help in adjusting the dose to compensate. Counseling on the concurrent use of marijuana and warfarin could pose to be particularly important considering ongoing debate of legalizing marijuana for medicinal purposes.

## **RECOMMENDATIONS FOR MANAGEMENT AND COUNSELING**

When a patient begins anticoagulation with warfarin, the initial patient education should include information on all aspects of warfarin therapy. Since warfarin is a medication associated with serious side effects and a narrow therapeutic index, it is imperative that patients are educated about this medication in detail. The following should be covered during and reiterated during each patient encounter:

- 1.** Explain that warfarin is an anticoagulant (“blood thinner”) and explain why the patient needs the medication based on his/her disease state.
- 2.** Explain how the medication works and reinforce that it reduces the chances of harmful clot formation.
- 3.** Explain the details of laboratory testing (type and frequency) that will be necessary and stress their importance. Also, make sure that the patient understands that follow-up is very important while taking warfarin.
- 4.** Explain the patient’s individual dose. Stress adherence and the importance of taking the medication at the same time each day, prefer-

ably in the evening. Evening dosing makes daytime dose adjustments simpler and can prevent the patient from receiving a dose that would raise an already elevated INR. Also, educate the patient regarding missed doses. It is never recommended to take a make-up dose of warfarin.

5. Explain the major medications, dietary supplements and herbal remedies that can interfere with warfarin therapy. Also, explain the dietary issues of vitamin K intake and intake of foods which affect warfarin metabolism. Recommend speaking to a pharmacist or physician before starting or stopping any diet, eating program or medication therapy, especially nonprescription drug therapy.
  - a. Specifically warn patient against concomitant use of aspirin or NSAIDs with warfarin unless approved by the warfarin prescriber.
6. Instruct the patient to notify all of their physicians, specialist providers, dentists, and caregivers that he/she is taking warfarin.
7. If patient is of childbearing age, warn the patient to avoid becoming pregnant while taking warfarin. Warfarin is listed as pregnancy category D for women with mechanical heart valves and pregnancy category X for all other women.
8. Recommend that the patient contacts his/her physician if the following is noticed:
  - a. Signs of illness, especially when vomiting, diarrhea, or fevers are noted
  - b. Prolonged bleeding from cuts/nosebleeds
  - c. Unusual bleeding from gums when brushing teeth
  - d. Red or dark brown urine
  - e. Red or tarry-black stools
  - f. Unusual bleeding
  - g. Pregnancy or planned pregnancy
  - h. Serious fall or trauma
9. Recommend for the patient to request all refills to be filled with product from a single manufacturer for consistent therapy. Explain that if the patient switches between different generic brands or between brand and generic, the lab values may fluctuate and be more difficult to control.

10. Recommend the purchase of a medical alert bracelet indicating active warfarin therapy. Explain the importance of this feature during an emergency.
11. Specifically warn the patient to avoid activities that may result in injury, cuts, or bruises. Also, encourage the use of soft bristle toothbrushes and electric razors to reduce the likelihood of unintentional injury.

Strictly from a dietary standpoint, a chart or booklet identifying foods high in vitamin K can be a helpful reference for the patient. Asking a patient to recall what types of foods or nutritional supplements they have eaten may help uncover foods high in vitamin K. Guidelines about consumption of foods that contain vitamin K should be offered to the patient, along with educating the patient on importance of a consistent intake, NOT AVOIDANCE of vitamin K-rich foods. Counseling patients on avoidance of vitamin K foods is not recommended, as this may prevent intake of other essential vitamins and minerals found in foods containing vitamin K. It may seem counter-intuitive, but vitamin K is needed in everyone's diet for bone health and proper synthesis of clotting proteins. Remember, goal INR is typically 2-3 and an INR above 3 is NOT the goal of therapy.


