THROMBOSIS PREVENTION

By Ronald Steriti, NMD, PhD

Introduction

Nature has designed a system the body uses to maintain and repair itself. When the vascular system is injured the body responds quickly to stop the bleeding and repair the damage. Circulating platelets are called into action to quickly seal the leak by forming a blood clot.

Not all blood clotting is desireable. Thrombosis is an abnormal blood clot inside a blood vessel. It is a pathologic condition that occurs when the body forms arterial or venous blood clots that are excessively large and obstruct blood flow. The blood clots can also detach from the vascular wall and travel in the blood. These free floating thrombi (now called emboli) can lodge anywhere in the cardiovascular system, including the lungs or brain (as in a thrombotic stroke).

Symptoms

The symptoms of thrombosis depend on where the clot is formed. Heart attacks, stroke, or pulmonary embolism are examples of localized clots that may have various symptoms. If a clot occurs in a coronary artery, a person can have a heart attack. If the clot occurs in an artery in the brain, a person can have a stroke. Clots that form anywhere inside the vascular system can travel elsewhere in the body, causing lethal damage to the lungs (pulmonary emboli), kidneys, or other parts of the body. Cancer patients are especially vulnerable to disability and death from abnormal clot formation inside the blood vessels, particularly in the veins. Symptoms may be totally different, strictly depending on the position of the clot.

Clotting can be localized, but it can also be generalized, such as in a condition called Disseminated Intravascular Coagulation, which also occurs when we die. Up to a point, aggressive medical management can reverse this condition.

Clots can stay where they form or travel to a different location. Whether the clot forms on the spot or travels, the size of the clot is secondary in importance to the location of the clot and the specifics of the area occluded. In general, clots in areas with less collateral circulation are more serious and may be life threatening.

Silent Strokes

Several recent studies have shown that there is a very high incidence of “silent” strokes in the elderly. Over time these “silent” strokes lead to memory loss and other neurological problems. This is of particular concern for people that are at risk for stroke.

An article published in the journal *Neurology* found that 28% of the 3,324 older participants in the Cardiovascular Health Study had evidence of silent infarcts discovered on cranial MRIs. The authors also found that high blood pressure, common and internal carotid wall thickness, and the presence of atrial fibrillation were associated with an increased risk of strokes in those with silent infarcts. (Bernick, Kuller et al. 2001)
The Blood Clotting System

The blood clotting system is activated when blood vessels are damaged, exposing collagen, the major protein that connective tissue is made from. Platelets circulating in the blood adhere to exposed collagen on the cell wall of the blood vessel and secrete chemicals that start the clotting process:

- Platelet aggregators cause platelets to clump together (aggregate). They also cause the blood vessels to contract (vasoconstrict) to reduce blood loss. Platelet aggregators include adenosine diphosphate (ADP), thromboxane A2, and serotonin (5-HT).
- Coagulants, such as fibrin, bind the platelets together to form a permanent plug (clot) that seals the leak.

Fibrin is formed from fibrinogen in a complex series of reactions called the coagulation cascade. The enzymes that comprise the coagulation system are called coagulation factors, which are numbered in the order that they were discovered. They include Factor XII, Factor XI, Factor IX, Factor X, Factor VII and Factor V. The activation of the coagulation factors results in the formation of thrombin which acts as a cofactor for the conversion of fibrinogen into fibrin.

After the leak has been sealed with a blood clot, the body responds with another set of chemical messengers that oppose the actions of these chemicals. These include:

- Platelet aggregation inhibitors and vasodilators, such as nitric oxide and prostacyclin (which is also known as prostaglandin I2, PGI2)
- Plasminogen activators that promote the breakdown of fibrin, such as tissue plasminogen activator (t-PA)
- Anticoagulants that inhibit enzymes in the coagulation cascade, such as antithrombin III (activated by heparin), and proteins C and S

As you can see, the blood clotting system is quite complex. In the healthy body a balance is created between the opposing chemicals (coagulants versus anti-coagulants, vasodilators versus vasoconstrictors, and platelet aggregators versus platelet aggregator inhibitors). The beauty of nutritional supplements is that they support the bodies natural mechanisms and allow the body maintain to its own equilibrium (homeostasis).

Causes

There are hundreds of possible factors that can precipitate blood clots. Our body is so designed that any circulatory disturbance in the blood flow can result in blood clots. This multiplicity of possible causes is a reason that circulatory problems and thrombosis are a major medical problem today.

Thrombosis can be caused by one or more of the following events:

- Injury to the cells that line the heart, arteries, and veins (endothelium).
- Sluggish blood flow contributes to venous thrombosis which usually affects the veins of the lower extremities. Venous thrombi may cause edema of the ankle and foot, but often are asymptomatic until they embolize.
- Alterations in arterial blood flow, which give rise to arterial thrombosis.
- Hypercoagulability (thick blood) can also cause thrombosis.
- Excess platelet aggregation, adhesiveness, and/or activity

Although anticoagulants (such as Coumadin and heparin) are the conventional treatment of choice for thrombosis prevention, thrombi arising solely from hypercoagulability are considered to be uncommon. There are quite a few risk factors for hypercoagulable states (see Table 1). Blood stasis and endothelial injury, however, may be a common underlying mechanism for many of these risk factors (see Table 2).

