

Blood Clot Prevention Battling a Dangerous Condition

Thrombi (blood clots) are a leading cause of death and disability in the United States (American Heart Association 2004). Blood clots are responsible for a grim litany of health problems, including stroke, heart attack, pulmonary embolism, and complications of cancer. Because of this intense danger, conventional physicians prescribe a number of powerful drugs to prevent blood clots. But these drugs have dangers of their own; if their use is not closely monitored, they may cause serious bleeding and even death.

Blood clots are a natural part of the healing process; blood thickens around an injured area, forms a protective scab, and eventually dissolves on its own. However, clots become dangerous when they interfere with the circulatory system.

The best way to manage blood clots is to prevent them from forming in the first place. By the time a patient has had a stroke or heart attack, there has already been a failure of preventive medicine. These patients may end up taking anticlotting medication for the rest of their lives. The Life Extension Foundation believes that people should lower their risk of debilitating injury from a blood clot by using dietary nutrients that have been shown to modulate the blood's ability to clot and to enhance the effectiveness of a prescription anticlotting medication.

Blood clots can block any of the blood vessels in our bodies, stopping the flow of blood. Or they may break off and travel through the circulatory system until they become lodged in a smaller artery or vein, causing tissue damage.

If this happens in an artery, any tissue that is downstream from the blockage will quickly become starved of oxygen and start to die. If it occurs in the coronary arteries that feed the heart, a heart attack may result. If this takes place in the arteries that feed the brain, an ischemic stroke or transient ischemic attack (TIA, also known as a ministroke) may result. Atrial emboli (blood clots that form in the heart chambers) can travel to the lungs, causing a potentially fatal blockage called a pulmonary embolism. In other instances, the clots can travel to the brain, causing a stroke. The US Centers for Disease Control and Prevention estimates that, if all forms of major cardiovascular disease were eliminated, life expectancy in the United States would rise by 7 percent (US Decennial for Life Tables for 1989-1991 1999).

Blood clots can also occur in the veins, which transport oxygen-poor blood from the body back to the heart. Blood clots may be caused by sluggish blood flow due to disease, injury to the vein, or even long periods of immobility. Sometimes these venous blood clots pose relatively little threat beyond cosmetic injury, such as in the case of varicose veins. However, if a blood clot forms in the deep veins of the legs (called deep vein thrombosis), there is a significant risk the clot will break off and travel to the lungs. Up to 90 percent of cases of acute pulmonary embolism are caused by blood clots that have traveled to the lungs from the legs. Pulmonary embolism is the cause of death or is a major contributing factor to death in up to 12 percent of patients who die in the hospital (Anderson FA Jr et al 1991).

Cancer is also associated with the risk of blood clots. Patients who have cancer often have hypercoagulable blood due to multiple disturbances in their metabolism and circulation. Patients with cancer are also more susceptible to infections. The ability of cancer to metastasize (spread) is determined at least in part by blood clotting factors that allow malignant cells to become fixed in capillaries (Hejna M et al 1999).

Blood clot treatment and prevention is a major focus of conventional medicine. Patients are advised to lower their risk through lifestyle modifications, such as exercising more and eating a healthful diet, and these patients may be prescribed medications that interfere with the blood's ability to clot. The most common of these is simple, over-the-counter, low-dose aspirin, which is widely recommended to prevent heart attacks and strokes. More powerful prescription anticoagulants are also routinely prescribed, including heparin and warfarin (Coumadin®). It is notoriously difficult to find the correct dosages for these drugs. Frequent blood testing is required to make sure patients are not being put at increased risk of bleeding from the medications. Newer, more controllable anticoagulants are on the horizon, but they have not yet been approved in the United States.

Dealing with an existing blood clot may be a true medical emergency. Physicians may have to perform emergency open-heart surgeries to reestablish blood flow. Angioplasty, a procedure in which a balloon-tipped catheter is used to open a blocked vessel, is becoming increasingly common in the treatment of heart attacks and other emboli. In the case of a stroke, powerful medications called thrombolytics may be prescribed. If given quickly enough, these medications may be able to dissolve a blood clot and limit permanent damage to the brain or heart.

The Life Extension Foundation recommends taking active steps to reduce the risk of serious injury from a blood clot. This means regular blood testing to keep track of levels of cholesterol, homocysteine, fibrinogen, and other substances that are closely tied to

blood clot risk. For patients at risk of blood clots, it means testing blood to track clotting risk. (These special tests are explained in more detail later in this chapter.) It also means exercising and eating healthy and using dietary supplements that have been shown to lower the risk of blood clot formation.

