

Stroke and Cerebrovascular Disease

Stroke Prevention

Cerebrovascular disease, including stroke, is the third-leading cause of death in the United States and a leading cause of disability among older Americans. Cerebrovascular disease occurs when the blood vessels supplying the brain with oxygenated blood are damaged or their function is compromised. If the blood flow is severely restricted, depriving the brain of adequate oxygen even briefly, a stroke can occur. It has been estimated that every 45 seconds, another American suffers from a stroke, often with debilitating consequences or even death. One in four men and one in five women over the age of 45 will suffer a stroke.

There are two main kinds of stroke. The most common, an ischemic stroke, occurs when an artery in the brain is blocked by a blood clot, usually because of atherosclerosis (the deposition of plaque on the inside of artery walls). Alternatively, a hemorrhagic stroke can occur when a portion of the arterial wall weakens and bursts. A stroke is a serious medical emergency that requires immediate medical attention. Time is a critical factor in stroke management: some experts now refer to strokes as “brain attacks” to stress the need for emergency treatment.

Researchers have conducted thousands of clinical trials searching for better ways to prevent and treat stroke victims. As a result, we have a robust knowledge of cerebrovascular disease, and we are learning more every day. As with atherosclerosis in the coronary arteries (coronary artery disease), the underlying cause of ischemic stroke can often be traced back decades, to early insults to the inner lining (endothelium) of the arteries that set a deadly chain reaction into motion. Now that they have identified endothelial dysfunction as a fundamental process of cardiovascular and cerebrovascular disease, along with the prime risk factors for endothelial dysfunction, such as high blood pressure and smoking, researchers are pursuing new therapies aimed at **stroke prevention** by improving the health of our arteries.

Stroke is primarily a condition of the elderly, mostly because of the cumulative effects of endothelial dysfunction, which can take decades to reach a crisis point. Nearly three quarters of all strokes occur in people who are over the age of 65, and the risk of stroke more than doubles every decade beyond the age of 55 (NINDS 2005).

Stroke is an insidious condition because of the nature of the anatomy of the brain. Heart disease is often preceded by a characteristic pain in the chest or arm (angina) or shortness of breath. These symptoms occur when the blood supply to the heart is temporarily reduced. The brain, however, lacks pain receptors, so temporary episodes of ischemia don't cause pain. Although there may be warning signs, the first signal of atherosclerosis in the brain is often a stroke.

When blood flow to the brain is briefly disrupted, causing what is called a ministroke, the symptoms are similar to those of a stroke (vision and speech difficulty, limited paralysis) but not as severe, and they usually subside within 24 hours. In the past, physicians viewed ministrokes as relatively benign events, or “near misses.” Today, we understand that not only are they damaging in their own right because of the deprivation of blood to the brain, but the presence of ministrokes is a major warning signal. **Any person suffering from suspected cerebrovascular disease should seek immediate medical supervision and comprehensive diagnostic testing to assess the likelihood of a stroke and take active steps to reduce the risk.**

KINDS OF STROKE

Strokes are caused either by an arterial blockage that reduces blood flow to the brain (ischemic stroke) or by a rupture in an artery that allows blood to spill into the surrounding area (hemorrhagic stroke). It is extremely important that the kind of stroke be identified as quickly as possible because each is treated differently. For example, if the stroke is caused by a blood clot (an ischemic stroke), drugs should be administered to help dissolve the clot. If, however, these drugs were administered to a person suffering from a bleeding stroke, the damage could be intensified because of increased bleeding (NINDS 2005).

Ischemic stroke. Ischemic stroke is responsible for 80 percent of all strokes (NINDS 2005). There are two kinds of ischemic stroke. The first, a thrombotic stroke, results from a blood clot (thrombus) forming in a vessel inside the brain and cutting off the blood supply to the tissues served by that vessel.

The second, an embolic stroke, occurs when a clot forms somewhere else in the body, breaks off, and travels to the brain. The clot can originate in a peripheral artery, in the heart itself, or in the arteries in the neck or brain. Among people with an abnormal heart rhythm called atrial fibrillation, clots can arise in the left atrium and travel through the left side of the heart and the aorta and into the brain. When the clot becomes lodged in the artery, the tissue beyond the blockage is starved of oxygen and begins to die.

Hemorrhagic stroke. The second category of stroke, hemorrhagic stroke, occurs when a vessel in or near the brain ruptures and leaks blood into the brain or surrounding tissues. In this case, the blood pushes against otherwise healthy brain tissue and compresses it. The increased pressure reduces blood flow into the area, and if the pressure becomes high enough, it can cause damage to brain cells. There are two primary kinds of hemorrhagic strokes, named according to the location of the bleeding (Stanford Stroke Center 2005):

- Subarachnoid hemorrhage occurs when blood floods the space between the brain and the skull.
- Intracerebral hemorrhage happens when an artery inside the brain ruptures, spilling blood into the surrounding brain tissue.

Hemorrhagic strokes are often caused by aneurysms, or weakened portions of the artery wall. An aneurysm may have no symptoms and go unnoticed for years. In many cases, the first sign of an aneurysm is a stroke.

