

## Coronary Artery Disease and Atherosclerosis

Atherosclerosis is perhaps the single most deadly disease in the United States, yet there is a good chance that most people, even those at high risk for heart disease, don't really understand how it develops. The fact is, long before any symptoms are clinically evident, atherosclerosis begins as a malfunction of specialized cells that line our arteries. Called endothelial cells, they are the key to atherosclerosis, and underlying endothelial dysfunction is the central feature of this dreaded disease.

Not every person who suffers from atherosclerosis has the risk factors we commonly associate with the disease, such as elevated cholesterol, but every single person with atherosclerosis has endothelial dysfunction. It is the unifying concept through which coronary artery disease must be understood. Atherosclerosis begins with inflammation and immune cell activation at the endothelial level, and they lead to endothelial dysfunction and eventually damage to the artery and formation of plaque. This process is hastened by high cholesterol, smoking, obesity, high blood pressure, and other risk factors for coronary heart disease.

Atherosclerosis takes a huge toll on our society. According to the American Heart Association, more than 64 million Americans suffer from some form of cardiovascular disease, making it the leading cause of death in the country. In 2001, cardiovascular disease was responsible for more than 39 percent of all deaths in the United States (American Heart Association: Heart Disease and Stroke Statistics 2004).

In the world of conventional medicine, atherosclerosis is a widely misunderstood disease, perhaps because of a fundamental misconception about the nature of the arteries themselves. In this antiquated view, the arteries have been thought of as stiff pipes that gradually become clogged with excess cholesterol floating around the bloodstream. The solution recommended most often has been to reduce the dietary consumption of fats in order to lower levels of cholesterol, triglycerides, and low-density lipoprotein (LDL) in the blood. Conventional medicine's preferred method of reestablishing blood flow in clogged arteries is through surgery (coronary artery bypass graft surgery) or by insertion of catheters bearing tiny balloons that crush the plaque deposits against the arterial walls (angioplasty), followed by the implantation of tiny mesh tubes (stents) to keep the arteries open.

There are problems with this view, however. For one thing, the grafts used to reestablish blood flow can also develop atherosclerotic plaque deposits. The same was true for balloon angioplasty; in their early years, up to half of all angioplasty procedures "failed" when the arteries gradually closed again. Even today, with the use of improved stents, the failure rate is between 10 and 15 percent, and many people have to undergo repeat angioplasty or even surgery.

Today, our understanding of atherosclerosis has literally redefined the disease. We now understand atherosclerosis as a chronic inflammatory disease that affects the way arteries function at the most basic level. Instead of viewing the arteries as pipes through which blood flows, we now understand that arteries are muscular organs that change and adapt to their environment and contract and expand in response to multiple factors, helping to raise and lower blood pressure and distribute blood throughout the body. Finally, we have begun to unravel the biochemical processes that underlie atherosclerosis.

This new understanding of atherosclerosis has yet to filter into mainstream medicine, but the most progressive and forward-thinking researchers are already developing novel ways to correct the endothelial dysfunction that underlies coronary heart disease. Life Extension Foundation is closely monitoring the state of research regarding this epidemic disease of normal aging.

### ENDOTHELIAL DYSFUNCTION: UNDERLYING ARTERIAL DISEASE

The cause and progression of atherosclerosis are intimately related to the health of the inner arterial wall. Arteries are composed of three layers. The outer layer is mostly connective tissue and provides structure to the layers beneath. The middle layer is smooth muscle; it contracts and dilates to control blood flow and maintain blood pressure. The inner lining consists of a thin layer of endothelial cells (the endothelium) that provides a smooth, protective surface. Endothelial cells prevent toxic, blood-borne substances from penetrating the smooth muscle of the artery. They also respond to changes in blood pressure and release substances into the cells of the smooth muscle that help change the muscle tone of the artery. Furthermore, endothelial cells secrete chemicals that provoke a protective response in the artery after an injury. This protective response includes signaling smooth muscle cells and white blood cells to congregate at the site of an injury.

As we age, however, the endothelium becomes leaky, allowing lipids and toxins to penetrate the endothelial layer and enter the smooth muscle cells. As a result, smooth muscle cells gather at the site of the injury, and the artery loses some flexibility. In response, the endothelium signals white blood cells to congregate along the cell wall. These white blood cells produce pro-inflammatory substances, such as leukotrienes and prostaglandins, as well as damaging free radicals that attack the endothelium (Touyz RM 2005). Toxins soon begin to penetrate into the arterial wall, where lipids such as LDL, cholesterol, and triglycerides

accumulate and become oxidized.