What You Have Learned So Far

To sum up:

- A blood clot is called a thrombus. Blood clots are a normal part of the healing process of wounds, but may be very dangerous if they occur abnormally within the circulation.
- Heart attacks, strokes, and pulmonary embolism can be caused by blood clots. Blood clots that trigger heart attack and stroke are the leading cause of death and disability in the United States.
- Blood clots are a major complication of cancer, which interferes with the body's natural coagulation system.
- Conventional medications to treat blood clots usually focus on prevention or on interfering with the blood's ability to clot. Low-dose aspirin is widely prescribed to help prevent blood clots. In an emergency situation, surgery may be necessary.
- Everyone at risk of a blood clot should have his or her blood tested regularly for such risk markers as cholesterol, fibrinogen, and homocysteine levels and prothrombin time. Many nutrients and supplements have been shown to lower the risk of blood clots.

THROMBOSIS AND CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is the single deadliest disease in the United States. An estimated 13.2 million people have CAD, or 6.4 percent of the population (American Heart Association 2004). An estimated 700,000 people in the United States will have their first heart attack this year. Another half a million will have another heart attack (American Heart Association 2004).

CAD occurs when the arteries feeding the heart become brittle and calcified. This process is called atherosclerosis and results in blockage of an artery. Atherosclerosis is often a lifelong process that begins in childhood and gradually worsens. Symptoms of atherosclerosis include angina (chest pain), shortness of breath, fatigue, leg pain, or other symptoms of poor circulation.

Researchers have made a great deal of progress unraveling the biochemical and physiologic cascade involved in atherosclerosis. The process often begins with mechanical damage from changes in blood pressure and the turbulent blood flow that exists at arterial branches. This stresses the intima layers (internal lining) of the arteries, which causes tiny tears that stimulate a combined healing and inflammatory response (Alexander RW 1995; Lee RT et al 2000; Massy ZA et al 1996).

These lesions attract blood platelets, which adhere to the vessel wall and cause smooth muscle cells on the walls of arteries to multiply. The smooth muscle cells have an increased permeability to platelets and lipids, especially low-density lipoprotein (LDL) cholesterol. As LDL increases at the site of the injury, it penetrates further into the arterial wall. This may occur very slowly at first, but the process speeds up under certain conditions or as part of normal aging. Even the arteries of children have been shown to have increased thickness in the presence of conditions such as obesity, diabetes, and high cholesterol (Aggoun Y et al 2005).

Over time, plaque begins to form on the interior arterial wall. The condition is aggravated by age as our endothelial cells gradually lose their ability to dissolve blood clots. Ultimately, the plaque deposit may become brittle and unstable and finally rupture. When the plaque ruptures, pieces of calcified plaque shower downstream into the artery, blocking it. Alternatively, a blood clot may rapidly form at the site of the injury. In either case, blood flow is restricted to a portion of the heart muscle, causing heart tissue damage.

THROMBOSIS AND STROKE

Similar to the risk that thrombosis poses in the heart, thrombosis in the brain can be a life-threatening situation. Blood clots that form in the carotid arteries may potentially detach and block blood flow to brain tissue beyond the blockage (causing an embolic stroke), or they may grow large enough to block blood flow within their native artery (a thrombotic stroke). Embolic strokes also occur when blood clots travel from elsewhere in the body into the arteries of the brain. This happens sometimes as a result of atrial fibrillation, a condition in which the upper chambers of the heart beat abnormally quickly, causing incomplete emptying of the atria and allowing the blood inside the chambers to form clots that are then pumped into the circulation.

While researchers used to distinguish between full-blown strokes and TIAs, there is a growing recognition that these are similar events differing only in magnitude. The damage to the brain from many TIAs can occur insidiously and lead to dementia that resembles Alzheimer's disease. According to one study, by the time people reach their 70s, one in three has had a silent stroke (Leary MC et al 2003). In a follow-up study, one in four survivors of a stroke had at least one silent stroke in the 2 years after his or her initial stroke (Corea F et al 2002). Among people who haven't had a major stroke, TIAs are considered warning signs of an impending stroke.

THROMBOSIS AND CANCER

Blood clots are also closely associated with cancer because of the way cancer interferes with the natural circulatory process. About 50 percent of all patients with cancer, and up to 95 percent of the patients with cancer who also have metastatic disease, show some abnormality in their coagulation system. Up to 11 percent of all patients with cancer have blood clots; hemorrhage occurs in about 10 percent. Thromboembolism and hemorrhage, as a whole, are the second most common cause of death among patients who have cancer (Lip GY et al 2002).