### Table 1: Risk Factors for Hypercoagulable States

<table>
<thead>
<tr>
<th>Myocardial infarction</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged bed rest or immobilization</td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Tissue damage (burns, surgery, fractures)</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Cancer</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>Late pregnancy, post-delivery</td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Heart valve replacements</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Lupus anticoagulant</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenia</td>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>Homocysteinuria</td>
<td>Thrombocytosis</td>
</tr>
</tbody>
</table>

### Table 2: Underlying causes of thrombosis

<table>
<thead>
<tr>
<th>Endothelial injury</th>
<th>Trauma from accidents, surgery, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After myocardial infarctions</td>
</tr>
<tr>
<td></td>
<td>On ulcerated plaques in advanced atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>From toxins in cigarette smoke</td>
</tr>
<tr>
<td></td>
<td>High cholesterol</td>
</tr>
<tr>
<td></td>
<td>Homocysteine</td>
</tr>
<tr>
<td></td>
<td>Bacterial toxins or endotoxins</td>
</tr>
<tr>
<td></td>
<td>Immune complex deposition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sluggish venous blood flow</th>
<th>Prolonged bed rest, immobilization, or reduced physical activity (movement is required to pump the blood through the veins back to the heart)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac failure resulting in decreased cardiac output, particularly right-sided heart failure</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Disseminated cancer</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Alterations in arterial blood flow</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarctions</td>
</tr>
<tr>
<td></td>
<td>Rheumatic heart disease, which leads to blocking of the mitral valve</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmias, including atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis (lipid deposits that clog the arteries)</td>
</tr>
<tr>
<td></td>
<td>Aneurysms (abnormal dilations of arteries)</td>
</tr>
<tr>
<td>Hypercoagulability (thick blood)</td>
<td>Genetic disorders, including deficiencies of Antithrombin III, Protein C, or Protein S, and fibrinolysis defects</td>
</tr>
<tr>
<td></td>
<td>Oral contraceptives cause an increase in plasma fibrinogen, prothrombin, and clotting factors VII, VIII, and X</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation, due to secretion of factors that activate coagulation factor X</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus, due to an antibody known as lupus anticoagulant</td>
</tr>
<tr>
<td></td>
<td>Autoantibodies against anionic phospholipids (cardiolipin)</td>
</tr>
</tbody>
</table>

**Conventional Prevention and Treatment**

Preventing thrombosis is essential for living. All of us need to prevent clots inside the circulatory system every single minute. Coagulation-anticoagulation is a “mechanism” that our body has to maintain in perfect balance. If this process of keeping an optimal balance between coagulation and anticoagulation fails, our lives can be in danger in a matter of minutes.

What we need for optimal function is to keep blood flowing well in all our vessels, whether small or big. When a leak (or damage) occurs in an artery or vein, we need to encourage the coagulation aspect of this balance in order to seal the leak.

On the other hand, whenever there is a significant disturbance (clot) in blood flow within a blood vessel, the consequences are often lethal.

Because so many factors can contribute to coagulation and therefore should be considered for prevention, it is difficult for conventional medicine to control them all. Mainstream medicine can exert control on some crucial steps in the coagulation cascade, but too often fails to influence them all.

**Prescription Drugs**

Several prescription drugs address different parts of the coagulation-anticoagulation system:

- **Coumadin** (warfarin) stops the production of several coagulation factors by interfering with vitamin K synthesis (their precursor molecule).
- **Aspirin** inhibits platelet aggregation.
- **Ticlopidine** (ticlid) inhibits platelet aggregation by interfering with the binding of fibrinogen to the platelet membrane. Ticlopidine is a prescription drug that may be of particular value as an alternative to aspirin. Ticlopidine is often considered in patients that have a high risk of thrombotic stroke and are intolerant of aspirin.
• **Heparin** increases the activity of antithrombin III, which prevents the conversion of fibrinogen to fibrin. Heparin is not absorbed by the GI tract and must be administered intravenously. It is usually only used in emergency situations (i.e., after a stroke).

• **Tissue plasminogen factor** (t-PA) activates plasmin which breaks apart fibrin. It is used in emergency situations to dissolve blood clots.

**Coumadin**

Coumadin is the most frequently prescribed drug for thrombosis prophylaxis (prevention). It is an anti-coagulant drug that was originally isolated from sweet clover in 1939. Coumadin is the active ingredient found in many commercial rat poisons and insecticides. It works by interfering with the synthesis of vitamin K, which forms several essential coagulation factors. Coumadin is used as a prophylaxis for myocardial infarction, stroke, arterial thromboembolism, and deep venous thrombosis. It is also used in patients with prosthetic heart valves.

Coumadin prolongs prothrombin time (PT) and thromboplastin time (APTT) but prothrombin time is used to guide treatment. The new standard, however, is the International Normalization Ratio (INR), which is described below.

Bleeding is the primary adverse effect of Coumadin therapy and is related to the intensity of anticoagulation, length of therapy, the patient's underlying clinical state, and the use of other drugs that may affect blood coagulation or interfere with Coumadin metabolism.

Minor bleeding from Coumadin therapy usually begins with ecchymoses (purple patches on the skin). The mucous membranes are affected causing epistaxis (nosebleed) and subconjunctival hemorrhage (bleeding under the mucous membranes covering the eyes and inner eyelids). Purple toe syndrome is also associated with Coumadin therapy. Hematuria (blood in the urine) may also occur. Major bleeding complications usually involve gastrointestinal and intracranial bleeding.

Coumadin has an extremely long list of contraindications and drug interactions (see the Thrombotic Stroke protocol for a complete list). Of particular concern is its use in elderly patients because they are more susceptible to the effects of anticoagulants, and have an increased possibility of hemorrhage. Several common drugs interact with Coumadin, including acetaminophen, cimetidine, estrogens and oral contraceptives, lovastatin, and thyroid hormones.

**WARNING** Do not take aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil, Nuprin, others), ketop (Orudis, Orudis KT, Oruvail), naproxen (Naprosyn, Aleve, Anaproxi), and others while taking warfarin, except under the supervision of your doctor. These over the counter medicines increase the risk of bleeding.

Coumadin also interacts with several nutritional supplements (such as ginkgo biloba, vitamin E, and essential fatty acids). There is much debate and confusion about the interactions between dietary nutrients and prescription anti-thrombotic medications regarding clot formation. For quite some time, there has been concern that certain supplements negatively affect the coagulation process, i.e., the nutrients could cause too much suppression of blood clotting factors and increase the risk of blood vessel bleeding.