At this point, the atherosclerotic process has begun in earnest. In response to the oxidized lipids, the body mounts an intensive immune response that causes more white blood cells to attack the fats, producing more inflammation within the arterial wall. In an attempt to heal the injury, smooth muscle cells begin to produce collagen to form a cap over the injury site. The mixture of oxidized lipids, white blood cells, and smooth muscle cells forms a plaque deposit. Over time, calcium accumulates on the deposit and forms a brittle cap. If this calcified plaque ruptures, a blood clot can form, and the clot may result in a heart attack or stroke.

All the processes described above, in which the inner arterial wall is damaged and normal endothelial function is compromised, are collectively referred to as endothelial dysfunction. Evidence of endothelial dysfunction can even be found in adolescents who are genetically prone to atherosclerosis. While this process occurs naturally to some degree in all people, it is aggravated by the traditional risk factors for heart disease, such as smoking and obesity (two of the leading modifiable risk factors for coronary artery disease). The following are additional risk factors:

- **Elevated LDL cholesterol.** LDL is dangerous because it can penetrate the endothelial wall and contribute to the creation of lipid foam, which forms the core of a plaque deposit. Oxidized LDL cholesterol also triggers within the endothelium an inflammatory process that accelerates atherosclerosis.
- **Hypertension.** High blood pressure is known to aggravate endothelial dysfunction, and leading researchers have identified the endothelium as an “end organ” for damage caused by high blood pressure. Many studies have shown that high blood pressure is dangerous, and Life Extension suggests a target optimal blood pressure of 119/75 mmHg (or lower).
- **C-reactive protein.** Inflammation is central to the endothelial dysfunction that underlies coronary artery disease. One good way to measure inflammation is through levels of C-reactive protein (CRP). Studies have shown that higher levels of CRP increase the risk of stroke, heart attack, and peripheral vascular disease (Rifai N 2001; Rifai N et al 2001). Stroke patients with the highest CRP levels (greater than 33 mg/L) are two to three times more likely to die or experience a new vascular event within a year than are patients with low levels (less than 5 mg/L) (Di Napoli M et al 2001).
- **Metabolic syndrome and diabetes.** Metabolic syndrome is a cluster of abnormalities that, when they occur in the same person, dramatically elevate the risk of heart disease. These abnormalities include elevated triglyceride levels, insulin resistance, abdominal obesity, elevated blood pressure, and low high-density lipoprotein (HDL). According to recent data, this condition affects about 20 percent of adult Americans. Diabetes is also a significant risk factor for coronary artery disease. High circulating levels of blood glucose (and insulin) cause microvascular damage that accelerates the atherosclerotic process, partly by accelerating endothelial dysfunction (Beckman JA et al 2002).
- **Homocysteine.** High homocysteine levels contribute to inflammation and the production of free radicals that attack endothelial cells and raise thrombotic risk (Riba R et al 2004). Mild elevations in serum homocysteine (homocysteinemia) can be caused by nutrient deficiencies, including deficiencies in folate and vitamin B12. The Life Extension Foundation identified the role of homocysteine in cardiovascular disease in its November 1981 issue of Life Extension magazine. Life Extension’s position has been confirmed by numerous studies showing that homocysteine, like cholesterol, is strongly associated with risk of heart disease (Haynes WG 2002; Guillard JC et al 2003).
- **Elevated fibrinogen.** Fibrinogen is involved in the blood clotting process. When a blood clot forms, fibrinogen is converted to fibrin, which forms the structural matrix of a blood clot (Koenig W 1999). Fibrinogen also facilitates platelet adherence to endothelial cells (Massberg S et al 1999). People with high levels of fibrinogen are more than twice as likely to die of a heart attack or stroke as people with normal fibrinogen levels (Wilhelmsen L et al 1984; Packard CJ et al 2000). This risk goes up even more in the presence of hypertension (Bots ML et al 2002).

Life Extension Foundation was the first research group to recognize the importance of fibrinogen as an independent risk factor for cardiovascular disease. Life Extension’s innovation was later corroborated in a study that found that individuals who had suffered heart attacks had significantly higher fibrinogen levels than healthy individuals (Ma J et al 1999). Other studies have shown that fibrinogen levels have a stronger association with cardiovascular deaths than cholesterol levels (Thompson SG et al 1995).