Various studies have shown the close connection between cancer and blood clots. In one pair of studies, two anticoagulants used to prevent blood clots (heparin versus low molecular weight heparin [LMWH]) were compared in the treatment of deep vein thrombosis. A significant number of patients with cancer were included in the pool of study subjects. In both studies, mortality rates were lower in the patients randomized to LMWH, but analysis of the death rates yielded a striking difference among the cancer patients (Green D et al 1992; Hejna M et al 1999; Hull RD et al 1992; Prandoni P et al 1992; Sciumbata T et al 1996). Cancer-related mortality with standard heparin was 31 percent versus 11 percent with LMWH. This suggests that LMWH might interfere with cancer's reliance on the blood coagulation system to grow and metastasize (Collen A et al 2000; Mismetti P et al 2001; Prandoni P 2001; von Tempelhoff GF et al 2000).

The Clotting Process

The vastly complex blood clotting system begins when blood vessels are damaged. This damage may occur externally, as in the case of a cut, or the damage may be from within, as in the case of atherosclerosis caused by elevated homocysteine or high LDL cholesterol levels.

In response to vessel damage, collagen in the blood vessel tissue is exposed to the bloodstream. Within seconds, platelets circulating in the blood adhere to exposed collagen and secrete chemicals that start the following steps in the clotting process:

1. Platelet aggregators cause platelets to aggregate (clump together) and vasoconstrict (contract) blood vessels, which reduces blood loss. (Adenosine diphosphate (ADP), thromboxane A₂, and serotonin are examples of some vasoconstrictors.)
2. Coagulants such as fibrin then bind the platelets together to form a permanent plug (clot) that seals the leak.

Fibrin is formed from fibrinogen in a series of reactions as part of the coagulation cascade. The enzymes that comprise the coagulation system are called coagulation factors, which are numbered in the order in which they were discovered. Some coagulation factors are responsible for accelerating the coagulation process (factor V, factor VIII, factor X, factor Xa, and factor IXa), while other blood factors (protein C, protein S, and thrombomodulin) are responsible for slowing and stopping the coagulation cascade. When it works correctly, this system results in the formation of thrombin, which helps convert fibrinogen into fibrin to plug the wound, and stop the growth of the blood clot at the appropriate time.

In the healthy body, a balance is created between the opposing chemicals—for example, coagulants versus anticoagulants, vasodilators versus vasoconstrictors, and platelet aggregators versus platelet aggregator inhibitors. Nutrient supplements can be used to maintain this balance.

RISK FACTORS FOR THROMBOSIS

The best way to avoid damage from a blood clot is to take preventive action. A person with multiple risk factors for blood clots may consider taking active steps to reduce his or her risk. Risk factors for a blood clot include:

- **Elevated homocysteine levels**—Homocysteine is an intermediary amino acid that is formed from the conversion of methionine into glutathione. High levels in the body indicate impaired homocysteine metabolism (via depressed methylation) or oxidative stress. Elevated homocysteine levels have been linked to increased risk of arterial blood clots (Ebbesen LS 2004). The Life Extension Foundation recommends keeping homocysteine levels between 7 and 8 millimoles per liter (mmol/L).
- **History of heart attack or CAD**—Atherosclerosis rarely occurs in isolation. Rather, it tends to be widespread throughout the body, so a history of atherosclerosis or heart attack translates into increased risk of blood clots.
- **History of stroke or TIA**—One of the strongest predictors of stroke risk is a history of previous stroke or TIA. All patients who have had an ischemic brain event should take steps to lower their risk of future (and possibly more serious) events.
- **Inflammation**—Chronic inflammation is associated with a variety of chronic diseases, including cardiovascular disease. C-reactive protein (CRP) is a sensitive indicator of inflammation throughout the body. A feature article in the May 2002 issue of *Scientific American* emphasized the link between chronic inflammation and the evolution of CAD (Libby P 2002). The Life Extension Foundation highly recommends measuring CRP levels using a high-sensitivity CRP blood test.
- **Elevated fibrinogen**—Fibrinogen has a number of effects in the blood coagulation process. It reacts with thrombin to

produce fibrin, it promotes platelet aggregation (which can lead to diminished blood flow), and it can cause platelets to bind together. An article in the journal *Neurology* found that prior stroke and elevated fibrinogen levels predicted new brain events in patients who have had a stroke (Beamer NB et al 1998).

