Patient information: Warfarin (Coumadin®)

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WHAT IS WARFARIN? — Warfarin (brand name Coumadin®, Warfilone®) is a prescription medication that interferes with normal blood clotting (coagulation). It is also called an anticoagulant. Many people refer to these medicines as blood thinners, although they do not actually cause the blood to become less thick, only less likely to clot.

The normal clotting mechanism is a complex process that involves multiple substances (clotting factors). These factors are produced by the liver and act in sequence to form a blood clot. In order for the liver to produce some of the clotting factors, adequate amounts of vitamin K must be available. Warfarin blocks the availability of vitamin K and limits the production of these clotting factors. As a result, the clotting mechanism is disrupted and it takes longer for the blood to clot.

WHY DO I NEED WARFARIN? — Warfarin is prescribed for patients who are at increased risk for developing harmful blood clots. This includes people with a mechanical heart valve, an irregular heart rhythm called atrial fibrillation, and people with certain clotting disorders. (See "Patient information: Atrial fibrillation" and "Patient information: The antiphospholipid syndrome".)

Warfarin is also used in people who have previously developed harmful clots, including patients who have had a stroke, heart attack, a clot which has traveled to the lung (pulmonary embolism), or a blood clot in the leg (deep venous thrombosis or DVT). In addition, warfarin may be used to prevent an existing clot from growing larger. (See "Patient information: Deep vein thrombosis (DVT)" and "Patient information: Ischemic stroke treatment" and "Patient information: Pulmonary embolism".)

WARFARIN MONITORING — The goal of warfarin therapy is to decrease the clotting tendency of blood, but not to prevent clotting completely. Therefore, the blood's ability to clot must be carefully monitored while a person takes warfarin. The dose of warfarin is adjusted, based on the results of periodic blood tests, to maintain the clotting time within a target range.

Prothrombin time (PT) — The most commonly used test to measure the effect of warfarin is the prothrombin time (called pro time, or PT). The PT is a laboratory test that measures the time it takes for the clotting mechanism to progress. It is particularly sensitive to the clotting factors affected by warfarin. The PT is also used to compute a value known as the INR (or International Normalized Ratio).

International Normalized Ratio (INR) — The INR is a way of expressing the PT in a standardized way; this ensures that results obtained by different laboratories can be reliably compared.

The longer it takes the blood to clot, the higher the PT and INR. The target INR range depends upon the clinical situation. In most cases the target INR range will be 2 to 3, although other ranges may be chosen if there are special circumstances.

If the INR is below the target range (ie, under-anticoagulated), there is a risk of clotting. If, on the other hand, the INR is above the target range (ie, over-anticoagulated), there is an increased risk of bleeding.

Dosing — When warfarin is first prescribed, a higher initial "loading" dose may be given. The dose is then adjusted downward until the INR is within the desired range. The PT and INR are monitored frequently until the appropriate dose is determined. Once the patient is on a stable dose, the PT and INR are monitored less frequently, generally once every two to four weeks.

The warfarin dose may be adjusted periodically in response to changes in the INR or other conditions. For example, having surgery may require a change in a patient's warfarin regimen. The dose of warfarin may also be changed if new medicines are added.

WARFARIN SIDE EFFECTS — The major complication associated with warfarin is bleeding due to excessive anticoagulation. Excessive bleeding, or hemorrhage, can occur from any area of the body, and patients on warfarin should report any falls or accidents, as well as signs or symptoms of bleeding or unusual bruising. Signs of unusual bleeding include bleeding from the gums, blood in the urine, bloody or dark stool, a nosebleed, or vomiting blood.

Because the risk of bleeding increases as the INR rises, the INR is closely monitored and adjustments are made as needed to maintain the INR within the target range. (See 'International Normalized Ratio (INR)' above.)

Warfarin can also cause skin necrosis or gangrene, which can cause dark red or black areas on the skin. This is a rare complication that may occur during the first several days of warfarin therapy.