A more progressive approach is to enable the patient to benefit from both coumadin and anti-platelet nutrients by adjusting the coumadin dose based on the bi-weekly blood test. For instance, if the INR increases while the patient is taking fish oil, vitamin E, ginkgo and garlic, then the dose of Coumadin could be lowered enough to bring the INR into the optimal range.
**Lab Tests**

If you are taking anti-coagulant drugs such as Coumadin or heparin, you need to be careful and check the blood regularly. This is even more necessary if there is a combination of drugs or over-the-counter medication (such as aspirin). With the cocomitant use of natural therapies and aspirin, the need for weekly or biweekly blood monitoring becomes even more important.

The INR standardizes prothrombin time to a control batch of thromboplastin (as the sensitivity of commercial thromboplastin reagents is variable), which allows comparisons between different samples and laboratories.

\[
\text{INR} = \frac{\text{patient PT}}{\text{control PT}} \times \text{ISI (International Sensitivity Index)}
\]

The target INR is 2.5, with a range of 2 to 3. A target of 2 with a range of 1.6 to 2.5 may be used in elderly patients to reduce the risk of hemorrhage. Some authorities, however, disregard age and recommend the higher target of 2.5.

For those taking Coumadin, the following lab tests are recommended weekly or biweekly:

- Prothrombin time (PT) and the International Normalization Ratio (INR)

In addition to prothrombin and INR, the following blood tests taken every 30 to 60 days to help precisely measure thrombotic risk are

- Partial thromboplastin time (PTT)
- Fibrinogen
- \(D\)-dimer of fibrin

**Thrombotic Risk Factors**

**Homocysteine**

Homocysteine is a potentially toxic chemical naturally formed in the body from the amino acid methionine. Normally, homocysteine is converted into beneficial compounds, including glutathione. Homocysteine metabolism requires vitamin B6, B12 and folic acid. If these nutrients are deficient, homocysteine will build up. Elevated homocysteine levels are found in 20-40% of patients with heart disease. Homocysteine has been shown to be a risk factor for cardiovascular disease, including atherosclerosis, heart attack and stroke.

Researchers have proposed that homocysteine causes the formation of reactive oxygen species, which damage endothelial cells, exposing the underlying cell matrix and smooth muscle cells. This, in turn, promotes the activation of platelets and leukocytes to repair the injury (i.e., the blood clotting system described above). Several studies have shown that homocysteine increases blood coagulation by inhibiting tissue fibrinogen activators, resulting in increased levels of fibrinogen and fibrin. (Coppola, Davi et al. 2000) (Kuch, Bobak et al. 2001) (Durand, Prost et al. 2001) (de Jong, van den Berg et al. 1998) (Selhub and D'Angelo 1998)

**Fibrinogen**

Fibrinogen is the precursor of fibrin, a coagulant protein that binds platelets together to form a blood clot. It has a role in normal and abnormal clot formation (coagulation) in the body.
During coagulation, fibrinogen reacts with thrombin, releasing four small fibrinopeptides to produce fibrin, which in turn produces an insoluble fibrin network generally referred to as a scab.

Fibrinogen also participates in the cellular phase of coagulation, acting to promote platelet aggregation, which may lead to diminished blood flow and delivery of oxygen to the body. Fibrinogen can also cause blood platelets to bind together, initiating abnormal arterial blood clots.

An article published in the journal *Neurology* described a study of cardiovascular lab tests in 136 patients with acute stroke, 76 patients with comparable risk factors for stroke, and 48 healthy controls. Statistical analysis found that prior stroke and fibrinogen levels predicted new events in stroke patients. After 1 year, fibrinogen levels remained elevated in stroke survivors. The authors concluded that fibrinogen levels are associated with increased risk of recurrent vascular events. (Beamer, Coull et al. 1998)

**Inflammation**

Chronic inflammation is associated with a variety of chronic diseases, including cardiovascular disease. C-Reactive protein (CRP) is a sensitive marker of inflammation that rises before the erythrocyte sedimentation rate (ESR) used by conventional medicine. C-reactive protein is a marker of systemic inflammation and unstable arterial plaque, both indictors of increased thrombotic risk.

An article published in the journal *Thrombosis Research* described a study of patients with acute thrombotic stroke prior to treatment. Those patients with elevated C-reactive protein also had significantly elevated plasma levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer of fibrin. Platelet aggregation induced by adenosine diphosphate (ADP) was also significantly higher in patients with elevated CRP, as compared to those with normal levels. The authors hypothesized that the activation of the blood coagulation and platelet aggregation system may be related to elevated CRP levels in stroke patients. (Tohgi, Konno et al. 2000)

**Lipoprotein A**

Lipoprotein A is an altered form of LDL cholesterol that has a structure nearly identical to plasminogen, a protein that forms plasmin which dissolves fibrin. Unfortunately lipoprotein A inhibits the breakdown of fibrin by competing with plasminogen. Lipoprotein A was found to be a key component in blood clots. (Rath, Niendorf et al. 1989) (Rath and Pauling 1990) (Rath and Pauling 1990) (Beisiegel, Niendorf et al. 1990)

Linus Pauling’s theory of heart disease focused on the adverse effects of lipoprotein A on the cardiovascular system. Drs. Pauling and Rath proposed that lipoprotein (a) acted as a surrogate (replacement) for vitamin C. They proposed that a deficiency of vitamin C resulted in the increased production of lipoprotein (a) which both hardened the arteries and caused blood clots. Linus Pauling recommended the use of high doses of pure vitamin C and lysine to both prevent and treat cardiovascular disease.
**Hypothyroidism**

The endocrine system is a complex mechanism where each of the organs impacts the others. A low functioning thyroid (hypothyroidism) would therefore impact other systems, including the cardiovascular system. Hypothyroidism is associated with increased cholesterol levels, atherosclerosis, and increased homocysteine. (Diekman, van der Put et al. 2001) (Kahaly 2000) (Hak, Pols et al. 2000) (Hussein, Green et al. 1999) (Diekman, Demacker et al. 1998) (Carantoni, Vigna et al. 1997) (Nedrebo, Ericsson et al. 1998)

The effect of hypothyroidism on the blood clotting system is currently controversial and is the focus of several recent studies. (Muller, Tsakiris et al. 2001) (Chadarevian, Bruckert et al. 1998)

**Comprehensive Lab Testing**

Optimal ranges of conventional lab tests are much narrower than the Standard Reference Ranges used in conventional medicine. It is important to emphasize that the “average” person does not feel particularly well and has the “average” risk of chronic disease. For many people this dismal fate is unacceptable.