- **Abnormal blood lipids**—Cholesterol's role in atherosclerosis and blood clotting is well documented. LDL cholesterol molecules, which are large and unstable, contribute to plaque formation on arterial walls. When plaque ruptures, the resulting blood clot may cause a heart attack or stroke. Elevated levels of triglycerides, another kind of blood lipid, are also associated with heart disease, while depressed high-density lipoprotein (HDL) cholesterol levels are associated with elevated risk of heart attacks and strokes.
- **Hypothyroidism**—A deficiency in thyroid hormone is associated with elevated levels of several clotting factors (Chadarevian R et al 2001; Muller B et al 2001) and with elevated homocysteine and depressed folate levels (Lien EA et al 2000; Nedrebo BG et al 2003). Supplemental thyroid hormone returns homocysteine levels to normal (Diekman MJ et al 2001; Hussein WI et al 1999). Furthermore, thyroid hormone inhibits LDL oxidation (Diekman MJ et al 2000). Hypothyroidism, even at levels detected only by an elevation of thyroid-stimulating hormone (TSH) level in the blood, is also a known risk factor for the development of atherosclerosis (Carantoni M et al 1997; Hak AE et al 2000).

If you are worried about developing blood clots, monitor your blood levels of these substances. Blood tests may be scheduled through your physician. These tests are also available through the Life Extension Foundation by calling 1-800-544-4440, or visit us online at www.lef.org.

Table 1 shows the standard reference ranges and ideal levels recommended by the Life Extension Foundation.

Table 1. Laboratory Tests and Procedures*

Blood Test	Standard Reference Range	Ideal Levels
TSH	0.4-5.0 ?U/dL	0.2-2.0 ?U/dL
Total cholesterol	100-199 mg/dL	180-200 mg/dL
LDL cholesterol	0-129 mg/dL	Under 100 mg/dL
HDL cholesterol	35-150 mg/dL	55-150 mg/dL
Triglyceride	0-199 mg/dL	40-100 mg/dL
Homocysteine	5-15 mmol/L	7-8 mmol/L
Fibrinogen	200-400 mg/dL	200-300 mg/dL
CRP	Up to 4.9 mg/L	Under 2 mg/L
DHEA	Men: 280-640 mcg/dL Women: 65-380 mcg/dL	Men: 500-640 mcg/dL Women: 250-380 mcg/dL

*TSH=thyroid-stimulating hormone; LDL=low-density lipoprotein; HDL=high-density lipoprotein; CRP=C-reactive protein; DHEA=dehydroepiandrosterone; ?U/dL=microunits per deciliter; mg/dL=milligrams per deciliter; mmol/L=millimoles per liter; mg/L=milligrams per liter; mcg/dL=micrograms per deciliter.

CONVENTIONAL TREATMENT OF BLOOD CLOTS: ANTICOAGULANTS, ANTIPLATELETS, AND THROMBOLYTICS

In general, the following three classes of prescription drugs are used to treat or prevent blood clots:

Anticoagulants

Anticoagulants are drugs that interfere with the blood's ability to clot. They are very powerful prescription medications whose dosages are monitored carefully. The effects of anticoagulants are known to be highly variable within each individual, so it is essential that a physician regularly monitor dosages by having the patient take frequent blood tests. A side effect of anticoagulants is increased risk of bleeding.

Some anticoagulant drugs used to prevent blood clots are:

- **Warfarin®**—Warfarin® inhibits the synthesis of coagulation factors such as factors II, VII, IX, and X and anticoagulant proteins C and S. (Warfarin® is discussed in greater detail later in this chapter.)
- **Heparin**—Heparin increases the activity of antithrombin III, which prevents the conversion of fibrinogen to fibrin. Heparin is not absorbed by the gastrointestinal tract and must be administered intravenously. It is usually used only in emergency situations (e.g., after a stroke).
- **Ximelagatran**—Ximelagatran belongs to a new class of anticoagulants. Instead of interfering with the blood coagulation factors, ximelagatran is a direct thrombin inhibitor. It appears to offer several major advantages over other anticoagulants. Although clinical studies are still ongoing, early results of the effectiveness of ximelagatran have been promising. (Ximelagatran is discussed in greater detail later in this chapter.)

Antiplatelets

Antiplatelets interfere with the ability of blood platelets to clump. The most common antiplatelet is aspirin, which is prescribed for millions of patients at risk of blood clots.