When to seek help — If there are obvious or subtle signs of bleeding, including the following, patients should call their healthcare provider **immediately**.

- Persistent nausea, stomach upset, or vomiting blood or other material that looks like coffee grounds
- Headaches, dizziness, or weakness
- Nosebleeds
- Dark red or brown urine
- Blood in the bowel movement or dark-colored stool
- Pain, discomfort, or swelling, especially after an injury
- After a serious fall or head injury, even if there are no other symptoms

The patient should also call if any of the following occurs:

- Bleeding from the gums after brushing the teeth
- Swelling or pain at an injection site
- Excessive menstrual bleeding or bleeding between menstrual periods
- Diarrhea, vomiting, or inability to eat for more than 24 hours
- Fever (temperature greater than 100.4º F or 38º C)

It is important to remember that warfarin is taken to reduce the risk of a clotting condition(s), such as a deep vein thrombosis or pulmonary embolism. If one or more of these symptoms develops, the patient should seek immediate medical attention. (See "Patient information: Deep vein thrombosis (DVT)" and "Patient information: Pulmonary embolism".)

PREGNANCY AND WARFARIN — Warfarin passes from mother to baby across the placenta and can interfere with normal blood clotting in the baby. This can lead to birth defects and other problems. A woman who becomes pregnant or plans to become pregnant while on warfarin therapy should notify her healthcare provider immediately.

Heparin, another anticoagulant, does not cross the placenta from mother to baby and is usually used instead of warfarin during pregnancy. Warfarin can be restarted after delivery.

Breastfeeding — Although warfarin does not pass into breast milk, a woman who wishes to breastfeed

while taking warfarin should consult her healthcare provider. Warfarin is considered safe for use in women who breastfeed.

OTHER RECOMMENDATIONS

Take warfarin on a schedule — Warfarin should be taken **exactly** as directed. Do not increase, decrease, or change the dose unless told to do so by a healthcare provider. If a dose is missed or forgotten, call the prescribing clinician for advice.

Warfarin tablets come in different strengths; each is usually a different color, with the amount of warfarin (in milligrams) clearly printed on the tablet. If the color or dose of the tablet appears different than those taken previously, the patient should immediately notify their pharmacist or healthcare provider.

Reduce the risk of bleeding — There is a tendency to bleed more easily than usual while taking warfarin. Some simple changes can decrease this risk:

- Use a soft bristle toothbrush
- Floss with waxed floss rather than unwaxed floss
- Shave with an electric razor rather than a blade
- Take care when using sharp objects, such as knives and scissors
- Avoid activities that have a risk of falling or injury (eg, contact sports)

Prevent falls — Falling may significantly increase the risk of bleeding. Taking measures to prevent falls is recommended, and could include the following:

- Remove loose rugs and electrical cords or any other loose items in the home that could lead to tripping, slipping, and falling.
- Ensure that there is adequate lighting in all areas inside and around the home, including stairwells and entrance ways.
- Avoid walking on ice, wet or polished floors, or other potentially slippery surfaces.
- Avoid walking on unfamiliar areas outside.

Warfarin and food — Some foods and supplements can interfere with warfarin's effectiveness. After being stabilized on a particular warfarin dose, consult a healthcare provider before making major dietary changes (eg, starting a diet to lose weight, starting a nutritional supplement or vitamin).

- Vitamin K — Eating an increased amount of foods rich in vitamin K can lower the prothrombin time and INR, making warfarin less effective, and potentially increasing the risk of blood clots. Patients who take warfarin should aim to eat a relatively similar amount of vitamin K each week. Some foods have a high level of vitamin K, including: kale, broccoli, spinach, collard or turnip greens, lettuce, Brussels sprouts, and cabbage (table 1). It is not necessary to avoid these foods. However, the patient should eat a relatively similar amount on a regular basis rather than eating a large serving occasionally.
- Cranberry juice — There have been mixed reports on the effect of cranberry juice in people who use warfarin to prevent blood clots. Some experts have reported that drinking cranberry juice while on warfarin can cause significant over-anticoagulation and bleeding [1]. However, a small study found that drinking one eight ounce serving of cranberry juice per day for seven days had no effect on the INR of seven men taking warfarin for atrial fibrillation [2]. It is possible that larger amounts could have a more significant effect.