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Standard Reference Range</th>
<th>Optimal Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>100-199 mg/dL</td>
<td>Between 180-200 mg/dL</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>0-29 mg/dL</td>
<td>Under 100 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>35-150 mg/dL</td>
<td>55-150 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0-199 mg/dL</td>
<td>40-00 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>65-109 mg/dL</td>
<td>70-00 mg/dL</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>5-15 mcmmol/L</td>
<td>Under 7.2 mcmmol/L</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>200-400 mg/dL</td>
<td>200-300 mg/dL</td>
</tr>
<tr>
<td>CRP</td>
<td>Up to 4.9 mg/L</td>
<td>Under 2 mg/L Some suggest &lt; 1.3 mg/L</td>
</tr>
<tr>
<td>DHEA</td>
<td>Men: over 80 mcg/dL</td>
<td>Men: 400-560 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Women: over 35 mcg/dL</td>
<td>Women: 350-430 mcg/dL</td>
</tr>
<tr>
<td>ProThrombin Time PT</td>
<td>generally 11-15 seconds</td>
<td></td>
</tr>
<tr>
<td>International Normalization</td>
<td>2 – 3, target = 2.5</td>
<td>1.6 - 2.5, target = 2</td>
</tr>
</tbody>
</table>
Consulting Your Physician

When over the counter supplements such as aspirin, vitamins, herbs, and oils are used as the primary anti-thrombotic therapy, the risk of undesirable side effects is reduced significantly. Although over the counter medications such as aspirin and natural therapies come with a lower risk of hemorrhaging, they should not be substituted for prescription medication if you are at a high risk for thrombosis. Some common conditions which cause a high risk of thrombosis include atrial fibrillation, valvular replacement, recurrent or chronic deep venous thrombosis, pulmonary embolism, or cancer.

In all circumstances requiring anticoagulation therapy or antithrombotic therapy, your doctor should be consulted if you desire to substitute your medication because the risk can be life threatening and the appropriate therapeutic dosing is crucial. Since medications such as Coumadin (warfarin), and heparin have a very narrow therapeutic range, anyone on these medications should have his or her blood tested frequently for one or more of the following: PT, PTT, INR. Once the effective dose is achieved, blood testing is recommended every two weeks to monitor the medication blood levels and avoid overdosing, which could lead to hemorrhaging. Blood levels should be more closely monitored if over the counter drugs or natural supplements that affect the clotting cascade are added to the regimen. Some of these supplements include vitamin E, ginkgo biloba, coenzyme Q10, garlic, ginseng, St. John’s wort, green tea, vitamin C, vitamin A, policosinol, Dong Quai, white willow, ipriflavone, and vinpocetine (periwinkle).

Nutritional Supplements

The nutritional supplements listed below have scientific studies specifically on their ability to reduce the risk of thrombosis. The bulk of the research focuses on inhibiting platelet aggregation. The supplements are divided into several broad categories based on their primary actions:

- Cholesterol-Lowering Supplements
- Natural Blood Thinners
- Lowering Homocysteine
- Anti-Inflammatories
- Antioxidants
- Sulfur-Containing compounds

The supplements in the Natural Blood Thinners category could have been put into other categories. Ginkgo and vitamin E, for instance, are very powerful antioxidants and essential fatty acids are known for their anti-inflammatory actions. Their blood-thinning effects are, however, much more important in the prevention of thrombosis.
**Cholesterol-Lowering Supplements**

**Policosanol**

Policosanol is a cholesterol-lowering agent derived from sugar cane wax. It can normalize cholesterol as well or better than drugs, without side effects.

Efficacy and safety have been proven in numerous clinical trials, and it has been used by millions of people in other countries. Policosanol can lower LDL cholesterol as much as 20% and raise protective HDL cholesterol by 10%. This compares favorably with cholesterol-lowering drugs which have the drawback of side effects such as liver dysfunction and muscle atrophy. (Mas, Castano et al. 1999)

Policosanol works by blocking the synthesis of cholesterol. It does not inhibit the HMG-CoA enzyme like the “statin” cholesterol-lowering drugs, but it may inhibit a different enzyme. Its exact mechanism is not known. However, like statin drugs, policosanol helps stop the formation of atherosclerotic lesions. This was proven in studies on rabbits fed a diet designed to create high cholesterol. (Noa, Mas et al. 1995)

Policosanol inhibits the formation of clots, and may work synergistically with aspirin in this respect. In a comparison of aspirin and policosanol, aspirin was better at reducing one type of platelet aggregation (clumping together of blood cells). But policosanol was better at inhibiting another type. Together, policosanol and aspirin worked better than either alone. (Arruzazabala, Valdes et al. 1997) (Stusser, Batista et al. 1998)

An article published in the journal *Pharmacology Research* described a randomized, double-blind, placebo-controlled study of policosonal and aspirin. Participants received either policosanol (20 mg per day), aspirin (100 mg per day), a combination of both, or placebo for 7 days. The effects on platelet aggregation are summarized below. (Arruzazabala, Valdes et al. 1997)

