

CORONARY ARTERY DISEASE

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DISEASE/CONDITION OVERVIEW

Coronary artery disease (CAD), or more specifically, coronary atherosclerotic heart disease, is the primary cause of death in the United States for both men and women. Most CAD results from the deposition of atheromatous plaque in the large and medium-sized arteries of the heart. A less frequent and usually idiopathic form of CAD is due to coronary spasm. Coronary artery atherosclerosis starts insidiously and is usually distributed irregularly in various blood vessels. Atherosclerotic blood vessels have reduced expansion with systole and abnormal wave propagation. This can reduce or obstruct blood flow to areas of the myocardium, sometimes with seeming abruptness, resulting in myocardial ischemia.

Some plaque formations are unstable and may undergo spontaneous rupture. These formations

are more closely associated with acute ischemic events. The four most common and serious complications of CAD are angina pectoris, unstable angina, myocardial infarction, and sudden cardiac death as the result of arrhythmias. Most evidence suggests that increased oxygen demand is the most frequent mechanism of provocation for angina pectoris. By contrast, the acute coronary syndromes of unstable angina and myocardial infarction are caused by disruption of plaque, platelet plugging, and coronary thrombosis. The peak incidence of clinical pathology for men is between the ages of 50 and 60, and for women, between the ages of 60 to 70.

Etiology

The exact pathogenesis of CAD is not clear, and no single theory adequately explains the atherosclerotic process. Two main explanations have been proposed: the lipid hypothesis and the chronic endothelial injury hypothesis. These explanations are probably interrelated and are certainly not mutually exclusive.

The lipid hypothesis speculates that elevation in lipid plasma levels promotes lipid penetration of arterial walls. In general, it is considered that this process is instigated by abnormal lipid metabolism or excessive dietary intake of cholesterol and saturated fats, particularly when coupled with a genetic predisposition. Low-density lipoproteins (LDLs) are the primary atherogenic lipid, whereas high-density lipoproteins (HDLs) have a protective effect and probably help mobilize LDLs.

When LDLs undergo oxidation in the body, they become harder to mobilize and locally cytotoxic. This is where the lipid hypothesis and endothelial injury hypothesis potentially overlap. According to the latter theory, the initial step in the formation of atherosclerosis is a weakening of the arterial glycosaminoglycans (GAGs) layer. GAGs protect the internal lining of the artery (the endothelium) and promote its repair. The exposed endothelial cells of the artery are subject to free-radical damage, and damage to the endothelial lining makes those sites more permeable to plasma constituents, particularly lipoproteins. Several factors, besides oxidized LDLs, can damage endothelial cells and induce plaque formation. These factors are immunologic, inflammatory, viral, chemical, mechanical, and physical in nature.

In response to cell injury, macrophages migrate from circulation into the cells that line the inside of the artery known as the subendothelial layer of the intima. Ultimately as this process continues, smooth muscle cells of the intima join connective tissue and intracellular and extracellular lipids to form fibrous plaque. Adhesion and aggregation of platelets and release of various growth factors further augment the fibrotic process, resulting in occlusion of the blood vessel lumen and potential for plaque disruption and thrombus formation.

Risk Factors

- Positive family history, particularly with onset before age 50 in same-sex parent
- Male gender
- Age

- Abnormalities in blood lipids/lipid metabolism, for example: high levels of LDL cholesterol and lipoprotein A; low levels of HDL cholesterol and serum vitamin E; hypertriglyceridemia
- High Waist/Hip Ratio (Rexrode et al, 1998)
- Elevated blood homocysteine
- Elevated fibrinogen (Bielak et al, 2000)
- High ultra-sensitive C-reactive protein (Danesh et al, 1998)
- High levels of iron stores (Salonen et al, 1992)
- Low levels of selenium (Suadicani et al, 1992)
- Sedentary lifestyle/poor physical fitness
- Cigarette smoking
- Alcohol abuse
- Diets high in animal fat and calories and low in fruits, vegetables, and fiber
- Diets low in polyunsaturated fatty acids
- Diets high in trans fats (Willett et al, 1993)
- Poor stress management
- High blood levels of insulin
- Decreased oxidative radical antioxidant capacity (ORAC) (Fazendas et al, 2000)
- Diabetes mellitus
- Hypertension
- Hypothyroidism

Prognosis

The primary adverse outcomes of angina pectoris are unstable angina, myocardial infarction (MI), recurrent MI, and sudden death resulting from arrhythmias. Prognosis for angina pectoris depends on the number of coronary vessels affected, severity of obstruction, left ventricular function, and the presence of complex arrhythmias. If ventricular function is normal and the patient is stable, prognosis is very good. Damage to the left main coronary artery or proximal anterior descending artery indicate high risk.

Diminished ventricular function has an adverse influence on prognosis, particularly in patients with atherosclerosis in three arteries. Prognosis is also associated with symptoms, and is better in patients with mild or moderate angina, and worse in those with severe exercise-induced angina.

In men with angina and no history of MI, normal resting ECG, and normal BP annual mortality is about 1.4%. With the presence of systolic hypertension, the rate rises to about 7.5%; with abnormal ECG, the rate is about 8.4%; and if both risk factors are present, annual mortality rate is 12%.

Signs and Symptoms

The most common signs and symptoms for the aspect of CAD most often seen by the clinical practitioner is angina pectoris. Other symptoms include:

- Vague, somewhat troublesome ache or severe, intense precordial crushing sensation
- Most commonly sensation is felt beneath the sternum or may radiate to the left shoulder and down the inside of the left arm; straight through to the back, into the throat, jaws, and teeth; occasionally down the inside of the right arm. Sometimes upper abdomen
- Typically precipitated by physical exertion or stress, persists for a few minutes, and subsides with rest or nitroglycerin
- Worse exertion after a meal
- Worse cold weather, walking into the wind, or first contact with cold air after leaving a warm room
- Modest increase in heart rate
- Significant elevation in systolic and diastolic blood pressure, but sometimes hypotension
- Diffuse apical impulse and more distant heart sounds
- Paradoxical second heart sound
- Fourth heart sound

Differential Diagnosis

- Peptic ulcer
- Chronic cholecystitis
- Esophageal spasm
- Reflux esophagitis

- Spontaneous pneumothorax
- Degenerative and inflammatory lesions of the left shoulder
- Thoracic outlet syndrome
- Anterior chest wall syndrome
- Inflammation of chondrocostal junctions
- Intercostal neuritis
- Cervical or thoracic spine or disk disease

Monitoring Parameters

As well as monitoring levels of LDL cholesterol, triglycerides, and LDL to HDL cholesterol ratios through laboratory values, patients at risk for developing CAD need to be assessed for any coexisting disorders that increase their risk. These include hypertension, hypercholesterolemia, diabetes, and hypothyroidism. Postinfarction management and CAD prevention require monitoring the patient's progress in reversing modifiable risk factors such as smoking. In addition, achievement of appropriate weight to height ratio is important. Studies have shown that increased levels of fitness and physical activity are associated with a lowered incidence of heart disease. No controlled trials have been done, however, to determine optimal intensity, frequency, duration, or type of exercise. It is important to perform a pre-exercise evaluation of the patient with CAD, which consists of history and physical examination to rule out, for example, valvular heart disease, ventricular hypertrophy, dangerous arrhythmias, and exercise-induced asthma. Older or sick patients should be monitored with an exercise stress test. Patients with high cholesterol levels should undergo lipoprotein analysis, body fat estimation, and dietary evaluation. In addition, obese patients should be evaluated for diet, thyroid function, and blood glucose and insulin levels (both fasting and post oral glucose administration).

WESTERN MEDICAL THERAPIES

This section is a brief overview of accepted Western medical therapies for CAD. It is beyond the scope of this protocol to provide dosing information for pharmaceutical medications or to describe treatment for acute medical emergencies such as myocardial infarction.