## ATHEROSCLEROSIS: NOT JUST A MAN’S DISEASE

For years, many people believed that atherosclerosis primarily affected men. In reality, however, heart disease is the leading killer of women in the United States. Atherosclerosis tends to affect men and women differently and at different times in their lives. Before menopause, women suffer less from heart disease than men of comparable age. After menopause, however, the gap closes with age until eventually women become more likely than men to suffer from heart disease (Sans S et al 1997; LaRosa JC 1992).

Heart disease in women is often undiagnosed because its symptoms are often different from the symptoms men experience. Women are less likely to suffer from the chest pain traditionally associated with coronary artery disease in men (McSweeney JC et al 2003), and their heart attacks tend to be atypical (Sannito N et al 2002). Among women, the pain associated with reduced blood flow (ischemia) may be felt in the upper abdomen or back instead of the chest, and the symptoms of an actual heart attack (myocardial infarction) may also be different from those typically experienced by men.

The issue of women and heart disease is further complicated by conflicting messages about hormone replacement therapy sent by

conventional medical research. For many years, doctors prescribed conventional hormone replacement therapy to reduce the risk of heart disease among menopausal women. In recent years, however, the wisdom of this approach has been called into question. Two arms of the large Women's Health Initiative study were stopped early when researchers discovered that women on conventional hormone replacement therapy were at a higher risk for coronary artery disease, heart attack, stroke, and breast cancer than other women. As a result of these findings, which were reported around the world, many women stopped using hormone replacement therapy, despite the possible benefits of estrogen therapy in reducing cardiovascular risk (Rosano GM et al 2003; Benagiano G et al 2004). Unfortunately, this study examined women using conjugated equine estrogens, which are estrogens derived from the urine of pregnant mares (Rossouw JE et al 2002). Life Extension supports hormone replacement therapy for menopausal women—providing that blood tests are performed to establish proper individualized dosing and that only bioidentical hormones be used. For more information on bioidentical hormone therapy, please see Female Hormone Restoration.

## SYMPTOMS AND DIAGNOSIS OF ATHEROSCLEROSIS

Symptoms associated with atherosclerosis depend on the stage of the disease. In the early stages, which may last for decades, it rarely has any symptoms. In the later stages, the symptoms are caused by the obstruction of blood flow.

In the coronary arteries, the most common symptoms of atherosclerosis in men are chest pain (angina) and shortness of breath. In the arteries of the legs (peripheral arterial disease), the most common symptoms are leg pain (claudication). Unfortunately, atherosclerosis that occurs in the brain often has no symptoms; the first indication of serious vascular disease in the brain is often a stroke. So-called mini strokes, which have temporary symptoms similar to those of full-blown strokes, are sometimes an important warning sign of an impending stroke.

If a plaque deposit in an artery ruptures, the symptoms are likely to be acute, often in the form of a heart attack, stroke, or pulmonary embolism. Each of these is a critical condition that requires immediate medical supervision. **People who suspect they may be suffering from one of these conditions should call 911 immediately.** Symptoms include fainting, seizures, breathlessness, pain, and cognitive impairment.

Blood testing is recommended for all adults. A comprehensive blood test will measure levels of LDL, HDL, VLDL, and triglycerides, as well as levels of C-reactive protein, homocysteine, and fibrinogen. Life Extension recommends blood testing at least annually. More frequent testing might be recommended to monitor progress after a patient begins a heart-healthy supplementation program.

People who have suffered a heart attack or stroke or who have symptoms indicative of coronary artery ischemia (such as chest pain) should see a physician. They may be required to undergo additional testing to determine the health of their coronary arteries. Additional tests include the following:

- **Angiography.** During this test, a catheter is inserted through a large artery, usually in the groin, and guided into the heart, where it is used to deliver contrast material into the coronary arteries. This contrast material is visible under x-ray. The test allows physicians to identify the location and degree of vascular occlusion.
- **Electrocardiogram.** This is an electronic readout of heart function that can reveal ischemic damage as a result of restricted blood flow.
- **Intima-media thickness.** This test uses ultrasound imaging to estimate the thickness of the intima, or inner layer of the arteries. An increase in intima-media thickness over time indicates that atherosclerotic vascular disease is worsening. This technique can also be used to measure the effectiveness of cardiovascular intervention therapies.
- **Computed tomography scanning.** This technique can assess the degree of calcification in the coronary arteries, which correlates strongly with atherosclerosis. Because of the risks associated with radiation exposure, Life Extension does not recommend computed tomography scanning unless absolutely necessary.