To aid the patient and prevent frustration and possibly medication non-adherence, suggest to the patient that keeping a consistent amount of vitamin K consumption throughout the week is the best way to consume the vitamin in moderation. For example, the patient can select two or three days in which the patient can eat one to two servings of vitamin K-containing foods. Reinforcing baseline education, as well as offering information on risks involved with INR fluctuations at subsequent visits, increases adherence to a consistent and stable vitamin K intake, allowing for improved maintenance of therapeutic anticoagulation in patients taking warfarin.

## SUMMARY

Warfarin is widely used in anticoagulation therapy and has a very narrow therapeutic index. There are numerous interactions, pharmacological and non-pharmacological, associated with its use. Food interactions are common as there are many foods that contain vitamin K, foods that interact with warfarin's metabolism and foods that may displace warfarin from plasma proteins thus altering its plasma blood levels. It can be concluded that consistency in diet is of the utmost importance and sudden variations

can cause significant adverse events.

Alcohol consumption is also an important non-pharmacological interaction to consider when developing dosing regimens for warfarin. Because alcohol is metabolized by a number of cytochrome P450 enzymes, it can affect the metabolism of warfarin in multiple ways. Alcohol consumption provides a challenge in dosing warfarin, but it is possible for a patient to consume alcohol and take warfarin as long as the clinician is aware of the amount and frequency of alcohol use and adjusts the dosing accordingly. Patients should be made well aware of the risks of consuming alcohol and should be encouraged to avoid binge drinking.

Tobacco use has documented interactions with warfarin as well. Smokeless tobacco and cigarette smoking exhibit two different mechanisms of action to reduce warfarin effects, and each should be handled accordingly. Patients should always inform health care providers of a decision to start or stop smoking or start or stop using smokeless tobacco to ensure a plan for monitoring subsequent INR changes is in place. Concurrent marijuana usage with warfarin has not thoroughly been investigated. However, there has been a report showing an interaction. Marijuana use should ideally be stopped once warfarin therapy is initiated due to the difficulty of predicting and quantifying how much marijuana use will increase warfarin's anticoagulant effect. The cornerstone of effective warfarin therapy is the relationship between health care providers and patient. It is imperative that providers be aware of and incorporate all potential food and lifestyle interactions into a patient's dosing regimen and counsel the patient on the best lifestyle and diet choices. By collecting this information, dosing warfarin appropriately, and making the patient aware of potential consequences, many adverse events can be avoided. 

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## CONTINUING EDUCATION QUIZ

Select the correct answer.

1. The International Normalized Ratio will \_\_\_\_\_ if a patient ingests significant amounts of foods that potentiate the effects of warfarin.
  - a. Decrease
  - b. Fluctuate
  - c. Increase
  - d. Stabilize
2. Which of the following components of grapefruit is thought to exert an inhibitory effects on CYP 3A4?
  - a. Asakusa-nori
  - b. Ergosterol
  - c. Flavanoid
  - d. Vitamin A
3. By consuming two mangos a week, there's a high probability that a patient's INR will increase.
  - a. True
  - b. False
4. Which of the following foods can cause a decrease in INR?
  - a. Cabbage
  - b. Mango
  - c. Soy milk
  - d. A, C, and D
5. Which of the following oils can cause an accumulation of vitamin K if consumed on a daily basis?
  - a. Canola
  - b. Olive
  - c. Mineral
  - d. A and B