Reversing the modifiable risk factors is usually the first step in prevention of CAD. This includes smoking cessation and dietary modification. In addition, a Western medical approach may often address the patient's stress management and exercise habits. Treatment is also directed at the coexisting conditions that are associated with increased risk for CAD. These include hypercholesterolemia, hypertension, and hypothyroidism. Cholesterol-lowering medications (the statins) are commonly prescribed for elevated cholesterol levels. Decreased levels of Coenzyme Q10 are associated with the use of statin drugs such as lovastatin and pravastatin (Mortensen et al, 1997).

Sublingual nitroglycerin is the medication of choice for an acute episode of angina, and as prophylaxis before activities likely to precipitate an attack. The beta-blockers propranolol, metoprolol, nadolol, and atenolol are used to prevent angina by decreasing myocardial oxygen requirements during exertion and stress. Beta-blockers work by reducing heart rate, myocardial contractility, and blood pressure to some extent. They have also been shown to prolong the life expectancy of patients with coronary disease following myocardial infarction.

Calcium channel blockers such as verapamil and diltiazem are used to prevent angina by decreasing myocardial oxygen requirements and inducing coronary artery vasodilation. Calcium channel blockers may be the medication of choice in patients with coronary vasospasm. They do not reduce postinfarction mortality, and have in some cases actually increased ischemia and mortality rates.

Coronary thrombosis, which leads to most myocardial infarcts and many syndromes of unstable ischemia, is usually addressed with platelet-inhibiting agents. Low doses of aspirin are usually prescribed for patients with angina. Low-dose aspirin has also been shown to reduce mortality and reinfarction rates in post-MI patients.

INTEGRATIVE MEDICINE STRATEGY

The goals of integrating a CAM approach with a Western medical approach to address coronary artery disease are to provide effective prevention, to minimize recurrence of pathology and complications, and to optimize a patient's ability to function.

A major strategy for prevention is to eliminate or definitely reduce as many of the modifiable risk factors for developing atherosclerosis as possible. Paramount among these are the areas of diet and lifestyle habits. For many patients, this goal will require huge changes, so it is important to individualize a treatment plan to maximize adherence and success. It is also important to perform a comprehensive cardiovascular evaluation for patients with a high familial risk for heart disease or stroke, or those who have had a previous MI or stroke. An integrative approach would include the following laboratory evaluations: LDL, HDL, and total cholesterol levels; lipoprotein A; fibrinogen; homocysteine; ferritin; and lipid peroxides. It would also include an EKG, an echocardiogram, or exercise stress test.

A strategy to address diet should focus on the most common areas of nutritional imbalance among people with heart disease. These include saturated fat excess, simple and refined carbohydrate excess, essential fatty acid deficiency, fiber deficiency, and fresh vegetable deficiency. There is some evidence that nutrient status plays a role in risk profile. Addressing antioxidant levels, for example, may protect against the damage caused by lipid peroxides and oxidized cholesterol. This means supplementation with antioxidants. Vitamin E, in particular, has an affinity for incorporation into the LDL-cholesterol molecule. In addition, a deficiency of vitamin E, as demonstrated by low blood levels, is considered a risk factor for the development of CAD. Ensuring adequate dietary fiber to prevent constipation is also part of a strategy to minimize free radical exposure.

There is mounting evidence that certain personality traits may predispose a person to developing CAD. These traits include manifesting attitudes of hostility and cynical distrust, repressing emotions, anxiety and worry, anger, depression, poor boundaries, a sense of urgency, and competitiveness. It is crucial to encourage patients to address these stress-related factors in their disease process. Exercise provides benefits in its own right and also alleviates the effects of stress. Optimal types of exercise may include aerobic, stretching, and resistance. In general, the goals of therapy will focus on correcting nutrient deficiencies, improving blood supply to the heart, and optimizing energy metabolism within the heart.

COMPLEMENTARY AND ALTERNATIVE (CAM) THERAPIES

There are a number of dietary interventions, herbal products, and dietary supplements that appear to be beneficial in the treatment and prevention of CAD.

Herbal Therapies

- **HAWTHORN (*Crataegus oxyacantha*)**
 - **EFFICACY:** Adult, possibly effective
 - **DOCUMENTATION:** Adult, fair
 - **DOSE:** Tincture (1:5): 4 to 6 milliliters (mL) (1 to 1.5 tsp) three times a day. Fluid extract (1:1): 1 to 2 mL (0.25 to 0.5 teaspoon three times daily. Solid extract (10% procyanidins or 1.8% vitexin-4'-rhamnoside): 100 to 250 milligrams three times daily (Murray & Pizzorno, 1998).
 - **PRECAUTIONS:** Precautionary use in children under 12 years (Fachinfo Crataezyma(R), 1996). The use of Crataegus during the first trimester is not recommended (Fachinfo Crataezyma(R), 1996).
 - **ADVERSE EFFECTS:** Higher doses can produce hypotension (Anon, 1994). High doses of Crataegus may produce arrhythmias (Anon, 1994a). When administering high doses, sedation may be caused by oligomeric procyanidins (Anon, 1994; Tyler, 1987). Accidental corneal scratches with a thorn from the hawthorn bush were reported to lead to blindness in 88 of 132 cases in Ireland (Duke, 1985).
 - **INTERACTIONS:** No human drug interaction data available.
 - **REGULATORY/SAFETY INFORMATION:** The American Herbal Products Association rated Crataegus as Class 1 (safe when used appropriately) for Adjustment Disorders, Atherosclerosis, Congestive Heart Failure, Exercise Performance, Hyperlipidemia, Hypertension, and Ischemia (McGuffin et al, 1997). British Herbal Pharmacopoeia lists Crataegus as cardioactive and hypotensive (Anon, 1996). Hawthorn leaf with flower is German Commission E

approved for decreasing cardiac output as described in functional stage II of New York Heart Association. All other forms of Hawthorn are listed in the Unapproved Herbs section (Blumenthal et al, 1998). Hawthorn is available in the United States under the Dietary Supplements Health and Education Act of 1994 (DSHEA).

- **COMPARATIVE EFFICACY:** In vitro data only. Unlike other inotropic agents, crataegus prolongs the effective refractory period (Joseph et al, 1995).
- **LITERATURE REPORTS:** Tincture of crataegus enhances cholesterol catabolism and suppresses cholesterol synthesis in vitro (Rajendran et al, 1996). One month of ingesting a hawthorn drink by human volunteers clinically diagnosed as hyperlipidemic was associated with lowered average serum cholesterol levels (Chen et al, 1995). The hawthorn drink was decocted from the natural plant and fortified with adequate amounts of vitamin C and zinc gluconate to enhance the antioxidative features of the plant. During the experimental period the 30 volunteers (25 females and 5 males, mean age 51.1 years) took no medications and drank 250 milliliters of hawthorn drink twice daily (Chen et al, 1995).
- **GARLIC (*Allium sativa*)**
 - **EFFICACY:** Adult, possibly effective
 - **DOCUMENTATION:** Adult, good
 - **DOSE:**
 - One garlic clove is roughly equal to 4 milligrams to 1 gram of garlic (Anon, 1998; Koch & Lawson, 1996).
 - Arterial occlusive disease, capsules: daily doses of 600 to 800 milligrams (Kiesewetter et al, 1993; Kiesewetter et al, 1993a; Harenberg et al, 1988).
 - Hyperlipidemia, capsules: daily doses of 600 to 900 milligrams (Agarwal, 1996; Holzgartner et al, 1992; Mader, 1990; Vorberg & Schneider, 1990).
 - **PRECAUTIONS:** Allergic reactions including contact dermatitis and asthma are possible (Asero et al, 1998; Lee & Lam, 1991; Kaplan et al, 1990). Not for use in pregnancy or lactation (McGuffin et al, 1997).
 - **ADVERSE EFFECTS:** A number of studies have shown garlic to have an effect on platelet aggregation. This effect may lead to post-operative bleeding (Petry, 1995). A decrease in blood pressure after garlic intake is possible (Fachinfo Kwai(R) N, 1997). Thrombophlebitis after intravenous infusion of commercial garlic extract at the infusion site has been observed (Davis et al, 1990). Abdominal discomfort, nausea, vomiting, and diarrhea are occasional adverse