The National Institutes of Health, together with the National Cholesterol Education Program, also offers an easy-to-use online test to help people determine their risk of a major cardiovascular event. The test relies on commonly used parameters such as age and weight to determine a 10-year Coronary Risk Profile. The Coronary Risk Profile can be accessed at <http://www.nhlbi.nih.gov/guidelines/cholesterol/>.

## CONVENTIONAL TREATMENT OF ATHEROSCLEROSIS

The treatment of atherosclerosis depends on the stage of the disease. Severe disease, in which an artery has significant blockage or unstable plaque deposits, may require intensive care. In most cases, however, less severe disease is treated with a combination of lifestyle changes (including dietary changes) and medication. The following dietary and lifestyle changes have been shown to slow, or even reverse, the effects of atherosclerosis:

- Reduce dietary saturated fats, cholesterol, and trans-fatty acids.
- Increase intake of fiber to at least 10 g daily.

- Consume at least five servings of fruits and vegetables daily.
- Ensure adequate intake of folic acid (400 to 1000 mcg daily) to reduce homocysteine levels.
- For obese people, lower weight and increase physical activity to reduce the risk factors for metabolic syndrome and to help control blood pressure and reduce cardiac workload.
- For people with hypertension, limit sodium intake and maintain adequate intake of potassium, calcium, and magnesium.
- Stop smoking. This is essential.

In addition to lifestyle changes, a number of medications may be used to control individual risk factors. These include the following:

- **Cholesterol-lowering drugs.** When cholesterol levels remain high despite adequate dietary changes, weight loss, and regular exercise, cholesterol-lowering drugs are often prescribed. The drugs most commonly used to lower LDL are the statin drugs: pravastatin (Pravachol®), simvastatin (Zocor®), and atorvastatin (Lipitor®). A new drug, Vytorin®, has recently gained popularity. Vytorin® is a combination pill containing ezetimibe (Zetia®) and simvastatin. It has been shown to lower cholesterol more effectively than either Lipitor® or Zocor® alone. Bile acid sequestrants are another class of drugs prescribed for reducing LDL. These include cholestyramine (Locholest®, Questran®) and colestipol (Colestid®). Other drugs used to lower cholesterol include gemfibrozil (Lopid®), clofibrate (Atromid-S), and probucol (Lorelco) (American Heart Association: Cholesterol-Lowering Drugs 2005). For more information, please see the chapter titled Cholesterol.
- **Antihypertensive drugs.** Drugs used to lower high blood pressure include beta blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, and diuretics. For more information on each class of drug, please see the chapter titled High Blood Pressure.
- **Antithrombotic drugs.** These drugs reduce the blood's ability to clot, thus reducing the risk of heart attack and stroke. The most common antiplatelet drug today is aspirin. Clopidogrel (Plavix®) is a popular antiplatelet prescription medication. However, many other drugs are prescribed to prevent thrombosis. Some are indicated for preventing stroke, deep vein thrombosis following surgery, or blood clots following arterial revascularization. The leading antithrombotic drugs include adenosine-diphosphate-receptor inhibitors, anticoagulants such as warfarin, thrombin inhibitors, glycoprotein IIa/IIIb inhibitors, phosphodiesterase inhibitors, and Pentoxifylline. For more information on reducing the risk of blood clots, please see the chapter titled Blood Clots.

People with advanced coronary artery disease may be recommended for a surgical or “minimally invasive” procedure. In general, there are two main interventional treatments aimed at reestablishing blood flow in diseased coronary arteries: coronary artery bypass grafting and catheter-based procedures such as angioplasty and coronary artery stenting. Unfortunately, neither surgery nor catheter-based procedures can stop the underlying disease progression, and patients might end up needing additional procedures, plus the use of expensive pharmaceuticals for life. Obviously, early intervention through dietary supplementation, exercise, and careful monitoring of risk factors is preferable. Even if surgery or angioplasty is necessary, patients should do everything possible to slow the progression of the disease and support a healthy endothelial layer.