- 6.** In regard to consuming alcohol, which type of alcohol intake will result in an increased risk of bleeding?
- Annual glass of champagne to toast New Year's Eve
  - Five 1.5 ounce servings (shots) of distilled spirits in one evening of poker
  - Daily consumption of a six-pack of beer
  - One glass of wine on the weekends with dinner
- 7.** Which of the following vitamins can decrease the effectiveness of warfarin?
- Vitamin B
  - Vitamin C
  - Vitamin D
  - Vitamin K
- 8.** Which of the following foods contains the highest amount of phytonadione?
- Asparagus
  - Avocado
  - Cabbage
  - Mangos
- 9.** Which of the following will cause increased absorption of vitamin K in gut?
- Gluten-free diet
  - High-fat diet
  - High-protein diet
  - Low-fat diet
- 10.** Processed and fast food items typically have higher amount of vitamin K because of the oils used in the preparation.
- True
  - False
- 11.** Patients should be asked about their daily consumption of:
- Alcohol
  - Energy bars
  - Supplemental nutrition
  - All of the above
- 12.** Drinking six beers daily for five years will result in \_\_\_\_\_ INR values.
- Decreased
  - Fluctuating
  - Increased
  - Stabilized
- 13.** What natural component is found in cranberries and is thought to increase the risk of bleeding in patients on warfarin therapy?
- Acetaminophen
  - Bergamottin
  - Naringenin
  - Salicylic acid
- 14.** When counseling patients on warfarin, the patient should be instructed to contact the physician if which of the following occur:
- Dark brown urine
  - Pregnancy
  - Slip and fall
  - All of the above
- 15.** Smoking cessation will increase the INR \_\_\_\_\_:
- Because of the high content of vitamin K in the tobacco.
  - By decreasing protein binding of warfarin.
  - By decreasing the clearance of warfarin.
  - By increasing the clearance of warfarin.
- 16.** Smokeless tobacco will decrease the INR \_\_\_\_\_:
- Because of the high content of vitamin K in the tobacco
  - By decreasing protein binding of warfarin
  - By decreasing the clearance of warfarin
  - By increasing the clearance of warfarin
- 17.** Excessive bleeding due to warfarin can be reversed by:
- Cholestyramine
  - Decreasing warfarin
  - Diuretics
  - Phytonadione

Karen is a 38-year-old woman with atrial fibrillation and has been on warfarin for the past 12 months after being diagnosed with a TIA. She has been well since that event. Karen presents to you today after being referred by her PCP to the Anticoagulation Clinic. Karen's INR as of this morning is 4.6. Until today, Karen's INR results have been stable and in the range of 2.0 to 3.0. (Her INR is measured every two weeks.) She has not recently began any new medications, but she states that she eats the same types of food in moderation as she has for the past year, with the addition of adding one glass of cranberry juice daily for the past three months to promote a healthy urine tract. She recently began smoking both tobacco and marijuana again. Karen has a PMH of TIA, hypertension, and glaucoma. Current medication: atenolol 50 mg once daily, ramipril 10 mg once daily, and warfarin 6 mg at night. On examination: BP 140/80 mmHg; pulse rate 65, irregular. The remainder of the physical examination is normal with no evidence of bruising, epistaxis or gastrointestinal bleeding.

18. Which of the following is most likely to increase Karen's risk of bleeding?
- Cranberry juice
  - High-protein diet
  - Marijuana
  - Tobacco
19. Grapefruit juice is a well known inhibitor for which of the following CYP liver enzymes?
- 1A2
  - 3A4
  - 2C19
  - A and B only
20. Which of following vitamins found in mango will inhibit the CYP 2C19 enzyme?
- Vitamin A
  - Vitamin B
  - Vitamin C
  - Vitamin K

## Food and Lifestyle Interactions With Warfarin

April 2, 2012 (expires April 2, 2015) • Activity Type: Knowledge-based

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 Phone number (store or home) \_\_\_\_\_  
 Store e-mail (if avail.) \_\_\_\_\_ Date quiz taken \_\_\_\_\_

### Quiz: Shade in your choice

	a	b	c	d	e		a	b	c	d	e
1.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	13.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	14.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	15.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	17.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	18.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	19.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	20.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Quiz: Circle your choice

21. Is this program used to meet your mandatory C.E. requirements?  
**a.** yes **b.** no
22. Type of pharmacist: **a.** owner **b.** manager **c.** employee
23. Age group: **a.** 21–30 **b.** 31–40 **c.** 41–50 **d.** 51–60 **e.** Over 60
24. Did this article achieve its stated objectives? **a.** yes **b.** no
25. How much of this program can you apply in practice?  
**a.** all **b.** some **c.** very little **d.** none

How long did it take you to complete both the reading and the quiz? \_\_\_\_\_ minutes