EFFECTS OF STROKE

Strokes are so feared because of their debilitating effects. Even ministrokes have been shown to reduce cognitive function (Mosley TH Jr. et al 2005), and large strokes can have serious, life-altering and life-threatening consequences. Common effects from stroke include the following:

- **Paralysis or weakness.** Paralysis, weakness, and tiredness are the most common effects from stroke. These effects may involve one side of the body or just the face or an arm or leg. A survivor also may lose the ability to recognize the need to urinate or to control bladder or bowel muscles, which can result in not getting to the toilet in time. Constipation can also occur. Incontinence problems are usually temporary, but they can be emotionally distressing.
- **Aphasia.** At least 25 percent of all stroke survivors lose the ability to speak, write, or understand spoken or written language. This condition can improve with therapy.
- **Spatial perception, thinking, and memory.** Stroke can damage areas of the brain that control memory, spatial relationships, learning, and awareness. Survivors may have significantly shortened attention spans or find short-term memory problematic. They may lose the ability to learn new tasks, follow a set of instructions, make plans, or carry out actions in sequential steps.
- **Mental health changes.** Depression, personality changes, and trouble controlling emotions are common after stroke because of the debilitating emotional effect of the trauma. Strokes can also damage the frontal cortex and other parts of the brain involved with emotion. Poststroke depression usually responds well to antidepressant medications and psychological counseling (NINDS 2005).

ENDOTHELIAL DYSFUNCTION AND STROKE RISK

Most strokes are caused by blood clots that form as a result of atherosclerosis (Gorelick PB 2002). Once known as “hardening of the arteries,” atherosclerosis occurs when the arteries become clogged with plaque deposits and the structure and function of the inner arterial wall (the endothelium) are compromised. If atherosclerotic plaque deposits become brittle and rupture, blood clots can form that lead to stroke. Scientists have spent decades unraveling the complicated biological processes that lead to atherosclerosis. We now understand atherosclerosis as a long-term disease, one that accelerates as we age, raising the risk of heart attack and stroke.

For many years, conventional science has depicted the arteries as pipes, often using plumbing analogies to describe procedures such as balloon angioplasty or endarterectomy, an operation in which plaque is stripped away from the linings of arteries. The problem with the plumbing analogy, however, is that the arteries are actually muscular, complex organs that play an active role in regulating blood pressure and other biological functions.

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 and contracts and dilates to help blood flow and maintain blood pressure. And the inner layer is a thin layer of endothelial cells and 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 tone of the artery. Furthermore, endothelial cells secrete chemicals that provoke a protective response in the artery after an injury.

In the event an artery is injured, the endothelium signals smooth muscle cells to gather at the site of the injury. Endothelial cells also signal white blood cells to congregate on the injured vessel wall, provoking an immune response. As we age, however, the endothelium becomes leaky, allowing lipids and toxins to penetrate the endothelial layer into the smooth muscle cells. As a result, smooth muscle cells gather at the site of the injury, and the artery in turn loses some flexibility. In response, the endothelium signals white blood cells to congregate along the cell wall. The endothelium is further weakened by the pro-inflammatory immune response, in which leukotrienes and prostaglandins contribute to inflammation, which aggravates the abnormal smooth muscle tone of the arterial wall (Touyz RM 2005). Toxins soon begin to penetrate into the arterial wall. Inside the artery, lipids such as low-

density lipoprotein (LDL) cholesterol and triglycerides accumulate and gradually become oxidized.

At this point, the atherosclerotic process has begun in earnest. In response to the oxidized lipids, the body mounts an 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.

All the processes described above, in which the arterial wall is damaged and normal endothelial function is compromised, are collectively referred to as endothelial dysfunction. Risk factors that aggravate endothelial dysfunction include high blood pressure, smoking, elevated LDL and triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, diabetes, elevated insulin levels, obesity, lack of exercise, and several recently identified risk factors, such as elevated levels of homocysteine and C-reactive protein. Each of these contributes to endothelial dysfunction of cerebral arteries and the subsequent increased risk of stroke.

High blood pressure, for example, is very strongly associated with stroke; in fact, high blood pressure is associated with about half of ischemic strokes. It is known that high blood pressure contributes to endothelial dysfunction. Cigarette smoke is another major risk factor because the smoke contains many toxins that contribute to endothelial injury, while homocysteine has been shown to cause the initial injury to the endothelium that begins the atherosclerotic process (Sainani GS et al 2002). Similarly, a Physician's Health Study found that men in the highest quartile of levels of C-reactive protein (an inflammatory marker that signals inflammation somewhere in the body) had twice the risk of ischemic stroke of those in the bottom quartile (Ridker PM et al 1997). Other studies have found that C-reactive protein is a strong independent predictor of a reduced survival rate after ischemic stroke (Di Napoli M et al 2001).

If researchers can identify drugs or supplements that support healthy endothelial function, it may be possible to slow the relentless advance of atherosclerosis and reduce the risk of the most common kind of stroke. One common therapeutic focus is nitric oxide, which causes arteries to dilate and improves blood flow. A nutrient or drug that improves the production of nitric oxide may have the potential to reduce the risk of stroke or other atherosclerotic insults.