effects of garlic therapy, sometimes resulting in discontinuation of therapy (Berthold et al, 1998; Morris et al, 1995; Candulea et al, 1995). Hematological abnormalities such as reduction in hematocrit values and plasma viscosity have been associated with garlic therapy (Jung et al, 1991). Very high doses of garlic may induce anemia (exact dose or percent reduction not stated) (Kasinath et al, 1997). Headache, myalgia, and fatigue have been observed secondary to therapeutic doses of garlic powder (Holzgartner et al, 1992). A feeling of fullness was reported in 5 patients and loss of appetite occurred in one patient taking garlic in a study of 98 patients (Holzgartner et al, 1992). Elevated ALP, AST, ALT, and urea were found in studies of prolonged high dose therapy (dose and duration of therapy not specified) with garlic products (fresh, oil, powder). These may have been signs of liver toxicity (Kasinath et al, 1997). Several cases of contact dermatitis after topical treatment with garlic have been reported (Lee & Lam, 1991; Kaplan et al, 1990; Bleumink et al, 1972). There have been several cases of garlic "burns" reported in the literature. These cases have mostly involved young children who have had the garlic in contact with the skin for hours to days at a time (Canduela et al, 1995). Burns have also been seen in adults (Farrell & Staughton, 1996). A 17-month-old child developed a second-degree burn after an 8-hour exposure to a garlic-petroleum jelly plaster that was applied to the skin of both feet. The lesions healed in 2 weeks (Parish et al, 1987). Body odor and halitosis are possible with garlic therapy (Berthold et al, 1998; Simons et al, 1995; Crohn & Drosd, 1941). Garlic smell was reported in 12% of the patients taking a daily dose of 800 milligrams of a garlic powder preparation (Mader, 1990).

- **INTERACTIONS:** Garlic may potentiate the anticoagulant effect of warfarin leading to increased risk of bleeding (Brinker, 1998).
- **REGULATORY/SAFETY INFORMATION:** German Commission E approved as an anti-lipidemic agent for use as supportive dietary measures of elevated levels of lipids in blood and preventative measures for age-dependent vascular changes (Blumenthal et al, 1998). The American Herbal Products Association rated Garlic Class 2b (not to be used during pregnancy) and Class 2c (not to be used while nursing) (McGuffin et al, 1997). Garlic is available both as a food and dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Garlic extract and bezafibrate were equally effective in treating patients with primary hyperlipidemia (Holzgartner et al, 1992). Clofibrate was a more effective antihyperlipidemic agent than garlic (Arora & Arora, 1981).
- **LITERATURE REPORTS:** The majority of studies showing a positive effect of garlic and garlic preparations in reducing the risk of cardiovascular mortality are those which use products that deliver a sufficient dosage of allicin. Since allicin is

the component in garlic that is responsible for its easily identifiable odor, several manufacturers have developed highly sophisticated methods in an effort to provide the full benefits of garlic without odor. These "odorless" garlic products concentrate alliin because alliin is relatively "odorless" until it is converted to allicin in the body. Products concentrated for alliin and other sulfur components and stabilized in enteric-coated tablets provide all the benefits of fresh garlic but are more "socially acceptable." Administration of aged garlic extract to 9 human volunteers resulted in a significant reduction in copper-mediated oxidation of human low density lipoprotein (LDL) in vitro. Study participants received either 6 grams of raw garlic or 2.4 grams of aged garlic extract daily for 7 days, resulting in a minimum of 15 milligrams allicin daily (Munday et al, 1999). Atherosclerotic plaque build up was stopped and in some patients even reduced with daily administration of 900 milligrams garlic (Kwai(R)). This 4-year randomized, double-blind, placebo-controlled study had 280 participants diagnosed with advanced atherosclerotic plaque formation and at least one established cardiovascular risk factor (Anon, 1999).

Garlic reduced total serum cholesterol and serum triglyceride levels compared to placebo over 1 to 3 months. Garlic reduced total cholesterol and LDL-cholesterol, in comparison to baseline values and to placebo treatment, in renal transplant patients. Garlic 680 milligrams twice daily (equivalent to 4080 micrograms of allicin) or placebo was given to 35 renal transplant patients for 12 weeks. Patients were also instructed in a cholesterol reduction diet (Silagy & Neil, 1994).

Garlic may lower blood cholesterol levels, even in apparently healthy individuals. In regards to lowering blood pressure, the degree of reduction in hypertensive patients can be quite significant (e.g., the risk of stroke is reduced by 30 to 40% and the risk of heart attack by 20 to 25%). Administration of garlic capsules to hyperlipidemic children did not result in statistically significant changes in fasting total cholesterol, low density lipoprotein cholesterol, high density lipoproteins, triglycerides, apolipoprotein B-100, lipoprotein (a), fibrinogen, homocysteine, or blood pressure. The study was a randomized, double-blind, placebo-controlled clinical trial of 30 patients (age 8 to 18 years) with familial hyperlipidemia and cholesterol greater than 4.8 millimoles/liter (185 milligrams/deciliter). These patients were treated for eight weeks with 300 milligrams (mg) of garlic extract (0.6 mg of allicin) three times a day (or placebo) (McCrindle et al, 1998).

Garlic's other effects in preventing atherosclerosis include reducing excessive platelet aggregation, promoting fibrinolysis, and inhibiting LDL oxidation (Murray & Pizzorno, 1998; Lawson, 1998; Orekhov & Grunwald 1997). Recent clinical trials failed to demonstrate a lowering of cholesterol by garlic (Berthold et al, 1998; Isaacsohn et al, 1998; Simons et al, 1995).

Garlic extract but not raw garlic prevents in vitro oxidation of human LDL. It is postulated that LDL oxidation plays a significant role in the development and progression of atherosclerosis (Munday et al, 1999). Garlic may increase fibrinolytic activity in healthy subjects and patients with ischemic heart disease but further controlled studies are necessary (Chutani & Bordia, 1981; Kiesewetter et al, 1990; Harenberg et al, 1988).

- **GUGGUL**

- **EFFICACY:** Adult, effective
- **DOCUMENTATION:** Adult, good
- **DOSE:**
 - Gugulipid (ethyl acetate extraction): 1200 to 1500 milligrams (mg) per day, in two or three divided doses (Sharma & Dwiveda, 1997; Nityanand et al, 1989).
 - Gugulipid (standardized to 25 milligrams (mg) gugalsterones per tablet): 75 mg per day in 3 divided doses (Beg et al, 1996; Anon, 1988) or two tablets twice daily (Singh et al, 1994).
 - Fraction A of gum Guggul (petroleum-ether extract): 0.5 gram two or three times daily (Kuppurajan et al, 1978; Malhotra et al, 1977; Kuppurajan et al, 1973; Malhotra & Ahuja, 1971).
 - Purified crude gum Guggul powder (various extracts): 3 to 6 grams per day in two or three divided doses (Singh et al, 1993; Verma & Bordia, 1988; Jain et al, 1987).
- **PRECAUTIONS:** Avoid during pregnancy due to possible emmenagogue and a uterine stimulant (McGuffin et al, 1997; Kakrani, 1981).
- **ADVERSE EFFECTS:** Mild gastrointestinal complaints such as diarrhea, nausea, hiccup, and mild abdominal discomfort have been reported mainly with crude extracts and are lessened or altogether eliminated with standardized gugalsterone (gugulipid) preparations
- **INTERACTIONS:** Caution should be exercised when adding guggul or gugulipid to a patient who has been stabilized on anticoagulation therapy (Mester et al, 1979). Due to bile sequestrant properties, guggul may in theory reduce absorption of fat-soluble nutrients or medications. A theoretical consideration which has not been studied. Since one of the mechanisms of action appears to be sequestration of bile in the intestinal lumen (Sharma & Dwivedi, 1997; Singh et al, 1994).