One important note for patients about to undergo coronary artery bypass surgery is the use of coenzyme Q10. It has been shown to improve heart function if taken before surgery (Rosenfeldt F et al 2005).

## NUTRITIONAL THERAPY

By the time surgery or angioplasty is recommended for atherosclerosis, preventive medicine has already failed. Because atherosclerosis is such a slow process, there is ample time for intervention before symptoms develop. Dozens of clinical studies have shown that reduction of individual risk factors can help slow or even reverse the damage caused by atherosclerosis, and reversing or slowing endothelial dysfunction should be a cornerstone of therapy.

Any program aimed at reducing the risk of heart attack or slowing the progression of atherosclerosis begins with comprehensive blood testing. This step is vital to designing a program that targets an individual's risk factors. For example, a person with high cholesterol might benefit more from a healthy nutritional program than someone with elevated risk of thrombosis. Similarly, people with high homocysteine levels should follow a program aimed at reducing homocysteine. That said, it is also important that all possible risk areas be addressed and adequate antioxidants consumed to protect against oxidant stress inside the arteries. The following chapters specifically address various risk factors for coronary artery disease:

- Blood Clots
- Homocysteine and Heart Disease
- High Blood Pressure
- High Cholesterol
- Inflammation

These chapters will provide an invaluable reference to people seeking to achieve the lowest possible risk for adverse cardiovascular events and can help in the design, under the supervision of a physician, of a program closely tailored to an individual's needs.

One nutrient that has received attention for its ability to directly improve endothelial function is propionyl-L-carnitine (PLC). PLC passes across the mitochondrial membrane to supply L-carnitine directly to the mitochondria, the energy-producing organelles of all cells. Carnitines are essential for mitochondrial fatty acid transport and energy production, which is important because heart muscle cells and endothelial cells burn fatty acids rather than glucose for 70 percent of their energy. By contrast, most cells generate 70 percent of their energy from glucose and only 30 percent from fatty acids (Kaiser KP et al 1987).

An animal study suggests PLC may help prevent or decrease the severity of atherosclerosis. In rabbits fed a high-cholesterol diet, which normally induces endothelial dysfunction and subsequent atherosclerosis, supplementation with PLC resulted in reduced plaque thickness, markedly lower triglyceride levels, and reduced proliferation of foam cells (Spagnoli LG et al 1995).

PLC also improves endothelial function by increasing nitric oxide production in animals with normal blood pressure and in animal models of hypertension. Nitric oxide is important because it helps keep arteries open. The increased nitric oxide production induced by PLC is related to its antioxidant properties; PLC reduces reactive oxygen species and increases nitric oxide production in the endothelium in the presence of superoxide dismutase and catalase (Bueno R et al 2005).

In human studies, PLC produced significant improvement in maximum walking distance with claudication (atherosclerotic peripheral vascular disease) and had no major side effects (Wiseman LR et al 1998).

**L-arginine.** This amino acid has attracted attention for its ability to improve endothelial function. L-arginine serves as the precursor of nitric oxide in the endothelium (Cockcroft JR 2005). Early studies with L-arginine to improve endothelial function have been small and have usually relied on intravenous L-arginine in high doses, however (Oka RK et al 2005). To find out whether L-arginine improved arterial function in people with peripheral arterial disease, as well as determine an optimal oral dose, a group of researchers from the University of California, San Francisco, looked at L-arginine's ability to improve walking distance and walking speed among people with peripheral arterial disease. The research group found in a pilot study of 80 patients that 3 g L-arginine daily improved both walking speed and distance (Oka RK et al 2005). Another study looked at the effects of oral L-arginine versus vitamin C in patients with stable coronary artery disease. L-arginine therapy of 10 g daily improved brachial artery dilation, a measure of endothelial function (Yin WH et al 2005).

While the association between L-arginine and nitric oxide is clear, a few newer studies have suggested that supplemental L-arginine alone may not boost nitric oxide in patients who recently had a heart attack. One study from Johns Hopkins Medical Institutions in Baltimore was stopped after researchers found an increased risk of death in heart attack patients taking L-arginine. There are several possible reasons for this, including the important point that nitric oxide can generate free radicals. Life Extension, however, notes that studies questioning L-arginine's effectiveness failed to provide the necessary antioxidants to counteract any elevation in free radicals caused by the supplement. Thus, Life Extension believes that any person taking L-arginine to lower blood pressure and improve blood flow should also take antioxidants, such as vitamin C and vitamin E.