It also makes sense to modify as many other risk factors as possible, including high blood pressure, cholesterol, and even infection. Studies have linked certain common infections to increased stroke risk, including Chlamydia pneumonia, Helicobacter pylori, cytomegalovirus, and C Pneumonia (Winkelstein JA et al 2001; Meier CR et al 1999; Nieto FJ et al 1999). The first National Health and Nutrition Examination Survey (NHANES) found that periodontal disease, though treatable, is a risk factor (Wu T et al 2000). Other studies indicate that patients hospitalized with bacterial and viral infections had increased risk of stroke within one week of the infection, highlighting the importance of infection, even in younger people (Grau AJ et al 1995, 1998, 1999).

What You Have Learned So Far...

- Stroke is the third-most-common cause of death in Americans, caused by blood clots blocking the flow of blood supplying oxygen to the brain or by hemorrhage in the blood vessels of the brain. One in four men and one in five women over the age of 45 will suffer a stroke.
- The most common risk factor is high blood pressure.
- An ischemic stroke occurs when the blood flow to the brain is disrupted because of a blood clot. A hemorrhagic stroke occurs when the blood flow to the brain is disrupted by a ruptured artery. Ischemic strokes account for about 80 percent of strokes.
- Ischemic strokes are closely associated with atherosclerosis and underlying endothelial dysfunction in the arteries. Any treatment that improves endothelial health may help lower the risk of a stroke.
- Stroke results in more long-term disabilities in the United States than any other disease.
- If a stroke is suspected, it is essential to get emergency medical care as soon as possible.
- Preventive measures can reduce the risk of having a stroke or a second stroke.

Warning Signs of Stroke

(NINDS 2005)

- Sudden weakness, numbness, or paralysis of the face, arm, or leg, particularly on one side of the body
- Sudden confusion or loss of speech or understanding of language
- Sudden loss of vision in one or both eyes
- Sudden severe headache with no apparent cause
- Sudden dizziness, loss of balance or coordination, or trouble walking

STROKE SCREENING: ADVANCES IN TECHNOLOGY

Although transient ischemic attacks are the most obvious warning signs of stroke, the risk of having a stroke can be gauged before an ischemic attack occurs. All that is required is diagnostic testing. Clearly, it is preferable to avoid a stroke through early intervention and preventive measures than to treat strokes that have already occurred.

In the past, the most accurate test to measure atherosclerosis was angiography. During this procedure, a catheter is threaded into the arteries and a special dye sensitive to x-ray is injected into the catheter. While this is an important test, it has some powerful limitations. First, it is invasive and therefore not practical as a widespread screening tool. Second, it can show the physician only the shadowy outlines of plaque inside arteries. It cannot measure the stability of the plaque or determine the health of the arterial wall.

Today, noninvasive imaging techniques are available to measure the health of the arterial wall and even determine the stability of the plaque deposits on the inside of the artery. Although these tests are most often used to diagnose existing strokes, they are also highly effective screening tools.

Advanced CT scanners, including a newly introduced 64-slice machine, are able to provide an unprecedented view of the arteries. No studies have yet been conducted on the value of this new technology in screening people for stroke risk. Older, 16-slice CT scanning is often recommended to evaluate the damage of ongoing strokes because of its specificity (Kirchhoff K et al 2002). CT scans, however, expose people to very high levels of radiation. For example, an average CT head scan exposes the body to as much radiation as 100 chest x-rays, or 243 days of natural background radiation, according to the European Commission's Radiation Protection Report, conducted in 2000.

Perhaps the most widely used screening tool for stroke is the carotid ultrasound, which provides physicians with valuable information on the health of carotid arteries. Using widely available and relatively inexpensive ultrasound technology, physicians can detect the degree of blockage in the carotid arteries and measure the thickness of the intima-media. The well-known Rotterdam study showed that if carotid intima-media thickness is greater than 1 mm, the risk of stroke is increased even if no arterial plaque is present (Hollander M et al 2003). The information obtained from ultrasound screening can be used to identify people at high risk of atherosclerosis.

A number of blood tests also measure vascular health and may help identify people at high risk of stroke. Life Extension believes that people should have at least annual blood tests for homocysteine, C-reactive protein, and fibrinogen, in addition to the more well-known tests, such as those for cholesterol and triglycerides. Homocysteine, C-reactive protein, and fibrinogen each have been shown to be elevated among people at risk of stroke.

REDUCING HOMOCYSTEINE TO LOWER STROKE RISK

At the 2001 meeting of the American Stroke Association, researchers reported studies showing that increasing levels of homocysteine are associated with elevated stroke risk. One of these presentations was a meta-analysis of 15 published studies and showed that mild to moderate elevations in homocysteine were independently associated with an astounding 86 percent increase in the risk of stroke (Kelly PJ et al 2000).

Folic acid and other B vitamins help decrease homocysteine concentrations. The metabolism of homocysteine has been linked to several vitamins, but particularly folic acid (folate), B6, and B12 (Schwammenthal Y et al 2004). The Vitamin Intervention for Stroke Prevention trial, among many studies, showed that homocysteine levels decreased and risk of stroke, death, and other coronary events fell by 21 percent in patients who received high doses of vitamin B12 (Spence JD et al 2005).

Another well-designed study found that giving B vitamins within 12 hours of an ischemic stroke reduced oxidative damage and the tissue inflammation marker C-reactive protein, regardless of homocysteine levels (Ullegaddi R et al 2004). Studies have also found that vitamin B6 alone is strongly associated with lower risk of cerebrovascular disease (Kelly PJ et al 2003).