- **REGULATORY/SAFETY INFORMATION:** Approved by the government of India in 1987 for the treatment of hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia (Anon, 1988; Satyavati, 1988). No German Commission E monograph has been issued. American Herbal Products Association's Class 2b (not to be used during pregnancy) (McGuffin et al, 1997). Guggul is available in the United States as a dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Gugulipid has demonstrated equivalent efficacy to clofibrate in clinical trials for the treatment of hyperlipidemia. (Malhotra et al, 1977; Nityanand et al, 1989; Kuppurajan et al, 1978).
- **LITERATURE REPORTS:** Several well-designed clinical trials using various extracts of guggul have reported significant lowering of triglycerides, total cholesterol (Singh et al, 1994; Nityanand et al, 1989), total serum lipids, low density lipoprotein-C, as well as significant increases in high density lipoprotein-C (Singh et al, 1994; Nityanand et al, 1989; Verma & Bordia, 1988). No serious adverse reactions have been reported. The duration of lipid lowering effects continues after discontinuation of therapy and has been reported in a range of 6 to 20 weeks (return time to baseline lipid profile) (Nityanand et al, 1989; Gopal et al, 1986). All extracts and formulations of guggul have been shown to produce benefit, although standardized preparations of gugulipid seem to be tolerated best. Gugulipid has demonstrated equivalent efficacy to clofibrate in clinical trials for the treatment of hyperlipidemia (Nityanand et al, 1989; Malhotra et al, 1977).
- **ONION (*Allium cepa*)**
 - **EFFICACY:** Adult, possibly effective
 - **DOCUMENTATION:** Adult, fair
 - **DOSE:** Atherosclerosis prevention, dried onion: 20 grams daily (Blumenthal et al, 1998).
 - **PRECAUTIONS:** Maternal intake of cruciferous vegetables such as broccoli and cauliflower, cow's milk, onion, or chocolate during exclusive breastfeeding is associated with colic symptoms in young infants (Lust et al, 1996).
 - **ADVERSE EFFECTS:** Botulism occurred in 28 people who ingested sautéed onions as part of their patty-melt sandwich. Type A *Clostridium botulinum* was also cultured from onion samples taken from the restaurant. Symptoms included diplopia, dry mouth, blurred vision, dysphagia, dysphonia, fatigue, dizziness, nausea, muscle weakness, extraocular muscle palsy, cranial nerve dysfunction, and respiratory failure. All persons were hospitalized, one died, and 12 required

ventilatory support (MacDonald et al, 1985). Mild temporary gastric distress was reported in a small number of patients consuming onion oil (Louria et al, 1985). Skin irritation led to treatment discontinuation in 3 of 9 patients applying a topical gel of onion extract and allantoin to postsurgical scars (Jackson & Shelton, 1999).

- **INTERACTIONS:** No human drug interaction data is available.
- **REGULATORY/SAFETY INFORMATION:** The German Commission E has issued a positive evaluation for *Allium cepa* bulb for the treatment of loss of appetite and the prevention of atherosclerosis (Blumenthal et al, 1998). The American Herbal Products Association has assigned no rating. onion, as a food or dietary supplement, is currently not regulated by the US Food and Drug Administration (FDA). The safety of onion is reflected by its worldwide use as a vegetable (WHO, 1999).
- **COMPARATIVE EFFICACY:** Not available.
- **LITERATURE REPORTS:** The co-administration of onion with a high-fat snack had positive effects on alimentary hyperlipidemia. Ten healthy adult males consumed 100 grams of butter with four slices of bread and serum cholesterol, plasma fibrinogen, and fibrinolytic activity were assessed. The subjects randomly received onion juice or its ether extract or garlic juice or its ether extract. Since onion and garlic were not directly compared, only the results of onion administration will be presented here. Onion was ingested as a single dose and was freshly extracted from 50 grams of onion; the essential oil was prepared by ether extraction of the juice and encapsulated. Simultaneous consumption of butter and onion juice resulted in an increase of 9.8% in coagulation time, which from butter alone had decreased by 13.3% (p less than 0.01); fibrinolytic activity increased by 15.7% after the initial decrease of 48.6% from fat-only administration (p less than 0.005). Plasma fibrinogen levels increased by 28.4% after butter administration and onion juice again reduced these levels to baseline. The rise in serum cholesterol produced by the fatty snack was completely prevented with onion juice co-administration (p less than 0.05). Results of administration of onion extract mimicked those of onion juice (Bordia et al, 1975; Bordia et al, 1972).

Onion and chaunga effectively ameliorated the hyperlipidemic effects of a high-fat diet. Eight healthy subjects consumed a high-fat diet for 7 days and then were co-administered 100 grams of onion or 100 grams chaunga daily for the next week. The high-fat diet resulted in a significant increase (p less than 0.05) in serum cholesterol (SC) of 17.6%, in serum triglycerides (STG) of 15.8%, and in serum total lipids (STL) of 12%. Co-administration of onion for 1 week lead to a decrease in SC of 12.2% (p less than 0.05), in STG of 12% (p less than 0.05), and STL of 7.9% (not significant) (Bakhsh & Khan, 1990).

A small (n=34) preliminary open study with many limitations suggested beneficial effects of onion oil (2 to 3 tablespoons daily for 2 months) in the treatment of mild to moderate hypertension (systolic less than 185 mmHg, diastolic less than 110 mmhg) and hypercholesterolemia (245 to 300 milligrams/deciliter). A decrease in cholesterol levels from 7% to 33% was reported along with a decrease to normal blood pressure values in many subjects. One subject experienced both a decrease in cholesterol levels and blood pressure. All other evaluable subjects experienced either a hypocholesterolemic or hypotensive effect or none (Louria et al, 1985). Further controlled trials are warranted to confirm these results. The liberal consumption of onion and garlic led to a favorable lipid profile in an epidemiological study of 206 subjects of varying ages from 78 families of the JAIN community in India. Consumption of garlic and onion occurred in the form of salad, chutney, pickles, or as a cooked vegetable. Subjects (n=70) consuming 600 or more grams of onion and 50 or more grams of garlic weekly had significantly lower serum levels of cholesterol (159.4 vs. 172; p less than 0.01), triglycerides (52.7 vs. 75.0; p less than 0.001), and phospholipids (5.95 vs. 6.35; p less than 0.002) compared to those (n=64) consuming only 200 or less grams of onion and 10 or less g of garlic weekly. Beta phospholipids were not significantly different between these 2 groups. Subjects (n=72) who had never consumed onion or garlic due to religious reasons had significantly higher serum lipid values than the other 2 groups (p less than 0.01 to p less than 0.001) (Sainani et al, 1979).

Dietary Supplements

- **ARGININE**

- **EFFICACY:** Adult, possibly effective
- **DOCUMENTATION:** Adult, poor
- **DOSE:**
 - Adult, endothelial dysfunction-related conditions: 6 to 8 grams daily for adults; 18 to 20 grams daily provides maximal benefit without significant side effects (Tenenbaum et al, 1998).
 - Adult, intractable angina pectoris: 9 grams daily for three months (Blum et al, 1999).
- **PRECAUTIONS:** Use with precaution in renal insufficiency (possible hyperkalemia), liver cirrhosis, uremia, anuria, or hepatic insufficiency (possible hyperkalemia or hyperdynamic state) (Parfitt, 1999) and diabetes (Massara et al,

1981). Because of its hypertonicity, parenteral infusions should be intravenous and arginine should be diluted to a 10% solution to prevent tissue injury should extravasation occur. Other preventive methods should include frequent assessment of intravenous patency and limited movement of the patient during infusion; excessive infusion rates can result in local irritation, flushing, nausea, or vomiting. Arginine has a high content of metabolizable nitrogen and the temporary effects of high loads of nitrogen on the kidney should be evaluated prior to administration. The chloride content of arginine is 47.5 mEq/100 mL which may be hazardous in patients with electrolyte imbalance (ie, hyperchloremic acidosis). Arginine has been found to promote the growth of Herpes simplex, especially if lysine levels are low (Marz, 1997). Because it stimulates growth hormone, L-Arginine should not be taken routinely by pregnant or breastfeeding women (Tenenbaum et al, 1998). L-arginine causes a release of growth hormone, insulin, glucagon, and prolactin (Calver, 1990).