<table>
<thead>
<tr>
<th>Reduction of platelet aggregation by aspirin and policosanol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induced by</strong></td>
</tr>
<tr>
<td>ADP</td>
</tr>
<tr>
<td>epinephrine</td>
</tr>
<tr>
<td>collagen</td>
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</tbody>
</table>

A related effect is that significant reductions in the level of thromboxane occur in humans after two weeks of policosanol. (Carbajal, Arruzazabala et al. 1998) Thromboxane is a blood vessel-constricting eicosanoid produced by platelets. (Note: eicosanoids are powerful chemicals created in cells that can do things like create fever to kill infections, make blood vessels in lungs expand so you can breathe, and reduce inflammation. The body could not function without eicosanoids. Problems arise when eicosanoid reactions are disrupted by drugs, disease, poor diet...
and other factors that interfere with their natural balance). There are no known adverse reactions with its use.

Policosanol is a cutting-edge natural supplement available from the Life Extension Foundation. It is primarily used to lower cholesterol. The normal dose is 10 mg per day, although some people may need only 5 mg or up to 20 mg per day. Cholesterol levels should be measured regularly as both high and low cholesterol levels are considered unhealthy.

**Aged Garlic**

Aged garlic has become a well-known and popular supplement for the cardiovascular system.

Garlic has been found to increase the synthesis of nitric oxide, a chemical messenger that inhibits platelet aggregation and vasodilates blood vessels. (Kim, Chun et al. 2001) (Kim-Park and Ku 2000) (Dirsch, Kiemer et al. 1998) (Das, Khan et al. 1995)

An article published in the journal *Nutrition* described a randomized, double-blind study of aged garlic on normal, healthy individuals. The researchers found that aged garlic inhibited platelet adherence and aggregation. Higher doses (7.2 grams per day) had a more profound effect than lower doses (2.4 grams per day). (Steiner and Li 2001)

The specific effects of aged garlic have been the subject of several studies. Aged garlic has been shown to inhibit platelet aggregation by adenosine diphosphate (ADP), epinephrine and collagen, although one study found that it did not affect ADP-induced aggregation. (Rahman and Billington 2000) (Steiner and Lin 1998)

One study examined the effects of consuming one fresh clove of garlic every day on men. After 26 weeks of garlic consumption, there was an approximately 20% reduction of serum cholesterol and about 80% reduction in serum thromboxane B2, a stable metabolite of thromboxane A2. Recall that thromboxane A2 is a platelet aggregator and vasoconstrictor secreted by platelets. (Ali and Thomson 1995) (Ali, Thomson et al. 1990)

**Niacin**

Niacin (vitamin B3) causes peripheral vasodilation (flushing) within about 20 minutes. Large doses of niacin (up to 6 grams a day) have been found to lower cholesterol levels.

A recent article published in the *American Heart Journal* described the Arterial Disease Multiple Intervention Trial (ADMIT), a multi-center, randomized, placebo-controlled trial to assess the feasibility of an antioxidant therapy on coagulation. Patients with peripheral artery disease randomly received low-dose Coumadin, niacin, an antioxidant vitamin cocktail, or placebo. Unexpectedly, the niacin treatment resulted in a significant decrease in fibrinogen. (Chesney, Elam et al. 2000)
Natural Blood-Thinners

Ginkgo biloba

Ginkgo biloba extract is made from the leaves of the oldest living tree. Ginkgo has a long history of medicinal use and has become a very popular herb to help improve memory, particularly in the elderly.

Ginkgo biloba has been shown to inhibit platelet aggregation induced by platelet-activating factor (PAF), but not by oxidative stress. (Akiba, Kawauchi et al. 1998)

An article published in the journal *Thrombosis Research* described a study of the effects of ginkgo biloba in combination with ticlopidine used to treat rats with experimentally-induced thrombosis. The combination of ginkgo biloba (40 mg/kg/day) and a small dose of ticlopidine (50 mg/kg/day) was shown to be comparable to a large dose of only ticlopidine (200 mg/kg/day). The combination also prolonged bleeding time by 150% and consistently decreased the thrombus weight. (Kim, Pyo et al. 1998)

Essential Fatty Acids

Essential fatty acids are found in healthy oils, such as flax, borage, perilla and fish oil. They are called “essential” because they are necessary for life. Essential fatty acids, including DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), are known to inhibit platelet aggregation and are included as contraindications with anticoagulant (warfarin) therapy. The contraindication is actually more of a strong caution to avoid thinning the blood too much. Recent studies involve determining which of the fatty acids are most effective.

Several recent studies examined the anticoagulant mechanisms of fatty acids. EPA, DHA and DPA (docosapentaenoic acid) were found to inhibit platelet aggregation induced by collagen and arachadonic acid, but no effect was seen in thrombin-induced aggregation. DPA was found to be the most potent inhibitor. The mechanism was related to the ability of these fatty acids to suppress thromboxane A2 formation by inhibiting cyclooxygenase-1. (Akiba, Murata et al. 2000) (Ikeda, Yoshida et al. 1998)

DPA (docosapentaenoic acid, adrenic acid) is an omega-6 fatty acid (22:5n6) that is synthesized from linoleic acid (an omega-6 fatty acid found in safflower and sunflower oils and corn). DPA is also known as adrenic acid because it is found primarily in the adrenal glands.