Other studies show that individuals with homocysteine levels elevated by 25 percent have increased risk of stroke of 11 percent. A meta-analysis of 20 studies reported that elevated homocysteine levels increased risk of ischemic heart disease by 32 percent and risk of stroke by 59 percent (Wald DS et al 2002). Multiple studies have shown folate to prevent endothelial dysfunction even in people with normal levels of homocysteine, high cholesterol, diabetes, and heart disease (Moat SJ et al 2004), which emphasizes the importance of the B vitamins (He K et al 2004, Bazzano LA et al 2002).

C-REACTIVE PROTEIN AND FIBRINOGEN

There is a clear association between elevated levels of C-reactive protein and fibrinogen and the incidence and severity of stroke. Also at the 2001 American Stroke Association meeting, researchers presented evidence that elevated C-reactive protein doubled or tripled the risk of stroke (Kelly PJ et al 2000). Another presentation showed that in those who have a major stroke, higher levels of C-reactive protein portended a high likelihood of having another vascular event, such as a heart attack or stroke, or of dying within the following year. Stroke patients with the highest C-reactive protein levels were nearly 2.4 times more likely to experience death or a vascular event within the next year than were patients with the lowest levels (Di Napoli N et al 2001).

Similarly, the Physician's Health Study found that apparently healthy men with the highest C-reactive protein levels had twice the risk of stroke, three times the risk of future heart attack, and four times the risk of future peripheral vascular disease (Ridker PM et al 1997). The Women's Health Study reported that C-reactive protein was the single strongest predictor of future vascular risk (Ridker PM et al 1998).

Elevated levels of fibrinogen are also associated with increased risk of stroke. Fibrinogen is a protein produced by the liver. It circulates in the blood and helps stop bleeding by helping blood clots form. Today's standard laboratory reference range for fibrinogen is between 193 and 423 mg/dL. That means according to conventional standards, fibrinogen levels as high as 423 mg/dL are acceptable.

However, a study reported in the Journal of the American Medical Association found that no matter what a patient's level was within the range tested (between 250 mg/dL and 562 mg/dL), an increase of 100 mg/dL was associated with a significantly increased risk of heart disease and stroke (Danesh J et al 2005). Another study found that those with high fibrinogen levels, above 343 mg/dL, had a twofold increase in the risk of heart attack (Ma J et al 1999). Fibrinogen levels can be reduced by taking dietary supplements such as fish oil and vitamin C and by lowering homocysteine.

RESPONDING TO A STROKE: SPEED MATTERS

Most of the damage from a stroke occurs within 24 hours following the event, so it is crucial that people get adequate treatment as fast as possible to reestablish blood flow and limit the damage. If stroke-like symptoms last for more than 10 to 15 minutes or worsen, call 911 without delay even if it is unclear whether a stroke has occurred (NINDS 2005).

Once a patient has arrived at the hospital, physicians will quickly seek to determine what kind of stroke (ischemic or hemorrhagic) occurred, then take steps to treat it. Diagnostic imaging tests are usually performed as soon as possible to determine the kind of stroke.

Treatment of ischemic stroke. The goal of acute therapy in ischemic stroke is to dissolve the blood clot as rapidly as possible (a process called lysis). Studies show that when thrombolytic (clot-busting) agents are administered within three hours of symptom onset, they can dramatically decrease damage (Burger KM et al 2005). These drugs are still effective if given within 4.5 hours of the stroke (Davalos A 2005). Unfortunately, however, most stroke patients do not receive the appropriate thrombolytic agent quickly enough (Burger KM et al 2005; Davalos A 2005).

The most common thrombolytic agent used is tissue plasminogen activator. It is typically administered intravenously, and newer methods using ultrasound-enhanced delivery promise to make this drug even more effective (Davalos A 2005).

After stroke, there is a significant risk of a repeat stroke. To help prevent secondary strokes, people may be prescribed anticoagulant therapy, including low-dose aspirin or long-term warfarin (Coumadin®) therapy, or antiplatelet therapy (such as Plavix®).

- **Anticoagulants.** These drugs work by preventing clot growth or preventing new clots from forming. Warfarin is the most common example. It is often used when a patient's doctor suspects that a blood clot has originated in the heart and traveled to the brain and lodged in a vessel, blocking blood flow and causing an embolic stroke. Anticoagulants are not indicated when there is increased risk of bleeding or in patients with uncontrolled high blood pressure (NINDS 2005).
- **Antiplatelet agents.** Antiplatelet agents work by preventing blood platelets from sticking to each other and forming a clot. Common examples are aspirin, dipyridamole, and clopidogrel. They are also often used to reduce the risk of stroke in individuals who have had a transient ischemic attack or to decrease the risk of a second ischemic stroke.

For more information on preventing blood clots, see the chapter titled Blood Clot Prevention.