- **ADVERSE EFFECTS:** Excessive arginine can cause diarrhea and may promote the growth of viruses such as Herpes simplex in susceptible individuals. Foods high in arginine include poultry, beef, salmon, shrimp, tuna, nuts, carob, chocolate, coconut, dairy products, gelatin, meat, oats, peanuts, soybeans, white flour, wheat, and wheat germ (Balch & Balch 1998; Marz, 1997). Increased nitric-oxide (NO) production after administration of l-arginine may cause profound hypotension when inducible NO synthase is overexpressed in vascular smooth muscle (Saijyo et al, 1998). Because l-arginine is contained in Fisher's solution and administered to patients with hepatic insufficiency as well as in synthesis of NO in cirrhotic patients, such patients should be monitored for development of hypotension, a reduction in peripheral resistance, and exacerbation of a decreased response to vasoconstrictors if l-arginine is administered. Phlebitis has occurred during arginine infusions (Imler et al, 1973). Numbness and headache can occur during intravenous infusion of arginine (AHFS, 1994). Nausea and vomiting occur in approximately 3% of patients receiving arginine infusion (Anon, 2000). Nausea and diarrhea have been reported by normal human subjects ingesting 30 grams of arginine hydrochloride daily (Vissek, 1986). Mild diarrhea was reported by a patient with Syndrome X taking 14 grams of L-arginine by mouth daily (Bellamy et al, 1998). Abdominal cramps and bloating were reported following oral administration of arginine in cystic fibrosis patients (Kattwinkel et al, 1972). In these patients, significant weight loss was also observed. Flushing can occur with rapid intravenous infusion (AHFS, 1994).
- **INTERACTIONS:** Several patients with hepatic impairment and a recent history of spironolactone use were reported to develop severe hyperkalemia upon initiation of arginine hydrochloride for management of metabolic alkalosis (AHFS, 1997). All patients had received spironolactone within two to three days prior to arginine. Severe hyperkalemia developed within several hours following initiation of arginine; death occurred in one patient

- **REGULATORY/SAFETY INFORMATION:** United States Food and Drug Administration's Pregnancy Category B (Briggs et al, 1998). Arginine is available in the United States as a dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Not available.
- **LITERATURE REPORTS:** Oral and intravenous supplementation with arginine produces endothelial nitric oxide that decreases blood pressure. As a result, arginine is being studied for use in heart and circulatory conditions such as angina pectoris, atherosclerosis, hypertension, coronary artery disease, and peripheral vascular disease. Provocative evidence exists for its effectiveness, but larger, long-term controlled trials are needed. L-arginine hydrochloride 60 millimoles (mmol), infused over 3 hours for seven consecutive days into the cubital veins of 5 men with atherosclerosis of the lower limbs, lowered blood pressure and levels of plasma cholesterol and plasminogen-activator inhibitor (PAI) in 2 men with hypertension and hypercholesterolemia only, while eliciting no significant changes in those parameters in the 3 whose blood pressure and cholesterol levels were normal (Korbut et al, 1993). Other research indicates that some forms of coronary disease may be produced by a relative deficiency in the substrate l-arginine rather than by endothelial dysfunction (Tousoulis et al, 1998). L-arginine enhances forearm-vessel dilatation from acetylcholine which should translate to systemic circulation (Quyyumi, 1998).
- **VITAMIN B6**
 - **EFFICACY:** Adult, possibly effective
 - **DOCUMENTATION:** Adult, good
 - **DOSE:** Adult, hyperhomocysteinemia: 2 to 50 milligrams daily (Anon, 1998a).
 - **PRECAUTIONS:** Use precaution when supplementing pyridoxine with concurrent levodopa treatment (Gilman et al, 1990).
 - **ADVERSE EFFECTS:** Low serum folic acid concentrations have been reported in patients with homocysteinuria receiving large doses of pyridoxine (500 to 1500 milligrams (mg) daily). It is unclear if this results from direct effects of large amounts of vitamins or changes in methionine and one-carbon metabolism in these patients (Bender, 1989). Peripheral sensory neuropathy or neuropathic syndromes have been associated with prolonged use of oral vitamin B6. Although these syndromes were initially observed following administration of high doses (2 to 6 grams daily) (AMA, 1986; Schaumburg et al, 1983), other reports have described peripheral neuropathy with lower doses (50 to 500 milligrams (mg) daily) (Bender, 1989; Dalton & Dalton, 1987; AMA, 1986; Parry & Bredesen,

1985). Neuropathic symptoms generally subside after withdrawal of pyridoxine. Despite this complication of vitamin B6 therapy, one investigator found no reports of peripheral sensory neuropathy in studies of patients with pyridoxine-dependency syndromes who were treated with vitamin B6 500 to 1500 mg daily (Bender, 1989).

- **INTERACTIONS:** Concomitant pyridoxine and amiodarone therapy has been reported to enhance amiodarone-induced photosensitivity reactions (Mulrow et al, 1985). Concomitant administration of contraceptives, hydralazine, isoniazid, or penicillamine plus pyridoxine may increase pyridoxine requirements (Anon, 1985). Pyridoxine in doses of 5 milligrams (mg) or more daily may appreciably reverse the effects of levodopa (Gilman et al, 1990).
- **REGULATORY/SAFETY INFORMATION:** United States Food and Drug Administration (FDA) Pregnancy Category A; if used in doses above the RDA it is classified as FDA Pregnancy Category C (Briggs et al, 1998). Vitamin B6 is available in the United States as a dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Not available.
- **LITERATURE REPORTS:** Hyperhomocysteinemia may be influenced by intake of vitamin B6, but the relationship does not appear to be as strong as that for folic acid or vitamin B12. Many trials have included vitamin B6 in homocysteine-lowering interventions but a recent meta-analysis concluded it does not provide significant additional benefit over a combination of folic acid and vitamin B12. Pyridoxine (250 milligrams/day (mg/d) and folic acid (5 mg/d) caused a statistically significant decrease in the mean fasting and post-load homocysteine concentrations (n=10). Pyridoxine (250 mg/d) alone (n=10) caused a statistically significant decrease only in post-load homocysteine concentrations. The study period was 6 weeks (Franken et al, 1994).

A cohort study assessed vitamin B6 and folate in relation to coronary heart disease (CHD). A total of 939 cases of coronary disease was studied using dietary and supplement questionnaires and risk factor analysis. Risk of CHD was decreased in those that used multiple vitamins, which provided the main source of vitamin B6 and folate. The study concluded that folate and vitamin B6 above recommended daily allowance may be important in prevention of CHD (Rimm et al, 1998).

In 304 patients with CAD, homocysteine was inversely correlated with measures of folic acid, vitamin B12, and pyridoxal 5'-phosphate. Low pyridoxal 5'-phosphate was seen in 10% of the CAD patients and 2% of controls (or 4.3, p less than 0.01). Low pyridoxal 5'-phosphate was considered by the authors as an

independent risk factor for CAD regardless of homocysteine levels (Robinson, 1995). The plasma pyridoxal 5'-phosphate level of 84 patients with acute myocardial infarction was 6.5 nmol/l lower compared to controls (95% CI 11.4-1.6). Red blood cell (RBC) pyridoxal 5'-phosphate was 0.63 mmol/l lower (95% CI -15.3, +2.7). The RR for ami in subjects in the lowest quartile of plasma PLP was 5.2 compared to those in the highest quartile (95% CI 1.4 - 18.9), suggesting a possible causal relationship (Kok, 1989).