## ANTIOXIDANT AND ANTI-INFLAMMATORY NUTRIENTS

Interestingly, only about half the people with coronary artery disease have more traditional risk factors, such as elevated cholesterol, smoking, high blood pressure, and obesity. Yet all patients with atherosclerosis suffer from endothelial dysfunction and the damaging effects of oxidized LDL, which provides an important building block for plaque deposits. Antioxidant therapy is therefore important to limit the oxidization of LDL and improve the health of the endothelium by limiting the damage caused by inflammatory cytokines. The following antioxidants are some of the most effective studied in atherosclerosis:

**Lipoic acid.** This naturally occurring antioxidant serves as a coenzyme in energy metabolism of fats, carbohydrates, and proteins. It can regenerate thioredoxin, vitamin C, and glutathione, which in turn can recycle vitamin E. Lipoic acid also helps manage proper serum glucose levels in diabetic patients (Packer L et al 2001). In animal studies, it has been shown to reduce endothelial dysfunction (Lee WJ et al 2005a). Human studies have found that lipoic acid improves endothelial function among people with metabolic syndrome (Sola S et al 2005). Lipoic acid works best in combination with antioxidants including vitamin E, coenzyme Q10, carnitine, and selenomethionine (Mosca L et al 2002).

**Garlic.** Aged garlic extract has been studied for its ability to reduce inflammation and the damaging effects of cholesterol in the endothelium (Orehov AN et al 1995). In one study of 15 men with coronary artery disease who were also being treated with statin drugs and low-dose aspirin, two weeks of supplementation with aged garlic extract significantly improved blood flow by improving endothelial function (Williams MJ et al 2005). Another study examined garlic's ability to improve exercise capacity in patients with proven coronary artery disease. This study of 30 patients found that garlic oil significantly lowered heart rate during a stress test on a treadmill and otherwise eased the heart's workload during the exercise (Verma SK et al 2005). Finally, high-dose garlic was studied in 152 people with atherosclerotic plaque. Over 48 months, the study participants experienced significantly less increase in plaque deposits than a control group, and an actual regression of plaque was seen in some participants, leading researchers to conclude that garlic had a "not only preventative but possibly also a curative role in arteriosclerosis therapy" (Koscielny J et al 1999).

**Ginkgo biloba.** Approximately one-third of Ginkgo biloba extract is made up of the flavone glycoside known as quercetin (Hibatallah J et al 1999). Quercetin has been shown to have antioxidant properties and inhibits LDL oxidation in experimental studies (Janisch KM et al 2004). Daily dosing with 120 mg Ginkgo biloba has been documented to reduce markers of lipid peroxidation in humans (Kudolo GB et al 2003). Higher doses (320 mg daily) have may be beneficial in reducing ischemia in patients with atherosclerosis (Mouren X et al 1994). Life Extension, however, cautions against using doses of ginkgo higher than 120 mg daily. This caution is based on the slight possibility that higher doses of ginkgo could induce too strong an antiplatelet effect, which could result in an internal blood vessel bleed.

**Quercetin.** The so-called French paradox is the phenomenon of low rates of heart disease in a country known for its high intake of fatty foods. Recent research suggests that one of the reasons French people are protected from heart disease is a high intake of quercetin, a potent antioxidant and polyphenol found in red wine (Kuhlman CR et al 2005). Numerous studies have examined quercetin and found it to be both a powerful antioxidant and a stimulator of nitric oxide, which inhibits endothelial proliferation, a hallmark of atherosclerosis (Kuhlman CR et al 2005). Studies have shown the following:

- In spontaneously hypertensive rats, quercetin, along with other bioflavonoids, preserved endothelial function by increasing nitric oxide and reducing blood pressure (Machha A et al 2005).

- A porcine study showed that quercetin has potent antioxidative properties and protects endothelial cells against induced dysfunction (Reiterer G et al 2004).

**Green tea extract.** Green tea extracts, which are rich in natural antioxidants and antiplatelet agents, are routinely used in Asia to lower blood pressure and reduce elevated cholesterol. In studies of smokers, 600 mL green tea (not extract) was shown to decrease markers of inflammation and decrease oxidized cholesterol, both of which are intimately involved in the development of atherosclerosis (Lee W et al 2005b). A Japanese study of 203 patients found that the more green tea patients drink, the less likely they are to suffer from coronary artery disease (Sano J et al 2004). This study supported an earlier study that found that greater green tea consumption was related to a reduced presence of coronary artery disease in Japanese men—although not in women (Sasazuki S et al 2000).