Treatment of hemorrhagic stroke. Acute treatment of hemorrhagic stroke focuses on surgery and medications. Surgical

procedures can help alleviate the damage (hematoma), but the condition of the patient before surgery is critical to the recovery rate. People who are conscious and have small blood clots often improve without surgery. But people in comas, who have large clots, do very poorly, regardless of treatment approach (National Stroke Association 2005)

After the acute treatment, medications may be prescribed to control blood pressure, which is a major risk factor for hemorrhagic stroke (Clarke CRA 1998). Prescription medications for lowering blood pressure include diuretics, calcium channel blockers, beta blockers, ACE inhibitors, and others. For more information on natural ways to lower blood pressure, see the chapter titled High Blood Pressure.

STROKE PREVENTION

Stroke prevention is a subject of much debate. Approximately 25 percent of people who recover from a first stroke will have a second within five years. While the chance of death and disability increases with each stroke, risk of another stroke appears to be greatest within the first year (National Stroke Association 2005).

Using measurements such as the degree of artery occlusion (how much of the carotid artery is blocked by atherosclerotic plaques), medical experts have sought to establish firm guidelines to help physicians choose between the various options, including medication, angioplasty, and surgery. Common prescription drugs used to help prevent stroke include antihypertensive agents (Gorelick PB et al 1999; Goldstein LB et al 2001), cholesterol lowering agents (statins), and antiarrhythmics to help control irregular heartbeats that might contribute to stroke risk. Angioplasty is a procedure in which a balloon is threaded into the artery and inflated rapidly, crushing the plaque against the arterial wall and opening the artery. The most common surgery used to prevent stroke is called carotid endarterectomy, in which the surgeon opens the arteries in the neck and strips away the inner lining of the artery.

While these strategies have been shown to work in specific circumstances, a common flaw also unites them: they are often used only after stroke risk has reached an unacceptable level. Life Extension prefers a much more proactive approach. By using advanced early screening tests to determine risk, then taking action to improve endothelial function and reduce blood risk factors (such as homocysteine and fibrinogen) and blood pressure, Life Extension seeks to maintain the lowest possible risk profile.

Diet. Multiple studies have found that a diet high in fruits and vegetables lowers risk of cerebrovascular disease and both ischemic and hemorrhagic stroke (Gariballa SE 2000; Sauvaget C et al 2003). Two major reviews recommended that public health policy promote increased dietary intake of antioxidant vitamin C, beta-carotene, vitamin E, B vitamins (including folate), potassium, calcium, magnesium, vitamin D, fiber, and omega-3 fatty acids to reduce risk of stroke (Gariballa SE 2000; Johnsen SP 2004). These vital nutrients can also be obtained through dietary supplements in conjunction with a healthy diet.

NUTRITIONAL SUPPORT FOR HEALTHY ARTERIES

Nutritional therapy in cerebrovascular disease associated with atherosclerosis has several interrelated goals. These include reversing endothelial dysfunction with nutrients that stimulate endothelial nitric oxide production, reducing inflammation, enhancing and restoring cerebral blood flow, and providing antioxidant support to reduce the level of damaging free radicals. A number of nutrients have been studied that often accomplish several of these goals.

The following nutrients protect the endothelium:

- **L-arginine.** L-arginine is a basic amino acid found in many proteins and is essential to growth and maintenance in all vertebrates. There is evidence that L-arginine plays a major role in maintaining blood vessel dilation and reducing blood pressure, a major risk factor for stroke. L-arginine helps lower blood pressure by serving as a precursor to nitric oxide, which helps keep blood vessels dilated and blood flowing easily (Chionglo BM et al 2006; Boger RH et al 2005).

In an animal model of stroke, L-arginine was shown to induce an endothelium-dependent increase in cerebral blood flow (Willmot M et al 2005). Among humans, intravenous L-arginine has been shown to alleviate all stroke-like symptoms if administered within 30 minutes of their onset (Koga Y et al 2005). Another study showed that intravenous L-arginine given to patients undergoing carotid endarterectomy surgery was able to reduce the number of embolic signals (restrictions in blood flow) for up to 24 hours after the surgery (Kaposzta Z et al 2001). Although these results are encouraging, oral L-arginine has not been studied in human stroke patients—although human studies have been conducted in heart attack patients and patients with cardiovascular disease.

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 among 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. By generating production of nitric oxide, L-arginine can raise free radical levels. 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.

- **Acetyl-L-carnitine.** Acetyl-L-carnitine is a derivative of carnitine. It is involved in the transport of fatty acid across the cell membrane, and it is used as energy in the mitochondria of the cell (Rebouche CJ 2006). It also provides the acetyl component for the synthesis of acetylcholine, an important neurotransmitter. One study has shown evidence that among stroke patients, acetyl-L-carnitine has a beneficial effect on abstract and concrete thinking and memory. The study concluded that acetyl-L-carnitine possesses antioxidant activity that offers protection against lipid peroxidation (Suslina ZA et al 2003). Two other studies reported that large doses of intravenous acetyl-L-carnitine significantly improved cerebral blood flow in patients with chronic cerebrovascular disease who had experienced ischemic stroke (Postiglione A et al 1991, 1990).
- **Propionyl-L-carnitine.** Like acetyl-L-carnitine, propionyl-L-carnitine plays an important role in fatty acid oxidation. Research has shown that propionyl-L-carnitine can help protect against endothelial dysfunction. One study in human endothelial cells showed that the carnitine derivatives stimulate the production of nitric oxide in the endothelium, which has an antioxidant, antiproliferative, and anti-inflammatory effect (Calo LA et al 2006). Another study found that propionyl-L-carnitine stimulated nitric oxide's ability to relax hypertensive arteries in rats (Bueno R et al 2005).