Studies show that aspirin can prevent heart attacks; however, more recent research have caused some confusion. While aspirin's effectiveness in heart attack prevention in men is well documented, a very recent study showed that aspirin is not as effective in preventing heart attacks in women. Based on these results, the authors of the study recommended that women younger than 65 years should avoid taking aspirin to prevent heart attacks because of the increased risk of bleeding. However, this type of aspirin therapy may be warranted in women older than 65 (Ridker PM et al 2005).

Other prescription antiplatelets include dipyridamole, clopidogrel (Plavix®), and ticlopidine (Ticlid™). Ticlopidine inhibits platelet aggregation by interfering with the binding of fibrinogen to the platelet membrane. It is a prescription drug that may be of particular value as an alternative to aspirin. Clopidogrel, meanwhile, is gaining popularity as an effective treatment for patients who have CAD and who have had a heart attack. It has been shown, in some cases, to enhance the effectiveness of aspirin (Doggrell SA 2005).

Thrombolytics

Thrombolytics break up existing blood clots in emergency situations such as a stroke or acute heart attack. The most commonly used thrombolytic is tissue plasminogen activator (TPA), which activates plasmin to break apart fibrin. Streptokinase is another TPA drug. In the case of stroke, rapid treatment with a thrombolytic has been shown to limit the amount of permanent brain damage.

WARFARIN AND NUTRIENTS: CAN THEY WORK TOGETHER?

Warfarin was originally isolated in 1939 from sweet clover. Interestingly, warfarin is the active ingredient found in many commercial rat poisons and insecticides, which work by encouraging bleeding. Warfarin is used to prevent heart attacks, arterial blood clots, and deep vein thrombosis. It is also used in patients who have prosthetic heart valves to prevent blood clots.

Bleeding is the primary side effect of warfarin therapy. Minor bleeding from warfarin usually begins with ecchymoses (purple patches on the skin). Then the mucous membranes are affected, causing nosebleed and bleeding under the mucous membranes that cover the eyes and inner eyelids. Hematuria (blood in the urine) may also occur. Major complications usually involve gastrointestinal bleeding and intracranial bleeding (bleeding within the brain).

Warfarin has an extremely long list of contraindications and drug interactions. Of particular concern is its use in elderly patients because they have an increased risk of hemorrhage. Several common drugs negatively interact with warfarin, including aspirin, cimetidine, lovastatin, thyroid hormones, and estrogens and oral contraceptives.

There is much debate and confusion about the interactions between dietary nutrients and warfarin. Patients who take warfarin are regularly warned about taking dietary antiplatelet agents, including Ginkgo biloba, green tea, vitamin E, garlic, and fish oil (Heck AM et al 2000). Other nutrients that may increase the risk of bleeding include angelica root, arnica flower, anise, asafetida, bogbean, borage seed oil, bromelain, capsicum, celery, chamomile, clove, fenugreek, feverfew, ginger, horse chestnut, licorice root, lovage root, meadowsweet, onion, parsley, passionflower, poplar, quassia, red clover, rue, sweet clover, turmeric, and willow bark (Heck AM et al 2000).

One nutrient, however, may have been unfairly swept up in this long list of contraindications. A few animal studies and case histories have claimed that coenzyme Q10 (CoQ10), a powerful antioxidant, is contraindicated in patients taking warfarin. However, a study of 24 patients (who were undergoing stable, long-term warfarin treatment) examined the effect of taking 100 mg of Ginkgo biloba and 100 mg of CoQ10 along with warfarin. Researchers found no change in the effects of warfarin therapy after a 1-month treatment period (Engelsen J et al 2003).

By following an ultra cautious approach regarding warfarin and nutrients, patients may be denying themselves the possibility of designing a personalized approach that relies on both warfarin and antiplatelet nutrient therapy. Major medical publications confirm the importance of lowering the risk of cerebrovascular stroke and heart attack by taking both antiplatelets and anticoagulants (Fasey N et al 2002; Hurlen M et al 2002).

Patients who wish to take this approach will need to work closely with their physicians and undergo regular blood testing. The test most often used to monitor warfarin therapy is prothrombin. This test measures the activity of various factors involved in the clotting process. It is expressed as the international normalized ratio (INR), which is a mathematical calculation that corrects for variability in prothrombin test results based on different laboratory testing agents used. Desired INR ranges vary, depending on underlying conditions. A target INR range of 2.0 to 3.0 is recommended for most conditions, while 2.5 to 3.5 INR is recommended for prosthetic heart valves.