  The best advice is probably to avoid consuming large amounts of cranberry juice, and to speak with a healthcare provider regarding any concerns about a possible interaction.

- Alcohol — Chronic abuse of alcohol affects the body's ability to handle warfarin. Patients on warfarin therapy should avoid drinking alcohol on a daily basis. Alcohol should be limited to no more than one to two servings of alcohol occasionally. In addition, drinking excessive amounts of alcohol can increase the risk of injury, and therefore bleeding.

Warfarin and medications — A number of medications, herbs, and vitamins can interact with warfarin (table 2 and table 3). This interaction may affect the action of warfarin or the other medication. If warfarin is affected, the dose may need to be adjusted (up or down) to maintain an optimal coagulation effect.

Patients who take warfarin should consult with their clinician **before taking any new medication**, including over-the-counter (non-prescription) drugs, herbal medicines, vitamins, or any other products. Some of the most common over-the-counter pain relievers, including acetaminophen (Tylenol®), aspirin, and nonsteroidal antiinflammatory drugs (such as ibuprofen [Advil®]) and naproxen (Aleve®), enhance the anticoagulant effects of warfarin. Vitamin E may increase the anticoagulant effects of warfarin. Consult a healthcare provider before adding or changing a dose of vitamin E or any other vitamin.

Wear medical identification — People who require long-term warfarin should wear a bracelet, necklace, or similar alert tag at all times. If an accident occurs and the person is too ill to explain their condition, this will help responders provide appropriate care.

The alert tag should include a list of major medical conditions and the reason warfarin is needed (eg, atrial fibrillation), as well as the name and phone number of an emergency contact. One device, Medic Alert®, provides a toll-free number that emergency medical workers can call to find out a person's medical history, list of medications, family emergency contact numbers, and healthcare provider names and numbers.

WHERE TO GET MORE INFORMATION — Your healthcare provider is the best source of information for questions and concerns related to your medical problem.

This article will be updated as needed every four months on our web site (www.uptodate.com/patients).

Related topics for patients, as well as selected articles written for healthcare professionals, are also available. Some of the most relevant are listed below.

Patient Level Information:

Patient information: Atrial fibrillation
Patient information: The antiphospholipid syndrome
Patient information: Deep vein thrombosis (DVT)
Patient information: Ischemic stroke treatment
Patient information: Pulmonary embolism

Professional Level Information:

Anticoagulation during pregnancy
Anticoagulation in older adults
Clinical use of coagulation tests
Correcting excess anticoagulation after warfarin
Outpatient management of oral anticoagulation
Overview of vitamin K
Therapeutic use of warfarin

The following organizations also provide reliable health information.

- National Library of Medicine

(www.nlm.nih.gov/medlineplus/healthtopics.html)

- National Heart, Lung, and Blood Institute

  (www.nhlbi.nih.gov/index.htm)

- National Institute of Neurological Disorders and Stroke

  (www.ninds.nih.gov/)

- United States Food and Drug Administration

  (www.fda.gov/downloads/Drugs/DrugSafety/ucm088578.pdf)

[1-7]

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7. Ansell J, Jacobson A, Levy J, et al. Guidelines for implementation of patient self-testing and patient self-management of oral anticoagulation. International consensus guidelines prepared by International Self-Monitoring Association for Oral Anticoagulation. Int J Cardiol 2005; 99:37.