The following nutrients enhance cerebral blood flow, reduce blood pressure, and reduce the size of stroke lesions:

- **Vinpocetine.** Vinpocetine has been widely studied for its ability to restore blood flow to the brains of stroke victims. It appears to have multiple effects that interfere with the ischemic cascade. Studies have shown that it reduces the depletion of adenosine triphosphate, which is the main cellular energy source, and functions as an antioxidant (Hadjiev D 2003; Vas A et al 2002). Recently, researchers have found that high-dose, intravenous vinpocetine (at doses up to 70 mg daily) is able to restore blood flow to the brain and reduce the size of ischemic stroke lesions, leading several researchers to identify vinpocetine as a potential therapy for the acute treatment of ischemic stroke (Szilagyi G et al 2005; Szapary L et al 2003; Dezsi L et al 2002). The protective effects are most pronounced in areas of the brain with the highest uptake (Szilagyi G et al 2005). These studies build on previous work showing that oral vinpocetine is also effective in enhancing cerebral blood flow (Dezsi L et al 2002).
- **CDP-choline.** CDP-choline is a chemical compound present in a wide array of foods. It plays a life-sustaining role in the normal function of all cells and the structural integrity and signaling capacity of cell membranes, and it moves fats in and out of cells throughout the body (Zeisel SH et al 2006). More than 70 countries, including Japan, use CDP-choline as a prescription drug to treat stroke (Adibhatla RM et al 2005). It appears to have a neuroprotective and reparative effect on cerebral ischemic lesions, reducing the size of lesions during 12 weeks of treatment (Warach S et al 2000). Several additional studies indicate that CDP-choline leads to significant decreases in lesion size and can be used safely in acute stroke treatment (Clark WM et al 1997; Tazaki Y et al 1988). Regrettably, some U.S. studies failed to demonstrate efficacy, and the Food and Drug Administration did not approve it as a drug.
- **Potassium, calcium, and magnesium.** Potassium can help lower blood pressure, decreasing risk of cerebrovascular disease and stroke (Sacks FM et al 2001; Suter PM 1999). Evidence has emerged that a balance of potassium, calcium, and magnesium may reduce platelet aggregation and improve insulin resistance. Other studies have shown that combining magnesium and calcium with potassium is more effective than any one of these supplements alone in reducing blood pressure, atherosclerosis, and risk of stroke (Ahsan SK 1998; Sacks FM et al 2001; Broadhurst CL 1997; Ravnskov U 1998; Gillman MW et al 1997; Ascherio A et al 1997; Tavani A et al 1997; Appel LK et al 1997).
- **Vitamin D.** There is evidence from clinical trials that vitamin D may play a modest role in blood pressure control and insulin metabolism, both important in slowing the progression of atherosclerosis and reducing risk of stroke (Dakshinamurti K et al 1996; Lind L et al 1995; Boucher BJ 1998). A recent study also showed that deficiencies in vitamin D and flavonoids may predict heart attack and stroke (Marniemi J et al 2005). This new finding is relevant because the NHANES III study, funded by the National Institutes of Health, estimated that 42 percent of African American women between 15 and 49 years of age and 32 percent of white men and women are vitamin D deficient. The overall average increases to 50 percent in the over-fifty population, and vitamin D deficiency is much higher than that in older people, who have decreased capacity to produce vitamin D from exposure to sunlight (Holick MF 2006).

Omega-3 fatty acids are another important nutrient for stroke victims and those at risk of stroke because of their ability to reduce inflammation. They are found in the oil of cold-water fish and in flaxseed oil. Most people get too much pro-inflammatory omega-6 fatty acids in their diet but not enough omega-3 fatty acids to balance the omega-6. The balance is essential in regulating blood pressure and also in reducing inappropriate platelet aggregation, inflammation, LDL, and other atherosclerosis risk factors (Knapp HR et al 1989; DeBusk RM 2000).

Randomized clinical trials have found that patients with high omega-3 fatty acid intake experienced decreased incidence of stroke (He K et al 2002; Jeerakathil TJ et al 2001). Omega-3 intake may also slow the progression of atherosclerosis (Kris-Etherton PM et al 2005). One study found that eating coldwater fish as little as once per month reduced risk of ischemic stroke (He K et al 2002). American Stroke Association data indicate that individuals may not get enough omega-3 fatty acids through diet alone; the association suggests that individuals who don't should consider taking a supplement. Those who have high levels of triglyceride (blood fat) may need larger doses of fish oil supplements (more than 4 g daily) than normally recommended for general prevention

purposes (Kris-Etherton PM et al 2005).