Because the prothrombin test does not reveal antiplatelet activity, however, it's also necessary for patients on combination warfarin/antiplatelet therapy to undergo regular bleeding time tests. In this test, a small prick is made in the skin, and the physician measures how long it takes for a clot to form and for bleeding to stop. The normal time range is 1 to 9 minutes.

By using these two tests in concert, it may be possible to develop a balanced program of anticoagulant and antiplatelet therapy that is uniquely suited to an individual, reduces the risk of blood clots, and cuts down on adverse effects associated with anticoagulant therapy.

Ximelagatran: A Possible Blockbuster

Already approved in Europe for certain conditions, ximelagatran is the most exciting anticoagulant news in the last 30 years. Developed under the trade name Exanta®, ximelagatran is a direct thrombin inhibitor.

So far, in early clinical studies, ximelagatran has shown great promise. Whereas warfarin requires frequent blood testing and dosage adjustment, ximelagatran may be given at a fixed dose. It also has fewer side effects and drug interactions than warfarin, and can be administered orally.

Ximelagatran has been tested against a wide variety of diseases and disorders, including atrial fibrillation (O'Brien CL et al 2005) and deep vein thrombosis (Feissinger JN et al 2005). It may be as effective as warfarin. However, it is more expensive.

As of this time, ximelagatran has not been approved for use in the United States because of concerns about liver toxicity. In some early studies, ximelagatran raised liver enzyme levels of some patients (Brinker A et al 2005).

A BALANCED APPROACH TO REDUCING BLOOD CLOT RISK

Many of the nutrients that have been shown to lower the risk of blood clots work by acting on underlying conditions, and they often have overlapping functions with other nutrients. For instance, an elevated homocysteine level is one of the risk factors for blood clots because homocysteine has been linked to CAD. So, there is overlap between the nutrients the Life Extension Foundation recommends to reduce homocysteine levels and those recommended to reduce the risk of blood clots. The same is true for nutrients recommended to treat certain cancers, stroke, and many other conditions.

It is important to remember that good health is truly a lifestyle decision, requiring a balanced, comprehensive approach to diet and nutrient supplementation. The Life Extension Foundation believes in promoting optimal health (not just in treating single diseases), because good health will enable us to live longer, happier, and more productive lives. Almost nowhere is this approach more important than in lowering the risk for blood clots. Contrary to excessive use of medications, supplying the body with what it needs to heal reduces adverse effects and causes less stress on the body.

Following are some of the nutrients that have been shown to reduce the risk of blood clotting:

- **Catechin and quercetin**—Catechin and quercetin are antioxidants that reduce the adhesion of blood platelets, possibly by decreasing the production of hydrogen peroxide (Pignatelli P et al 2000).
- **Curcumin**—Curcumin, a dietary spice derived from turmeric, is known to be anti-inflammatory, anticarcinogenic, and antithrombotic (Shah BH et al 1999).
- **Dehydroepiandrosterone (DHEA)**—Among its many anti-aging properties, DHEA has been shown to reduce inflammation by inhibiting cytokines, or chemicals that promote inflammation within blood vessels (Straub RH et al 2000). With reduced inflammation, less platelet aggregation and LDL migration into the vessel walls occurs. This can lead to less blood clot formation and atherosclerosis.
- **Essential fatty acids**—Essential fatty acids are found in healthy oils, such as flax, borage, perilla, and fish oils. Essential fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are known to inhibit platelet aggregation and reduce the risk of blood clots. Several studies have found that essential fatty acids exhibit antiplatelet activity. Essential fatty acids were shown to inhibit collagen-induced and arachidonic acid-induced platelet aggregation. No effects were seen in thrombin-induced aggregation (Akiba S et al 2000; Ikeda I et al 1998). An Australian study found that omega-3 fatty acids (those rich in alpha-linolenic acid, such as flaxseed and perilla oils) were more effective at platelet inhibition than omega-6 fatty acids (those rich in linoleic acid, such as sunflower oil) (Allman MA et al 1995). A German study reported the same result; an omega-3 to omega-6 ratio of 15:1 caused a significant decrease of collagen-induced platelet aggregation (Stroh S et al 1991).
- **Folic acid**—Because of the danger of homocysteine and its close association with prothrombotic diseases such as CAD, the Life Extension Foundation recommends keeping homocysteine levels between 7 and 8 mmol/L. Folic acid and folate are critical elements in any homocysteine-lowering program, as both have been shown to reduce plasma homocysteine levels (Durand P et al 2001).
- **Garlic extract**—Aged garlic extract is a well-known supplement for lowering cholesterol and improving the cardiovascular system. It has a number of beneficial effects. Garlic increases the synthesis of nitric oxide, which inhibits platelet aggregation and vasodilates blood vessels (Das I et al 1995; Dirsch VM et al 1998; Kim KM et al 2001; Kim-Park S et al 2000). It inhibits platelet aggregation (Rahman K et al 2000; Steiner M et al 1998) and lowers cholesterol by as much as 20 percent (Ali M et al 1990; Ali M et al 1995). Garlic also reduces atherosclerotic plaque volume while lowering blood pressure and increasing HDL cholesterol (Siegel G et al 1999).
- **Ginkgo biloba**—Ginkgo biloba is a natural antiplatelet. An article in the journal *Thrombosis Research* described a study of the effects of Ginkgo biloba in combination with ticlopidine when used to treat rats with experimentally induced thrombosis. The combination of Ginkgo biloba (40 mg/kg daily) and a small dose of ticlopidine (50 mg/kg daily) was shown to be comparable to a large dose of ticlopidine (200 mg/kg daily). The combination also significantly prolonged bleeding time and consistently decreased the thrombus weight (Kim et al 1998).
- **Grape seed extract**—Grape seed and skin have been shown to inhibit platelet aggregation (Keevil JG et al 2000).
- **Green tea**—Green tea catechins, which include epigallocatechin gallate, have an antiplatelet effect (Son DJ et al 2004). Green tea also inhibits fibrinogen (Kang WS et al 1999; Kang WS et al 2001; Sagesaka-Mitane Y et al 1990).
- **N-acetyl-L-cysteine**—N-acetyl-L-cysteine enhances the effect of L-arginine, which promotes creation of nitric oxide (Anfossi G et al 1999; Anfossi G et al 2001). An adverse effect of this is the creation of free radicals. It may be helpful to take N-acetyl-L-cysteine with gamma tocopherol and L-arginine to minimize free radical damage.
- **Nattokinase**—This enzyme, which was isolated from a traditional Japanese soy food called natto, has been shown to reduce fibrin levels (Chang CT et al 2000).
- **Nettle leaf**—In Germany, nettle leaf is an herb (*Urtica dioica*) with a long tradition as an adjuvant remedy in the treatment of arthritis. Like DHEA, nettle leaf has anti-inflammatory effects that work by inhibiting chemicals that cause inflammation

within blood vessel walls (cytokines) (Obertreis B et al 1996; Obertreis B et al 1996; Teucher T et al 1996). Reduced inflammation lowers the risk of blood clot formation.

- **Niacin**—Niacin favorably modifies fibrinogen and LDL cholesterol (Chesney CM et al 2000; Johansson JO et al 1997; Philipp CS et al 1998) and is the recommended agent for lowering lipoprotein(a) (Batiste MC et al 2002).
- **Policosanol**—Isolated from sugar cane wax, policosanol has demonstrated a powerful cholesterol-lowering ability. Policosanol is at least as effective as aspirin in reducing platelet aggregation (Arruzazabala ML et al 1997; Carbajal D et al 1998). Policosanol also improves cholesterol metabolism, in one study increasing HDL cholesterol by 18.4 percent and reducing triglycerides by 14.1 percent (Castano G et al 1999). In a study of heart disease patients with myocardial ischemia, policosanol improved exercise electrocardiogram responses, an effect that was augmented by aspirin (Stusser R et al 1998).
- **Tomatoes**—Tomatoes contain lycopene, a well-known and powerful antioxidant that may be particularly effective in blocking the oxidation of LDL cholesterol. Among all fruits tested for their antiplatelet property, tomatoes had the highest activity (Dutta-Roy AK et al 2001).
- **Vitamins C and E**—Vitamin E inhibits collagen-induced platelet activation by blunting hydrogen peroxide formation (Pignatelli P et al 1999). Vitamins C and E together are associated with an enzyme (paraoxonase) that improves cholesterol levels (Jarvik GP et al 2002).

For More Information

Blood clots are usually caused by an underlying disorder or condition, which means that successful management of the underlying condition can reduce the risk of getting a debilitating blood clot. Other chapters that may be of interest include:

- Hyperhomocysteinemia

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

If you have risk factors for blood clots, we recommend that you take an active role in lowering your risk—through blood tests, dietary nutrients, and positive lifestyle changes. Exercise is an excellent method to reduce the risk of blood clots because of its proven ability to decrease the level of blood fibrinogen (El Sayed MS et al 1999; Imhof A et al 2001; Koenig W et al 2000; Verissimo MT et al 2001). Any exercise program should be launched only under the supervision of a physician.