GRAPHICS

Foods with moderate to high levels of vitamin K

Food name	Serving size	Vitamin K (micrograms)
High level vitamin K foods		
Kale, frozen (cooked or boiled, drained)	1/2 cup	570
Kale, fresh, (cooked or boiled, drained)	1/2 cup	530
Spinach, frozen (cooked or boiled, drained)	1/2 cup	514
Spinach, raw	1 cup	150
Collard greens, frozen (cooked, drained)	1/2 cup	530
Turnip greens, frozen (cooked, drained)	1/2 cup	425
Brussels sprouts, frozen (cooked, drained)	1/2 cup	110
Moderate level vitamin K foods		
Asparagus, frozen (cooked, drained)	1/2 cup 4 spears	72 48
Asparagus, fresh (cooked, drained)	4 spears	30
Broccoli, frozen (cooked, drained)	1/2 cup	60
Broccoli, fresh (cooked, drained)	1 spear	52
Broccoli, raw	1/2 cup	40
Lettuce (butterhead, Boston, bibb)	1/2 head	80
Lettuce (iceberg, crisphead)	1/2 head	65
Lettuce (romaine, cos)	1 cup	57
Lettuce (green leaf)	1 cup	97
Okra, fresh (cooked, drained)	1/2 cup	32
Okra, frozen (cooked, drained)	1/2 cup	44
Cabbage (cooked, drained)	1/2 cup	73
Cabbage, raw	1/2 cup	21
Cabbage, savoy (raw)	1/2 cup	24
Cabbage, Chinese (cooked, drained)	1/2 cup	28
Coleslaw (fast food-type)	3/4 cup	56
Saurkraut, canned	1/2 cup	41
Peas, frozen, with pod (cooked, drained)	1/2 cup	24
Peas, fresh, with pod (cooked, drained)	1/2 cup	20
Peas, green, frozen (cooked, drained)	1/2 cup	18

Celery, raw	1/2 cup	17
Beans, green or yellow, fresh (cooked, drained)	1/2 cup	10
Oil, canola	1 tablespoon	17
Oil, olive	1 tablespoon	8
Oil, other (including peanut, sesame, safflower, corn, sunflower, soybean)	1 tablespoon	3 or less
Green tea, brewed in hot water	3.5 ounces	0.3

Data from: US Department of Agriculture, Agricultural Research Service. 2006. USDA Nutrient Database for Standard Reference, Release 19. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/nutrientdata. Note: Release numbers change as new versions are released.

Medications that interfere with the effect of warfarin

Increased warfarin effect
Acetaminophen
Allopurinol
Anabolic steroids
Aspirin
Amiodarone
Capecitabine
Cephalosporins
Cimetidine
Ciprofloxacin
Clofibrate
Clopidogrel
Diclofenac
Disulfiram
Erythromycin
Fluconazole
Fluorouracil (5-FU)
Selective serotonin reuptake inhibitors (eg, Fluoxetine)
Glucagon
Influenza virus vaccine
Metronidazole
Macrolide antibiotics
Omeprazole
Sulfamethoxazole/trimethoprim
Tamoxifen
Thyroid hormone
Tolbutamide

Decreased warfarin effect
Azathioprine
Antithyroid drugs
Carbamazepine
Dicloxacillin
Glutethimide
Griseofulvin
Haloperidol
Nafcillin
Oral contraceptives
Phenobarbital
Rifampin
Vitamin K

This is only a **partial list**. Please refer to the warfarin drug information topic for additional drug interactions. Some drugs may have multiple, opposing effects on warfarin; in such cases, the drug may increase or decrease the effect of warfarin, depending on which aspect of the drug interaction is dominant in that particular patient.

Anticoagulant herbal ingredients

Anticoagulants
Alfalfa
Angelica
Aniseed
Arnica
Asafoetida
Celery
Chamomile, German
Chamomile, Roman
Clove
Fenugreek
Feverfew
Fucus
Garlic
Ginger
Ginkgo
Ginseng, Panax
Horse-chestnut
Horseradish
Liquorice
Meadowsweet
Poplar
Prickly ash, northern
Prickly ash, southern
Quassia
Red clover
Willow

Data from: Newall, CA, Anderson, LA, Phillipson, JD. Herbal Medicines: A Guide for Health-Care Professionals, The Pharmaceutical Press, London 1996, p.282.