An Australian study found that omega-3 fatty acids (those rich in alpha-linolenic acid, such as flaxseed and perilla oil) were more effective than omega-6 fatty acids (those rich in linoleic acid, such as sunflower oil). (Allman, Pena et al. 1995) This same result was also reported in a German study which found that an omega-3 to omega-6 ratio of 15:1 caused a significant decrease of collagen-induced platelet aggregation. (Stroh and Elmadfa 1991)

Vitamin E

Vitamin E (tocopherol) is a potent antioxidant that has been shown to increase prostaglandin I2 synthesis, one of the platelet aggregation inhibitors and vasodilators. As such, vitamin E should be used with caution when taking anticoagulant drugs (such as Coumadin). Vitamin E is depleted by estrogen, birth control pills, and chlorine.
A recent study found that vitamin E was able to inhibit collagen-induced platelet aggregation at concentrations achievable in blood after supplementation. The researchers also showed that the mechanism by which vitamin E worked was by blunting hydrogen peroxide formation which mediates arachadonic acid metabolism and phospholipase C activation in platelet aggregation induced by collagen. (Pignatelli, Pulcinelli et al. 1999)

Vitamin E should be used with care (under the advise of a knowledgeable physician) in patients on anticoagulant drugs (Coumadin, Warfarin).

**Vitamin K**

Vitamin K plays a unique role in the clotting system by contributing to both coagulation and anti-coagulation. Vitamin K is precursor of coagulation factors II, VII, IX and X. Vitamin K is also a cofactor for the synthesis of protein C and S. Protein C is a proteolytic enzyme that acts as an anticoagulant by inactivating clotting factors V and VIII, and by increasing production of tissue plasminogen activator.

An article published in the journal *Lancet* recommended that asymptomatic patients on Coumadin, should consider low-dose vitamin K if blood-clotting time, as measured by the international normalized ratio (INR), is between 4.5 and 10.0. The article described a multi-center, double-blind, placebo-controlled, randomized trial in which patients received either placebo or 1 mg of vitamin K orally. Patients given vitamin K had a more rapid decrease in the INR than those given placebo, and fewer of them had bleeding episodes during the follow-up period. The authors concluded that low-dose vitamin K therapy rapidly lowers INR values in patients taking warfarin and may be effective in preventing hemorrhage (one of the common side effects of Coumadin therapy). (Crowther, Julian et al. 2000) (Crowther, Donovan et al. 1998)

Vitamin K counteracts the action of Coumadin and is strictly contraindicated in patients on anticoagulant drug therapy.

**Lowering Homocysteine**

Homocysteine has slowly become accepted by conventional medicine as a risk factor for cardiovascular disease. Clinical research has shown that vitamins (folic acid, vitamin B6 and vitamin B12) are very effective at lowering homocysteine levels. It has been proposed that homocysteine activates the blood clotting system by damaging endothelial cells.

An article published in *Thrombosis Research* described a study of 11 people with high homocysteine levels (above 16), 11 of which had atherosclerosis. After an 8-week treatment with folic acid (5 mg per day orally), vitamin B6 (300 mg per day orally) and vitamin B12 (1000 mcg per week intramuscularly), homocysteine levels dropped from 20 to 10. Vitamin treatment was also associated with a significant decrease in the markers of thrombin formation, including thrombin-antithrombin III complexes and prothrombin fragment 1+2 concentrations in peripheral venous blood. Bleeding time became prolonged by about 60 seconds. (Undas, Domagala et al. 1999)
**Anti-Inflammatories**

**Curcumin**

Curcumin is the Latin name for the common yellow spice turmeric. Curcumin is commonly used for its anti-inflammatory effects. Curcumin has also been shown to lower cholesterol.

Recent research has examined the mechanism of the anti-platelet action of curcumin (turmeric). Curcumin was shown to inhibit platelet aggregation induced by ephedrine, adenosine diphosphate (ADP), platelet-activating factor (PAF), collagen and arachadonic acid. Curcumin acted most strongly against aggregation by PAF and arachadonic acid. The mechanism appeared to be related to curcumin’s inhibition of thromboxane A2. (Shah, Nawaz et al. 1999) Curcumin should be taken with meals to avoid the possibility of gastric irritation.

**Licorice**

Glycyrrhizin, an anti-inflammatory compound isolated from *Glycyrrhiza glabra* (licorice), was found to inhibit platelet aggregation induced by thrombin. The authors proposed that the anti-inflammatory effect of glycyrrhizin may be due to its anti-thrombin action. (Francischetti, Monteiro et al. 1997)

Other researchers identified isoliquiritigenin, an aldose reductase inhibitor purified from licorice (*Glycyrrhizae radix*), as a platelet aggregation inhibitor. (Tawata, Aida et al. 1992)

Licorice is one of the most important herbs in Chinese medicine, and is found in almost all of the Chinese Patent Formulas. Excessive amounts of licorice can increase blood pressure and water retention. One cup of licorice tea in the morning helps to increase your energy.

**Antioxidants**

**Quercetin and Catechin**

Quercetin and catechin are bioflavonoids with strong antioxidant properties. Quercetin is primarily used for its beneficial effects on allergies.

A recent article published in the *American Journal of Clinical Nutrition* found that catechin and quercetin inhibited the collagen-induced platelet adhesion. The authors proposed that the effects may be due to the ability of catechin and quercetin to decrease hydrogen peroxide production. (Pignatelli, Pulcinelli et al. 2000)

Quercetin may also inhibit platelet aggregation by its antioxidant properties. (Xie, Lu et al. 1996)

Another study examined the inhibition of thrombin-induced platelet aggregation by a semi-synthetic derivative of quercetin. The authors found that quercetin inhibited platelet aggregation by inhibiting calcium mobilization and influx. (Liu and Liang 2000) (Liu, Song et al. 1999)
Green tea

Green tea has become very popular for the prevention and treatment of a wide range of diseases. Green tea protects the cardiovascular system and may prevent cancer.