- **VITAMIN B12**

- **EFFICACY:** Adult, effective
- **DOCUMENTATION:** Adult, good
- **DOSE:** 0.5 milligram daily (Anon, 1998a)
- **PRECAUTIONS:** Vitamin B12 therapy can mask folic acid deficiency (Anon, 2000). Folic acid in large doses can correct the megaloblastosis of vitamin B12 deficiency but does not prevent progression of neurologic complications. In the absence of vitamin B12 therapy, neurologic damage may become irreversible (Anon, 2000). Hypersensitivity to any component of vitamin B12 formulations or to cobalt is considered a contraindication.
- **ADVERSE EFFECTS:** Injection site pain has been infrequently reported with intramuscular or subcutaneous injections of cyanocobalamin (Anon, 2000; AMA, 1991).
- **INTERACTIONS:** Ascorbic acid in doses as low as 250 milligrams can destroy up to 81% of the cyanocobalamin in a moderate vitamin B12-containing meal and up to 25% in a high vitamin B12-containing meal. They also demonstrated that supplemental vitamin C (2 grams/day up to 26 months) had no effect on serum vitamin B12 levels (Herbert & Jacob, 1974). Statistical examination of the data demonstrated that the long-term use of vitamin C in the patients was actually correlated with higher serum vitamin B12 levels. Subsequent research confirmed that high doses of vitamin C did not adversely affect vitamin B12 in vitro or in vivo and that vitamin C may actually have a protective effect on serum vitamin B12 (Marcus et al, 1980).
- **REGULATORY/SAFETY INFORMATION:** Vitamin B12 is available in the United States as a dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Not available.
- **LITERATURE REPORTS:** A meta-analysis was conducted to assess vitamin B12 and folic acid supplementation on blood homocysteine concentrations. Data was

collected on 1114 patients in twelve trials. The study found a 25% reduction in blood homocysteine concentrations with dietary folic acid and similar effects in the range of folic acid 0.5 to 5 milligrams (mg) daily. The study concluded that daily folic acid (0.5 to 5 mg) and vitamin B12 (0.5 mg) might reduce blood homocysteine concentrations 25%-33% (Anon, 1998a).

- **L-CARNITINE**

- **EFFICACY:** Adult, possibly effective
- **DOCUMENTATION:** Adult, good
- **DOSE:** Cardiovascular disease, oral: 2 to 4 grams daily (Davini et al, 1992; Cherchi et al, 1985).
- **PRECAUTIONS:** Hypersensitivity to carnitine is a contraindication.
- **ADVERSE EFFECTS:** Possible gastric discomfort (Yesilpek et al, 1998; Plioplys & Plioplys, 1997; Campos et al, 1993).
- **INTERACTIONS:** No human drug interaction data available.
- **REGULATORY/SAFETY INFORMATION:** L-Carnitine is available as a dietary supplement in the United States under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Not available.
- **LITERATURE REPORTS:** L-Carnitine supplementation improved heart rate, arterial pressures, angina, and lipid patterns in a controlled study of patients who had experienced a recent myocardial infarction. Patients (n=81) received 4 grams L-carnitine daily for a year and were compared with a control group (n=79). Clinical cardiac parameters were measured at the beginning, and at 30, 90, 180, 270, and 360 days. Compared to the control group, the L-carnitine group had an improvement in heart rate; in systolic and diastolic arterial pressure; a decrease in angina; and improvement in lipid patterns (Davini et al, 1992).

L-carnitine supplementation improved symptoms of angina in a double-blind, randomized, placebo-controlled, crossover study. Men (n=44) with chronic stable angina received either 2 grams L-carnitine daily or a placebo in 4 week treatment periods with a 10-day wash-out period between treatments. Patients receiving L-carnitine had less angina (22.7%) than those receiving a placebo (9.1%) (Cherchi et al, 1985).

L-carnitine may improve exercise tolerance in patients with stable angina

pectoris. Patients (n=12) received 900 milligrams L-carnitine daily for 12 weeks after receiving a placebo for 4 weeks. Treadmill exercise was evaluated at the end of the placebo and at 4 and 12 weeks during the treatment period. Exercise time significantly increased during the L-carnitine treatment, after 4 weeks and at 12 weeks. There was less ST depression after the 12-week treatment period (Kamikawa et al, 1984).

- **COENZYME Q10**

- **EFFICACY:** Adult, possibly effective
- **DOCUMENTATION:** Adult, fair
- **DOSE:**
 - Adult, heart disease, oral: 100 to 300 milligrams (mg) daily.
 - Adult, stable angina, oral: up to 600 mg daily (Greenberg & Frishman, 1990).
- **PRECAUTIONS:** Concomitant therapy with hypolipidemic agents may lower plasma concentrations of endogenous Coenzyme Q10 in hyperlipidemic patients (Watts et al, 1993). Coenzyme Q10 may reduce insulin requirements in diabetics (Matthews et al, 1993).
- **ADVERSE EFFECTS:** Irritability or agitation, headache, and dizziness have occurred rarely during oral coenzyme q10 therapy (Feigin et al, 1996; Baggio et al, 1994; Baggio et al, 1993; Lampertico & Comis, 1993; Wilkinson et al, 1976). It is unclear if any of these effects are definitely drug-related. Fatigue and increased involuntary movements were reported in patients with Huntington's chorea taking high doses (Feigin et al, 1996). Coenzyme Q10 is better absorbed when taken with food such as peanut butter. Irritability or agitation, headache, and dizziness have occurred rarely during oral coenzyme q10 therapy (Feigin et al, 1996; Baggio et al, 1994; Baggio et al, 1993; Lampertico & Comis, 1993; Wilkinson et al, 1976). It is unclear if any of these effects are definitely drug-related. Fatigue and increased involuntary movements were reported in patients with Huntington's chorea taking high doses (Feigin et al, 1996). Skin rash and pruritus are infrequent complications of oral coenzyme Q10 therapy (less than 0.5% of patients) (Baggio et al, 1994; Baggio et al, 1993; Lampertico & Comis, 1993; Langsjoen et al, 1990a).
- **INTERACTIONS:** Decreased levels of Coenzyme Q10 are associated with the use of statin drugs such as lovastatin and pravastatin (Mortensen et al, 1997). Coenzyme Q10 is better absorbed when taken with food such as peanut butter.
- **REGULATORY/SAFETY INFORMATION:** Coenzyme Q10 is available as a

dietary supplement in the United States under the Dietary Supplements Health and Education Act of 1994 (DSHEA).

- **COMPARATIVE EFFICACY:** Not available.
- **LITERATURE REPORTS:** The ability of oral coenzyme Q10 to protect the ischemic myocardium is suggested in small double-blind studies involving patients with stable angina pectoris (Mortensen, 1993; Greenberg & Frishman, 1990; Kamikawa et al, 1985). With doses of 150 to 600 milligrams daily, coenzyme Q10, compared to placebo, has significantly prolonged exercise duration and reduced exercise-induced ischemic ST-segment depression. However, angina symptoms and nitroglycerin consumption were not reduced significantly in one study (Kamikawa et al, 1985). Additional larger controlled trials are required to evaluate the potential place in therapy of oral coenzyme Q10 in angina. Intravenous coenzyme Q10 (1.5 milligram/kilogram once daily for 7 days) was effective in increasing mean exercise time in chronic stable angina patients in one double-blind study. Blood pressure, heart rate, and the double-product were not altered significantly by coenzyme Q10 or placebo (Greenberg & Frishman, 1990).
- **VITAMIN E**
 - **EFFICACY:** Adult, possibly effective
 - **DOCUMENTATION:** Adult, good
 - **DOSE:**
 - Antiplatelet effects: 200 to 400 international units/day (Calzada et al, 1997; Steiner, 1993).
 - Coronary heart disease prevention: 100 to 800 international units/day (Kushi et al, 1996; Azen et al, 1996; Stephens et al, 1996; Takamatsu et al, 1995; Rimm et al, 1993; Stampfer et al, 1993).
 - **PRECAUTIONS:** bleeding time should be monitored in patients with blood clotting disorders or those taking anticoagulant medication (Kappus & Diplock, 1992).
 - **ADVERSE EFFECTS:** Vitamin E had no effect on hemostasis in two studies. High doses of vitamin E (800 IU to 900 IU daily) had no effect on bleeding time, prothrombin time, or other biochemical parameters associated with bleeding (Meydani et al, 1998; Kitagawa & Mino, 1989). Vitamin E (tocopherol) has been implicated in the development of thrombophlebitis and pulmonary embolism (Roberts, 1979; Roberts, 1981). These effects are controversial since prior literature has proposed that Vitamin E be used for the prevention of

thromboembolic disease (Kanofsky & Kanofsky, 1981). A severe inflammatory response occurred in 3 patients using topical Vitamin E after chemical peel or dermabrasion of the face (Hunter & Frumkin, 1991). The Vitamin E and vitamin A in a cosmetic cream were thought responsible for eczematous lesions experienced by a 19-year-old woman (Bazzano et al, 1996).