Patients already taking anticoagulants may also consider adding antiplatelet dietary nutrients under the supervision of their physician. In this case, the Life Extension Foundation recommends frequent blood testing for prothrombin test time and bleeding time to make sure there is no enhanced risk of bleeding.

The Life Extension Foundation's recommended protocol to reduce the risk of blood clots includes:

Cholesterol-lowering nutrients:

- **Policosanol**—10 mg in the evening
- **Garlic**—500 to 1000 mg daily
- **Niacin**—1000 to 3000 mg daily

Antiplatelet nutrients:

- **Low-dose aspirin**—81 mg daily
- **Ginkgo extract**—120 mg daily
- **Fish oil (essential fatty acids)**—1400 mg of EPA and 1000 mg of DHA
- **Nattokinase**—430 mg daily
- **Vitamin E**—400 international units (IU) daily of alpha-tocopherol succinate
- **Gamma tocopherol**—350 to 400 mg
- **N-acetyl-L-cysteine**—250 mg three times daily, with 200 to 400 mg of gamma tocopherol and 1800 to 3600 mg of L-arginine two to four times daily

Homocysteine-lowering nutrients:

- **Folic acid**—800 to 2400 micrograms (mcg) daily, with vitamin B12
- **Vitamin B12**—1000 mcg
- **Vitamin B6**—250 to 750 mg daily

Anti-inflammatory nutrients:

- **Curcumin**—800 to 1600 mg daily
- **DHEA**—25 to 50 mg daily
- **Nettle leaf**—1000 mg daily

Antioxidants:

- **Vitamin C**—2.5 to 6 grams daily
- **Lycopene**—15 to 30 mg daily
- **Quercetin**—500 mg daily
- **Grape seed extract**—300 mg daily
- **Standardized green tea extract**—725 mg capsules daily

BLOOD CLOT PREVENTION SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Curcumin

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Folic acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

Ginkgo biloba

- Individuals with a known risk factor for intracranial hemorrhage, systematic arterial hypertension, diabetes, or seizures should avoid ginkgo.
- Do not use prior to or after surgery.
- Avoid concomitant use of ginkgo with NSAIDs, blood thinners, diuretics, or SSRI's.
- Gastrointestinal symptoms (nausea and diarrhea) may occur.
- Allergic skin reactions may occur.
- Elevations in blood pressure may occur.

Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

NAC

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

Nattokinase

- Do not take nattokinase if you have a blood coagulation disorder.

Niacin (nicotinic acid)

- Do not take high doses of nicotinic acid (1.5 to 5 grams daily or more) if you have liver dysfunction, an unexplained elevation in your serum aminotransferase (transaminase) level, active peptic ulcer disease, arterial bleeding, or if you consume large amounts of alcohol.
- Consult your doctor before taking high doses of nicotinic acid if you have a history of jaundice, peptic ulcer disease, gastritis, disease of the liver or bile ducts, gout, kidney dysfunction, or cardiovascular disease (especially acute myocardial infarction or unstable angina).
- Consult your doctor before taking high doses of nicotinic acid if you have diabetes. High doses of nicotinic acid can negatively affect glucose tolerance. Monitor your serum glucose level frequently if you take nicotinic acid and have diabetes.
- Have your doctor monitor your serum aminotransferase level if you take high-doses of nicotinic acid.
- Nicotinic acid may cause flushing, principally of the face, neck, and chest. This flushing is thought to be prostaglandin-prostacyclin mediated. Histamine may also play a role in the flushing.
- Nicotinic acid can cause dizziness, palpitations, rapid heartbeat, shortness of breath, sweating, chills, insomnia, nausea, vomiting, abdominal pain, and muscle pain.
- High doses of nicotinic acid can cause blurred vision, macular edema, toxic amblyopia, and cystic maculopathy.

Policosanol

- Consult your doctor before taking policosanol if you take aspirin or warfarin (Coumadin) or if you have hemophilia. Policosanol can have antithrombotic activity, and policosanol may enhance the antithrombotic properties of aspirin.
- Discontinue using policosanol before any surgical procedure.
- Policosanol can cause rash, headache, insomnia, weight loss, and gastrointestinal symptoms such as nausea and diarrhea.

Quercetin

- Quercetin can cause headache, mild tingling of the extremities, and gastrointestinal symptoms such as nausea.

Vitamin B6

- Individuals who are being treated with levodopa without taking carbidopa at the same time should avoid doses of 5 milligrams or greater daily of vitamin B6.

Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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