The following nutrients are antioxidants:

- **Coenzyme Q10.** Coenzyme Q10 (CoQ10) is a powerful antioxidant found in the energy-producing center of the body's cells. It is involved in making the molecule known as adenosine triphosphate, which is the cell's major energy source. CoQ10 provides several weapons against atherosclerosis and stroke; it prevents oxidation of LDL, reduces total cholesterol and triglyceride levels, improves insulin sensitivity, decreases glucose levels, and lowers blood pressure, among other things (Ernster L et al 1995; Digiesi V et al 1994, 1990; Langsjoen PH et al 1999; Morisco C et al 1993; Kontush A 1997). The primary food sources of CoQ10 are meat and seafood.
- **Green tea.** Green tea catechins, which are rich in flavonoids, possess powerful antioxidant properties that have been studied in the context of limiting damage due to ischemic stroke. Animal studies have shown that green tea extract limits the size of stroke lesions in a dose-dependent manner when administered immediately after an ischemic episode, leading researchers to suggest that green tea may have promise in the acute treatment of ischemic stroke (Suzuki M et al 2004; Lee SY et al 2003). Another study found that animals that had a high intake of green tea experienced less cerebral damage after a stroke than did their counterparts who weren't consuming green tea (Hong JT et al 2001).
- **Beta-carotene.** Beta-carotene is an antioxidant. Large long-term studies have found that daily dietary intake of beta-carotene plays a protective role against atherosclerosis and decreases risk of ischemic stroke (Hak AE et al 2004; Hirvonen T et al 2000). Rich sources of beta-carotene include carrots, squash, green leafy vegetables, milk, lean meat, fish, and poultry.
- **Vitamin C.** Vitamin C, also known as ascorbic acid, is a water-soluble antioxidant that protects other compounds from oxidation by being oxidized itself. While it has been shown to lower blood pressure (Duffy SJ et al 1999), other long-term follow-up studies in human beings have found that vitamin C also reduces risk of cardiovascular and heart disease and stroke (Simon JA 1992; Enstrom JE et al 1992; Gale CR et al 1995). A small, well-designed study also found that giving antioxidant vitamins, particularly vitamin C, within 12 hours of an ischemic stroke increased antioxidant capacity, reduced inflammation, and reduced the oxidation of dangerous lipids (Ullegaddi R et al 2005). An earlier, 20-year follow-up study reported that higher vitamin C concentrations reduced incidence of both ischemic and hemorrhagic stroke (Yokoyama T et al 2000). Another study examined the benefit of vitamin C in overweight men with high blood pressure and found that low plasma levels of vitamin C were associated with increased risk of stroke (Kurl S et al 2002).

Although vitamin C provides cerebrovascular benefits when taken alone (Hirvonen T et al 2000), studies have shown that it may be more powerful when combined with other nutrients, vitamins, minerals, and antioxidants (Galley HF et al 1997; Sacks FM et al 2001; Fotherby MD et al 2000; Toivanen JL 1987; Hajjar IM et al 2001).

- **Vitamin E.** Vitamin E is an antioxidant. It regulates oxidation reactions and protects polyunsaturated fatty acids and vitamin A. A large study supplying people with foods that have high levels of vitamin E (plant oils, green leafy vegetables, whole grains, butter, liver, egg yolk, milk, nuts, and seeds) found that higher intake of vitamin E helped reduce risk of death from stroke (Yochum LA et al 2000). Another study reported that eating foods high in antioxidant vitamins C and E helped lower the incidence of stroke, especially notable in smokers (Voko Z et al 2003).

A study from Helsinki looked at vitamin E supplementation in high-risk individuals with high blood pressure and concluded that although vitamin E supplementation may increase the risk of hemorrhagic stroke, this small risk was outweighed by its protective effect against ischemic stroke (Leppala JM et al 2000). Studies have also shown benefits of vitamin E in improving insulin sensitivity and glucose metabolism, thereby lowering risk of atherosclerosis and stroke (Barbagallo M et al 1999).

NUTRIENTS THAT INCREASE GLUTATHIONE

Glutathione is the major cellular antioxidant and has a central role in the antioxidant systems that help the body respond to oxidative insults. When glutathione levels are low, oxidative stress is more likely to occur (Thomas JA 2006). Deficiency in glutathione has been associated with atherosclerosis (Morrison JA et al 1999), and evidence indicates that increasing glutathione levels through diet or supplementation may reverse endothelial damage by enhancing nitric oxide production (Prasad A et al 1999). A number of nutrients have been shown to improve glutathione levels:

- **N-acetylcysteine.** N-acetylcysteine (NAC) is an antioxidant that helps overcome oxidative stress and enhance glutathione levels (Jiang B et al 1999; Vasdev S et al 1997, 1996; Meister A et al 1986; Lu Q et al 2001). Moreover, NAC lowers homocysteine and lipoprotein that can lead to atherosclerotic changes and helps reverse platelet aggregation that can result in blood clots (Gavish D et al 1991; Wiklund O et al 1996; Bostom AG et al 1996; Hultberg B et al 1997; Horowitz JD 1991).
- **Garlic.** Garlic has a long history of medicinal use. It supplies a component of glutathione metabolism, and it is an antioxidant that helps reduce damage from free radicals. Studies have demonstrated that garlic also slightly lowers cholesterol and has antiplatelet effects that help prevent blood clots (Barrett S 2006; Chang HS et al 2005).
- **Selenium.** Selenium is a metallic and essential trace element required for glutathione peroxidase. Deficiencies in selenium can produce oxidative stress as well as other stresses that make people vulnerable to infection or disease. It has also been shown to protect against the effects of cerebral ischemia (Ansari MA et al 2004; Schweizer U et al 2004).