- **INTERACTIONS:** Vitamin E has been shown to enhance the response to oral anticoagulants, perhaps due to an interference with the effect of vitamin K in clotting factor synthesis (Hansten, 1981; Hansten & Horn, 1989; Anon, 1982; Corrigan & Ulfers, 1981). Concomitant administration of cholestyramine resin and fat-soluble vitamins may cause malabsorption of these vitamins (Prod Info Questran®, 1989). Although colestipol may interfere with absorption of fat-soluble vitamins, several studies have demonstrated only minor decreases in vitamin A and vitamin E concentrations during colestipol therapy (Probstfield et al, 1985; Schlierf et al, 1985; Anon, 1980; Schwarz et al, 1980).
- **REGULATORY/SAFETY INFORMATION:** U.S. Food and Drug Administration Pregnancy Category A (Briggs et al, 1998). Vitamin E is available in the United States as a dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA)
- **COMPARATIVE EFFICACY:** Under certain circumstances, synthetic vitamin E (dl-alpha tocopherol, all-rac-alpha tocopherol) may be inferior to natural vitamin E (d-alpha tocopherol, RRR-alpha tocopherol). Natural vitamin E may have up to 2 times the bioavailability of synthetic at therapeutic dosages, though potency labeling standards assume only a 36% advantage of natural vitamin E (Acuff et al, 1994). The addition of vitamin E to aspirin therapy reduced the incidence of ischemic cerebrovascular events among patients with a history of transient ischemic attacks (TIAs). One hundred TIA patients randomly received either aspirin 325 milligrams per day plus placebo or aspirin plus vitamin E 400 international units daily in a double-blind fashion. After 2 years, the aspirin-only group had experienced 6 ischemic attacks and 2 recurrent TIAs while the combination treatment group experienced 1 ischemic attack and 1 recurrent TIA (p less than 0.05). There was no difference in incidence of hemorrhagic events (Steiner et al, 1995).
- **LITERATURE REPORTS:** Vitamin E is extremely versatile in both preventive and therapeutic applications, though rarely is it used alone. In prevention, vitamin E may be the most important nutrient supplement, as apparently effective doses are quite beyond maximum dietary intake. Evidence exists for the positive influence of vitamin E on the pathogenesis and incidence of coronary heart disease and ischemic cerebrovascular events (in conjunction with aspirin). The European WHO/MONICA study found hypertension, hyperlipidemia, and smoking explained only 20% of the marked differences in CAD mortality. A 7-

fold intergroup variation in mortality from CAD was found in the analysis of 16 European population groups encompassing 1,954 persons. Low vitamin E blood levels emerged 62% predictive of mortality from CAD ($p=0.003$); elevated cholesterol data was 17 % predictive ($p=0.03$); low vit A levels, 4% ($p=0.05$); and diastolic blood pressure 4% ($p=0.05$) (Gey et al, 1991).

Vitamin E appears to act through several mechanisms, including antioxidant, immunomodulation, and antiplatelet effects. It appears to act as an anti-oxidant within membranes preventing propagated oxidation of unsaturated fatty acids (Spielberg et al, 1979). It is possible vitamin E reduces atherosclerosis and subsequent coronary heart disease by preventing oxidative changes to low-density lipoproteins (LDL) (Fuller et al, 1996; Simons et al, 1996; Wander et al, 1996; Rimm et al, 1993; Stampfer et al, 1993). Thromboembolic disease may be prevented with vitamin E supplementation (Calzada et al, 1997; Steiner, 1993).

ery large studies in women (Kushi et al, 1996; Stampfer et al, 1993) and in men (Rimm et al, 1993) show that groups with higher intakes of vitamin E (from diet and supplements) have lower risk for major coronary disease than those with lower intakes. Vitamin E administration at 200 international units (IU) daily for 2 weeks has resulted in reduction of platelet adhesion by 44% to 75%. After an additional 2 weeks at a dose of 400 IU, platelet adhesion reduction was 77% to 82% (Steiner, 1993; Jandak et al, 1989).

The effects of vitamin E on platelet adhesion appear to be independent of the effects of aspirin on platelet aggregation (Steiner et al, 1995). Gamma-tocopherol and alpha-tocopherol both function as antioxidants but by different mechanisms. Both may be necessary for maximum protection against heart disease. Some alpha-tocopherol supplementation studies have failed to show a protective effect; however, in at least one (Kushi et al, 1996), a protective effect was found for dietary vitamin E but not for supplemental vitamin E. Gamma-tocopherol is the principal form of tocopherol in the diet, whereas alpha is the most common form in supplements. Gamma-tocopherol may be more effective protection against certain types of lipid peroxidation. Taking supplements that are predominantly alpha-tocopherol can displace gamma-tocopherol and may not be advisable (Christen et al, 1997).

- **FOLIC ACID**

- EFFICACY: Adult, effective
- DOCUMENTATION Adult, excellent
- DOSE: Adult, hyperhomocysteinemia: 500 to 5000 micrograms daily (Anon, 1998a).

- **PRECAUTIONS:** Pernicious anemia and megaloblastic anemia caused by vitamin B12 deficiency is a contraindication. Folic acid doses above 0.1 milligram per day may obscure vitamin B12 deficiency; hematologic remission may occur while the neurologic symptoms progress (Prod Info Folic acid tablets, USP(R), 1995).
- **ADVERSE EFFECTS:** Folic acid therapy corrects the anemia associated with vitamin B12 malabsorption but does not prevent the neurological deterioration which may develop (Dickinson, 1995). Gastrointestinal disturbances following oral doses of 5 milligrams three times daily have been reported and include nausea, abdominal distention, discomfort, flatulence, and a constant bad or bitter taste in the mouth (Prod Info Folic acid tablets(R),1995; Hunter et al, 1970). Folic acid has been implicated with zinc depletion. Healthy volunteers receiving folic acid between 400 to 500 micrograms/kilogram/day demonstrated plasma zinc level decreases. Folic acid is believed to interfere with zinc absorption (Kakar & Henderson, 1985). The weight of current evidence suggests that up to 5 to 15 milligrams daily of folic acid does not have significant adverse effects on zinc status in healthy, nonpregnant individuals (Butterworth & Tamura, 1989).
- **INTERACTIONS:** Concurrent use of folic acid and phenytoin has resulted in increased seizure frequency and decreased phenytoin levels in some patients (Berg et al, 1983a; Baylis et al, 1971).
- **REGULATORY/SAFETY INFORMATION:** U.S. Food and Drug Administration's Pregnancy Category A if administered in doses below 0.8 milligram/day (mg/d) or Category C if doses higher than 0.8 mg/d (Briggs et al, 1998). Folic acid is available in the United States as a dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Not available.
- **LITERATURE REPORTS:** The efficacy of folic acid for hyperhomocysteinemia is very well documented. Studies have looked at the efficacy of folic acid alone and folic acid in combination with other B vitamins. The most potent effect appears to be from folic acid in combination with vitamin B12. Plasma total homocysteine levels are a strong predictor of mortality in patients with coronary artery disease (CAD) (Nygard et al, 1997), although the mechanism of how homocysteine affects the development of CAD is not known. Neither is it known whether lowering serum homocysteine influences mortality from CAD. Hyperhomocysteinemia may also be involved in the development of premature and/or recurrent venous thromboembolic disease (D'Angelo et al, 1997).