A recent study published in the journal *Thrombosis Research* examined the effects of green tea catechins (tannins) and epigallocatechin on platelet aggregation. Both substances inhibited platelet aggregation induced by adenosine diphosphate (ADP) and collagen in rats. They also inhibited platelet aggregation induced by ADP, collagen, and epinephrine in human blood samples. (Kang, Lim et al. 1999)

Japanese researchers found that green tea inhibited aggregation of rabbit platelets. They identified the catechins (tannins) as the active principle, and that epigallocatechin suppressed collagen-induced platelet aggregation at a concentration of 0.2 mg/mL. Epigallocatechin also inhibited platelet aggregation induced by thrombin and platelet-activating factor (PAF). (Sagesaka-Mitane, Miwa et al. 1990)

Tomato

The essence of tomatoes, lycopene, has been shown to have strong antioxidant properties. Lycopene may be particularly effective in blocking the oxidation of LDL cholesterol.

An article published in the journal *Platelets* described a study of fruits on human platelet aggregation in vitro. Researchers found that tomato extract inhibited both ADP and collagen-induced aggregation by up to 70%. The anti-platelet components were found to be concentrated in the yellow fluid around the seeds. Grapefruit, melon and strawberry were also found to have anti-platelet activity, but to a lesser extent. (Dutta-Roy, Crosbie et al. 2001)

Grape Juice

Grapes have become a fairly popular recently due to several studies that found that consuming one cup of red wine a day had beneficial effects on the cardiovascular system. Grapes contain proanthrocyanadins (which impart the blue color) that are concentrated in the seeds and skin. Studies have shown that the antioxidant power of grape seed-skin extract is 50 times greater than vitamin E and 20 times greater than vitamin C.

A recent article published in the journal *Circulation* described a study that examined the effects of purple grape juice on platelets. Lab tests (in vitro) found that purple grape juice inhibited platelet aggregation, increased nitric oxide production, and decreased superoxide formation. The researchers then conducted a study with 20 healthy subjects that consumed 7 mL/kg per day of purple grape juice for 14 days. Purple grape juice supplementation inhibited platelet aggregation, increased platelet nitric oxide production, and decreased superoxide formation. The authors proposed that purple grape juice may have beneficial effects in cardiovascular disease. (Freedman, Parker et al. 2001)

An article published in the journal *Nutrition* described a study in which ten healthy subjects drank 5 to 7.5 mL/kg per day of either purple grape juice, grapefruit juice, or orange juice for one week. Drinking purple grape juice reduced platelet aggregation by 77%. Orange and grapefruit juice had no effect. The authors proposed that the flavonoids in grape juice may decrease the risk of thrombosis. (Keevil, Osman et al. 2000)
Sulfur-Containing Compounds

N-Acetyl-L-Cysteine
The amino acid N-Acetyl-L-Cysteine (NAC) inhibits platelet aggregation by several mechanisms, including

- Increasing the anti-platelet aggregating effects of L-arginine which promotes endogenous synthesis of nitric oxide (Anfossi, Russo et al. 2001) (Anfossi, Russo et al. 1999)
- Affecting platelet-derived growth factor, a key player in fibrosis (Okuyama, Shimahara et al. 2001) (Durante, Peyton et al. 1999)

N-Acetyl cysteine is an antioxidant that is helpful in breaking up pulmonary and bronchial mucus. NAC is also a precursor of glutathione.

Onions
Onion juice has been shown to reduce in vitro human platelet aggregation. To retain their health benefits, onions should be eaten raw or lightly steamed as high heat inactivates the active ingredients.

The anti-platelet aggregation action of onion is attributed to sulfur compounds called thiosulfonates. The strongest thiosulfonates are allicin, propyl propane thiosulfinate, and ethyl ethane thiosulfanate. All three of these thiosulfonate compounds were shown to be significantly more potent platelet aggregators than aspirin at nearly equivalent doses. (Briggs, Xiao et al. 2000)

The antithrombotic effects of Welsh onion juice was examined in a study using 9 week old rats. Two days after treatment (2 g/kg/day), the raw Welsh onion juice consumption significantly lowered systolic blood pressure, prolonged the bleeding time, and diminished platelet adhesion as compared to controls. The authors also found that boiled onion juice had no effect. (Chen, Chen et al. 2000)

A recent article in the journal Nutrition described a study in which onion juice was administered 20 minutes after coronary arteries of dogs were mechanically damaged (narrowed). Treatment with onion juice eliminated the induced cyclic flow reduction within 2.5 to 3 hours in all 5 of the treated dogs. The authors concluded that onion juice may help prevent platelet-mediated cardiovascular disorders, but noted that the effects may be greater in dogs than in humans. (Briggs, Folts et al. 2001)

Miscellaneous

Ginseng
Ginseng has been a staple of Chinese medicine for over 5,000 years and is highly valued by the Chinese people. Ginseng is available from several different countries (China, Japan, Siberia, Korea), each with unique properties.
A recent study conducted in Korea examined the antithrombotic effects of Korean Red Ginseng and a combination of five herbs (Korean Red ginseng, Ganoderma, Cinnamon, Licorice and Laminaria). Both were administered to rats with blood stasis induced by high molecular weight dextran. The researchers found that both compounds significantly inhibited thrombin and collagen-induced platelet aggregation. They also found that the combination formula was more effective than the ginseng alone. (Yun, Do et al. 2001)

Panax ginseng is also being studied for its antithrombotic effect. Ginsenosides, a component of ginseng, have been found to be relatively potent antagonists to platelet activating factor. (Jung, Kim et al. 1998)

A Japanese study found that Panax ginseng extract significantly decreased platelet adhesiveness and reduced cholesterol levels in rats when administered 6 days before and after hepatectomy (liver removal). (Cui, Sakaguchi et al. 1999)

Inositol hexaphosphate

Inositol hexaphosphate (IP6) is the phosphorylated form of inositol, one of the vitamin B complexes.