**Vitamin C (ascorbic acid).** Vitamin C inhibits damage caused by oxidative stress. In cigarette smokers, daily supplementation with 500 mg vitamin C significantly decreased the appearance of oxidative stress markers (Dietrich M et al 2002). Another study showed that supplementation with 500 mg vitamin C and 400 IU vitamin E daily significantly reduced the development of accelerated coronary arteriosclerosis following cardiac transplantation (Fang JC et al 2002). Vitamin C's benefits seem especially profound in people who suffer from both diabetes and coronary artery disease. One study demonstrated that, in this group, vitamin C significantly improved vasodilation (Antoniades C et al 2004).

**Vitamin K.** Vitamin K is steadily gaining attention for its ability to reduce calcification and help prevent cardiovascular disease (Jie KSG et al 1996). Evidence for the ability of vitamin K to prevent calcification can also be found in an animal study in which researchers administered the anticoagulant warfarin to rats. Warfarin is known to deplete vitamin K. At the end of the study, all the animals had extensive calcification, suggesting they had lost the protective effect of vitamin K (Howe AM 2000).

**Vitamin E.** Vitamin E is often studied in conjunction with vitamin C for its potent antioxidant powers. It has been shown to decrease lipid peroxidation and inhibit smooth muscle cell proliferation, platelet aggregation, monocyte adhesion, oxidized LDL uptake, and cytokine production—all of which occur during atherosclerosis (Munteanu A et al 2004; Harris A et al 2002). In cultured arterial endothelial cells, vitamin E increased the production of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation (Wu D et al 2004). Most vitamin E supplements come in the form of alpha tocopherol. Life Extension recommends about 400 IU alpha tocopherol a day, along with at least 200 mg gamma tocopherol and 100 mg of coenzyme Q10. There is a concern that taking only the "alpha" form of vitamin E could deplete the body of gamma tocopherol, a critically important antioxidant. Coenzyme Q10 helps regenerate oxidized vitamin E in the body.

## HORMONE THERAPY FOR HEALTHY ARTERIES

Atherosclerosis is closely associated with hormonal changes in women. However, after menopause, as the levels of all sex hormones decline, the rates of atherosclerosis go up. Both men and women experience significant decline of hormones that play a role in maintaining healthy arterial function. Atherosclerosis is known to increase at the same time that hormone levels are decreasing as a result of age. Overall, levels of dehydroepiandrosterone (DHEA), testosterone, and other hormones decline in aging humans—the same group that is especially at risk for atherosclerosis.

**DHEA.** DHEA is a precursor to sex hormones such as testosterone and estrogen. Levels of steroid hormones, including DHEA, decline with the age-associated onset of a variety of medical conditions, including chronic inflammation, hypertension, and atherosclerosis. Levels of DHEA in humans are inversely correlated with inflammatory markers (Sondergaard HP et al 2004). Animal studies show a protective role for DHEA in preventing atherosclerosis. Providing DHEA to human vascular endothelial cells in culture increases nitric oxide synthesis, which boosts blood flow (Simoncini T et al 2003). A study showed that men with high levels of DHEA tended to have greater protection against aortic atherosclerosis progression (Hak AE et al 2002).

**Phytoestrogens.** Following menopause, circulating levels of estrogen are depleted. Phytoestrogens are plant hormones with estrogenic activity. In postmenopausal women, phytoestrogens appear to have estrogen-like benefits such as protection against osteoporosis (Atkinson C et al 2004; Crisafulli A et al 2004a) and possibly hot flashes (Crisafulli A et al 2004b). Phytoestrogens have also been shown to improve vascular function, which tends to decline with age. In one study genistein, a phytoestrogen, provided in a daily 54-mg supplement for one year, significantly improved endothelium-dependent vasodilation in postmenopausal women. Moreover, its benefits were as substantial as those observed in women receiving an estrogen-progestin regimen (Squadrito F et al 2003).

For more information on bioidentical hormone replacement, please see [Female Hormone Restoration](#) and [Male Hormone Replacement](#).