DHEA AND STROKE

Dihydroepiandrosterone (DHEA) is the most abundant adrenal androgen in the body. It can be converted into both testosterone and estrogen, and many studies have shown that DHEA levels decline as people age. In recent years, researchers have investigated the relationship between DHEA levels and cerebrovascular disease, found compelling evidence that low levels of DHEA are associated with cerebrovascular disease, and even identified DHEA as a possible therapy for the treatment of ischemic stroke.

In one study, researchers hypothesized that DHEA functions as a neuroprotective agent that protects the central nervous system and brain against a variety of insults. After performing the study on rabbits, they found that DHEA, at a daily dose of 50 mg/kg, was able to significantly reduce the damaging effects of ischemia. Perhaps better yet, the protective effect of DHEA was durable, meaning that it lasted more than four days.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Life Extension believes that the best approach to stroke is to take aggressive steps to reduce the risk of stroke. This includes blood testing to monitor critical markers of vascular risk, such as cholesterol levels, C-reactive protein, homocysteine, and others. As you can see from the chart below, Life Extension's recommended ranges for risk factors are somewhat below the suggested standard ranges often used by conventional medicine. These reference ranges were designed for a "normal" person, and considering that heart disease and stroke are the first and third leading causes of death in the United States, we think that average isn't good enough. For more information on blood testing, call 1-800-544-4440.

Blood Test	Standard Range	Life Extension's Optimal Range
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	Under 7 mmol/L
Cholesterol	Up to 199 mg/dL	Between 180–220 mg/dL
LDL	Up to 100 mg/dL	Less than 100 mg/dL
HDL	No lower than 35 md/dL	More than 50 mg/dL
Triglycerides	Up to 199 mg/dL	Less than 100 mg/dL

The following dietary supplements may help improve endothelial function and cerebral blood flow and reduce the risk of stroke:

- **L-arginine**—1800 to 9000 milligrams (mg) daily
- **Acetyl-L-carnitine**—1000 mg daily
- **Propionyl-L-carnitine**—1000 mg daily
- **Vinpocetine**—15 to 25 mg daily
- **CDP-choline**—250 mg daily

- **Potassium**—99 mg daily or more, based on blood test results
- **Calcium**—1200 to 1500 mg daily, with 800 international units (IU) vitamin D3
- **Magnesium**—500 mg daily
- **Omega 3 (from fish oil)**—1400 mg daily EPA and 1000 mg daily DHA
- **CoQ10**—100 to 200 mg daily
- **Green tea**—725 mg daily. A decaffeinated form is available for people sensitive to caffeine.
- **Beta-carotene**—10,000 to 25,000 IU daily
- **Vitamin C**—2000 mg daily
- **Vitamin E**—400 IU daily (alpha tocopherol) and 200 mg daily gamma tocopherol)
- **NAC**—600 mg daily
- **Garlic**—600 to 1200 mg daily
- **Selenium**—200 micrograms (mcg) daily
- **Vitamin B6**—250 mg daily
- **Vitamin B12**—300 to 500 mcg daily
- **Folate (folic acid)**—800 mcg daily
- **DHEA**—15 to 75 mg daily, followed by blood testing at 3 to 6 weeks to make sure optimal blood levels are maintained

CEREBROVASCULAR DISEASE AND STROKE 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.

Calcium

- Do not take calcium if you have hypercalcemia.
- Do not take calcium if you form calcium-containing kidney stones.
- Ingesting calcium without food can increase the risk of kidney stones in women and possibly men.
- Calcium can cause gastrointestinal symptoms such as constipation, bloating, gas, and flatulence.
- Large doses of calcium carbonate (12 grams or more daily or 5 grams or more of elemental calcium daily) can cause milk-alkali syndrome, nephrocalcinosis, or renal insufficiency.

Choline

- Do not take choline if you have primary genetic trimethylaminuria.
- Choline can cause fishy body odor, excessive perspiration, hypotension (low blood pressure), depression, and gastrointestinal symptoms such as nausea and diarrhea.

Coenzyme Q10

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

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.

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.

Magnesium

- Do not take magnesium if you have kidney failure or myasthenia gravis.

NAC

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

Potassium

- Do not take potassium if you have hyperkalemia (a greater-than-normal concentration of potassium in the blood).
- Consult your doctor before taking potassium for potassium deficiency.
- Potassium can cause rash and gastrointestinal symptoms such as nausea, vomiting, and diarrhea.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

Vinpocetine

- Do not take vinpocetine if you have a history of allergic or hypersensitivity reactions to any vinca alkaloids.
- Consult your doctor before taking vinpocetine if you take warfarin (Coumadin). Have your international normalized ratio monitored frequently by your doctor if you take vinpocetine and warfarin.
- Consult your doctor before taking vinpocetine if you have low blood pressure (including transient low blood pressure or orthostatic hypotension). Prolonged use of vinpocetine may lead to slight reductions in systolic and diastolic blood pressures.
- Vinpocetine can cause temporary rapid heartbeat, pressure headache, facial flushing, dizziness, insomnia, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.

Vitamin A

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

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 D

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.

Vitamin E

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

For more information see the Safety Appendix

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