An article published in *Anticancer Research* described a study of the effects of inositol hexaphosphate (IP6) on platelet aggregration measured in whole blood obtained from healthy volunteers. The researchers found that IP6 significantly inhibited platelet aggregation induced by adenosine diphosphate (ADP), collagen and thrombin. (Vucenik, Podczasy et al. 1999)

Soy Sauce

Japanese researchers found that alkaloids found in commercially available soy sauce inhibited platelet aggregation. (Tsuchiya, Sato et al. 1999)

Digestion

Digestion is a process that is key to life. Evaluating and supporting digestion is a central part of natural therapies. Pepsin is a gastric enzyme that is responsible for protein digestion. Pepsin is formed when pepsinogen, which is secreted by chief cells of the stomach, is cleaved by hydrochloric acid.

Studies have shown that platelet aggregation was decreased by about 50% at a (slightly acidic) pH of 6.4. Pepsin enhanced the effect. (Green, Kaplan et al. 1978)

A study published in the journal *Thrombosis Research* found that type I collagen that was digested by pepsin was unable to initiate platelet aggregation. (Hill, Baugh et al. 1985)

An article published in the journal *Gut* described research that explored the mechanism by which most upper gastrointestinal hemorrhages stop spontaneously. Researchers simulated a hemorrhage by infusing blood in healthy volunteers and then measured acid and pepsin secretion. They found that gastric acid and pepsin secretion decreased by 30% and 43% respectively during the hour following the infusion. The authors proposed that this may be a protective response. (Fullarton, Boyd et al. 1989)
**Exercise**

The effects of exercise on fibrinogen levels have been extensively studied. Several studies show that regular exercise lowers fibrinogen levels and reduces the risk of thrombosis. (Imhof and Koenig 2001) (Verissimo, Aragao et al. 2001) (El-Sayed, Sale et al. 2000) (El-Sayed, Jones et al. 1999) (Koenig and Ernst 2000)

Regular exercise is well known to provide a host of health benefits, particularly on the cardiovascular system.

**Summary**

Prevention of blood clots is a complex task that involves keeping a fine balance in place between the process of coagulation and anticoagulation. Patients on prescription medication as well as any combination of these with over-the-counter anti-inflammatories or aspirin need close monitoring by periodic laboratory testing of their blood. Patients on supplements (such as vitamins, herbs, or oils) need their risk factors (fibrinogen and homocysteine) evaluated in the same way. However, a close monitoring of the coagulation balance is not usually necessary in otherwise healthy people.

WARNING: Never change anticoagulation medication without physician approval, because thrombosis, bleeding, and sudden death may occur.

Thrombosis prevention involves several diverse mechanisms, including:

- Reduce and repair injury to endothelial cells
  - Lower cholesterol levels
  - Lower homocysteine levels
  - Lower C-reactive protein levels
- Improve venous blood flow
  - Exercise
  - Address peripheral vascular disease, which may be related to diabetes or intermittent claudication
- Improve arterial blood flow
  - Reduce atherosclerosis
- Anti-coagulation
  - Decrease platelet adhesiveness
  - Support fibrinolysis
  - Reduce inflammation
  - Lower fibrinogen levels

Several lab tests are highly recommended to assess the cardiovascular system and guide appropriate treatment, including cholesterol and triglyceride levels, homocysteine, prothrombin time, fibrinogen, and C-reactive protein.
The following supplements have shown anti-thrombotic action by lowering cholesterol, fibrinogen, or homocysteine, acting as a natural blood thinner or anti-inflammatory, and inhibiting platelet aggregation.

1. Policosanol has a profound effect on lowering cholesterol, inhibiting platelet aggregation, and preventing thrombosis. Policosanol Tabs contain 5 mg of policosanol. The average person uses 10 mg a day to achieve optimal cholesterol levels. Some people may only need 5 mg a day, while others may require 20 mg a day. Cholesterol levels should be monitored regularly as levels below 150 may be dangerous.

2. Garlic may be very useful in lowering cholesterol levels.

3. Low-dose aspirin is widely recommended to help thin the blood and prevent strokes. One tablet a day with a heavy meal is recommended.

4. Ginko biloba is a powerful antioxidant, thins the blood, and improves memory. Use ginkgo with caution when taking anticoagulants.

5. Essential Fatty Acids: Including Alpha linolenic acid (ALA) and docosahexaenoic acid fish oils. Suggested doses are:
   - Super GLA/DHA (six 1000 mg capsules a day) To provide high potencies of anti-inflammatory fatty acids
   - Perilla Oil (six 1000 mg capsules a day) To provide high potencies of precursors to EPA and DHA

6. Vitamin E is an antioxidant and blood-thinner. The recommended dose for most people is 400-500 IU of alpha tocopherol, 210 mg of gamma tocopherol and at least 50 mg of the tocotrienols. Vitamin E should be used with caution with warfarin as it thins the blood.

7. Vitamin K may be considered in those that are not currently taking Coumadin. Vitamin K should not be taken by those on anticoagulant drug therapy (Coumadin or Heparin).

8. Vitamin B6, 100-1000 mg per day is recommended to lower homocysteine

9. Folic acid (800-2400 mcg/day and B12 (300 to 2000 mcg/day).

10. Trimethylglycine should be considered if homocysteine levels are elevated.

11. Curcumin is well-known for its anti-inflammatory action. It has also been shown to inhibit platelet aggregation. Curcumin should be used with caution in patients with biliary tract obstruction because it stimulates secretion of cholesterol bile acids from the liver through the bile duct into the intestines. High doses of curcumin on an empty stomach may contribute to stomach ulcers or gastric irritation.

12. Quercetin is am antiplatelet agent. About 500 mg/day is suggested.

13. Green tea inhibits several factors involved in abnormal platelet aggregation.

14. Tomatoes have been shown to inhibit platelet aggregation. Lycopene, the main constituent of tomatoes, is a powerful antioxidant. Lycopene is available in supplement form.

15. Grape juice has been shown to inhibit platelet aggregation. Grapes contain proanthocyanadins that are concentrated in the skin and seeds.
References


Crowther, M. A., D. Donovan, et al. (1998). "Low-dose oral vitamin K reliably reverses over-