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Atherosclerosis is a far-reaching disease with devastating consequences. Life Extension's program for reducing the risk associated with atherosclerosis is based on aggressive measures to promote a healthy endothelium and reduce risk factors associated with

coronary artery disease. Because all adults are at risk of atherosclerosis, all adults should make the necessary lifestyle changes to protect their arteries. This means getting adequate exercise under the supervision of a physician and eating a diet rich in fruits and vegetables and low in saturated fat. Also, weight loss by obese and overweight adults is an important element in reducing risk of atherosclerosis.

People who have risk factors for atherosclerosis should take measures to modify them. Risk factors such as diabetes, high blood pressure, abnormal cholesterol, obesity, elevated homocysteine, elevated risk of blood clots, and a pro-inflammatory state are covered elsewhere in this book. The ideal nutritional approach to atherosclerosis takes into consideration all existing risk factors and attempts to modify each one.

Blood testing is a very important part of any risk-reduction program for coronary heart disease. Healthy adults should have their blood tested at least once a year. People who have heart disease or multiple risk factors should have their blood tested twice a year to monitor their progress. A comprehensive blood test will measure levels of blood lipids, C-reactive protein, homocysteine, fibrinogen, and other blood markers. Regular blood pressure monitoring is also important. Life Extension recommends an optimal blood pressure reading of 119/75. Life Extension also recommends that people aim for low levels of C-reactive protein, LDL, homocysteine, and other markers of disease. The following table summarizes the optimal ranges for various blood levels:

<b>Blood Test</b>	<b>Standard Range</b>	<b>Life Extension's Optimal Range</b>
Fibrinogen	Up to 460 mg/dL	Less than 300 mg/dL
C-reactive protein	Up to 4.9 mg/L	Less than 0.55 mg/L (men) Less than 1.5 mg/L (women)
Homocysteine	Up to 15 mmol/L	7–8 mmol/L
Cholesterol	Up to 199 mg/dL	180 to 200 mg/dL
LDL	Up to 100 mg/dL	Less than 100 mg/dL
HDL	No lower than 40 mg/dL	More than 50 mg/dL
Triglycerides	Up to 199 mg/dL	Less than 100 mg/dL

Finally, the following nutrients have been shown to improve endothelial function and reduce the damage caused by oxidized LDL, slowing the progression of atherosclerosis:

- **Folic acid**—800 to 5000 micrograms (mcg) daily
- **Vitamin B12**—300 to 2000 mcg daily
- **EPA and DHA**—1400 milligrams (mg) EPA and 1000 mg DHA daily
- **PLC**—1000 to 2000 mg daily
- **L-arginine**—3000 to 12,000 mg daily (in 3 divided doses)
- **Lipoic acid**—150 to 300 mg daily
- **Garlic**—1200 mg daily (Kyolic aged garlic extract)
- **Ginkgo biloba**—120 mg daily
- **Green tea extract**—725 mg daily (93 percent polyphenols)
- **Quercetin**—500 to 1000 mg daily (water-soluble quercetin)
- **Vitamin C**—1000 to 3000 mg daily
- **Vitamin E**—400 international units (IU) daily (with 200 mg gamma tocopherol)
- **Vitamin K**—10 mg daily
- **Vitamin B6**—100 to 750 mg daily

In addition, bioidentical hormone therapy may be recommended, depending on blood testing results. For more information on comprehensive blood testing, please call 1-800-544-4440.

### **Product Availability**

All the nutrients and supplements discussed in this chapter are available through the Life Extension Foundation. For ordering information call 1-800-544-4440, or visit us online at [www.lef.org](http://www.lef.org).

### **ATHEROSCLEROSIS 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:

#### **Acetyl-L-Carnitine**

- Acetyl-L-carnitine can cause gastrointestinal symptoms such as nausea and diarrhea.

## **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.

## **L-Arginine**

- Do not take L-arginine if you have the rare genetic disorder argininemia.
- Consult your doctor before taking L-arginine if you have cancer. L-arginine can stimulate growth hormone.
- Consult your doctor before taking L-arginine if you have kidney failure or liver failure.
- Consult your doctor before taking L-arginine if you have herpes simplex. L-arginine may increase the possibility of recurrence.

## **Lipoic Acid**

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

## **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.

## Vitamin K

- Do not take vitamin K if you are taking warfarin sodium unless, the vitamin K is specifically prescribed by your physician.

For more information see the Safety Appendix

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