A meta-analysis of 12 trials examining the effects of supplemental folic acid on blood homocysteine levels showed that supplements of 0.5 to 5 milligrams (mg) folic acid could be expected to reduce blood homocysteine by a quarter to a third.

Absolute and proportional reductions were greatest in persons with high pretreatment homocysteine and low pretreatment folic acid. Addition of vitamin B12 reduced blood homocysteine by another 7%. Vitamin B6 did not lower homocysteine any further. The average concentration of blood homocysteine in Western populations is 12 micromoles/liter (Anon, 1998).

The progression of carotid plaque was prevented with supplements of folic acid and vitamins B6 and B12 in an open, uncontrolled study of hyperhomocysteinemic patients. Subjects (n=38) averaged 57.9 years of age, most had histories of one or more cardiovascular risk factors, and all qualified for vitamin treatment by unexplained progression of atherosclerosis and plasma homocysteine levels above 14 micromoles/liter. Vitamin therapy consisted of folic acid 5 milligrams daily for patients treated from 1994 to 1996; more recently patients received folic acid 2.5 milligrams, vitamin B12 250 micrograms, and pyridoxine 25 milligrams daily. Mean follow-up was 4.4 years during which average progression was positive before vitamin treatment and slightly negative thereafter (Peterson & Spence 1998).

A meta-analysis was conducted to assess folic acid and vitamin B12 supplementation on blood homocysteine concentrations. Data was collected on 1114 patients in twelve trials. The study found a 25% reduction in blood homocysteine concentrations with dietary folic acid and similar effects in the range of folic acid 0.5 to 5 milligrams (mg) daily. The study concluded that daily folic acid (0.5 to 5 mg) and vitamin B12 (0.5 mg) might reduce blood homocysteine concentrations 25%-33% (Anon, 1998). A cohort study assessed folate and vitamin B6 in relation to coronary heart disease (CHD). A total of 939 cases of coronary disease was studied using dietary and supplement questionnaires and risk factor analysis. Risk of CHD was decreased in those that used multiple vitamins, which provided the main source of vitamin B6 and folate. The study concluded that folate and vitamin B6 above recommended daily allowance may be important in prevention of CHD (Rimm et al, 1998).

- **MAGNESIUM**

- **EFFICACY:** Adult, possibly effective
- **DOCUMENTATION:** Adult, good
- **DOSE:** 200 to 400 milligrams three times a day (Murray & Pizzorno, 1998).
- **PRECAUTIONS:** Contraindications include heart block (Gilman et al, 1990), severe renal disease (Gilman et al, 1990), and toxemia in the 2 hours preceding delivery (Anon, 2000). Precautionary use is recommended in impaired renal function. There are a few studies that indicated that baseline doses of Magnesium increased risk of myocardial infarction (Galloe et al, 1993; Elwood et al, 1992)

- **ADVERSE EFFECTS:** Infusion of magnesium sulfate during labor as convulsion prophylaxis in 9 preeclamptic women resulted in greatly increased bleeding times. The regimen was referred to as the "standard convulsion prophylaxis treatment." Bleeding times were measured ante partum and immediately after discontinuation of the infusion, usually 12 to 24 hours postpartum. The average increase in bleeding time was 164 percent. In the one woman whose bleeding time was measured 5 hours after discontinuation of infusion, there was no difference in the ante and post partum measurements. Three control preeclamptic women (no magnesium infusion) showed no change in bleeding time. Adverse consequences were not discussed (Kynczl-Leisure & Cibils, 1996). A case of Wernicke's encephalopathy has been reported from magnesium depletion. An 85-year-old woman had been taking 40 milligrams of co-amilofruse for 3 years. Diuretics can cause magnesium depletion and was suspected of provoking Wernicke's encephalopathy. She was given 500 milligrams chelated magnesium daily and her symptoms of cogwheel rigidity, grasping reflexes, and tetany subsided in 4 weeks. Improvement was observed in her Korsokoff amnesia (McLean & Manchip, 1999). Excess magnesium, by direct action on blood vessels and by ganglionic blockade causes vasodilation (Prod Info Magnesium Sulfate, 1995). Cardiac toxicity progresses with increasing serum magnesium levels. Conduction time is increased with lengthened P-R and QRS intervals, the rate of S-A nodal impulse formation is decreased, and cardiac arrest in diastole may develop (Gilman et al, 1990). An intravenous bolus of magnesium sulfate 4 grams, used to prevent eclampsia, caused cardiopulmonary arrest in a 21-year-old woman (Richards et al, 1985). Although the patient was resuscitated and a normal infant was delivered, the patient died as a result of cerebral hypoxia. Magnesium used to treat eclampsia was associated with profound hypotension in 2 women. In one of the patients the serum magnesium was not above what is normally considered to be toxic; the magnesium level was not measured in the other case. Both women were hypovolemic at the time of hypotension which probably contributed to the hypotension. Blood pressure returned to normal after discontinuation of magnesium and intravenous fluids (Bourgeois et al, 1986). Hypotension has been reported with oral magnesium citrate and a ureteral irrigation with a product containing magnesium (Renacidin(R)) (Fassler et al, 1985). Magnesium in high doses decreases neurotransmitter release (Dukes, 1981), thus producing a peripheral neuromuscular blockade (Gilman et al, 1990; Dukes, 1981). Magnesium trisilicate is known to absorb large quantities of thiamine which has led to beri-beri and subsequent heart failure (Dukes, 1981). Magnesium sulfate administration for the treatment of preterm labor was associated with a maternal hypothermia in a 30-year-old woman as well as fetal and maternal bradycardia (Rodis et al, 1987). Two cases of sustained hyperkalemia (7.2 milliequivalents/liter (mEq/L) associated with intravenous magnesium sulfate therapy for eclampsia have been reported (Spital & Greenwell, 1991). Magnesium salts are reported to cause diarrhea (Dukes, 1980b). Paralytic ileus is a rare

complication of magnesium sulfate when used as a tocolytic (Hill et al, 1985). Infusions of magnesium sulfate for tocolysis has also caused neonatal meconium-plug syndrome and ileus in infants after delivery. A 35-year-old man treated with magnesium oxide 0.38% irrigations (100 milliliters/hour) for a period of 2 weeks for the dissolution of urinary calculi developed deep respiratory depression with 6 breaths/minute and a serum level of 13 milliequivalents/liter. Irrigations were discontinued and respiration and magnesium serum levels returned to normal (Dukes, 1980a). Two cases of acute maternal pulmonary edema have been reported after concomitant administration of betamethasone and magnesium sulfate (Dukes, 1981). A fixed drug eruption was caused by magnesium trisilicate in a 50-year-old woman (Sehgal et al, 1986). It was not determined which component of the preparation caused the eruption. Intravenous magnesium sulfate caused urticaria in 2 women being treated for preterm labor. The eruption appeared 30 minutes after initiating intravenous therapy in both patients. The magnesium was stopped in both cases because of the rash (Thorp et al, 1989). A 35-year-old woman with a triplet pregnancy developed osteoporosis after undergoing magnesium sulfate tocolysis and bed rest for the last 65 days before delivery (Levav et al, 1998). Rickets in the newborn may result from prolonged magnesium sulfate administration in the second trimester of pregnancy (Lamm et al, 1988).

- **INTERACTIONS:** Concomitant magnesium sulfate and aminoglycosides can produce neuromuscular weakness and possibly paralysis (L'Hommedieu et al, 1983; Watson et al, 1983). Some medications, including magnesium salts, lithium, local anesthetics, procainamide, and quinidine, may enhance the neuromuscular blocking effect of cisatracurium (Prod Info Nimbex(R), 1998). Dose adjustments of cisatracurium may be needed when these agents are being used. When used to retard premature labor, concomitant nifedipine and magnesium has been reported to cause exacerbated hypotensive and neuromuscular blockade effects. Although not reported for felodipine, a similar interaction may occur with felodipine and magnesium (Snyder & Capewell, 1989; Waisman et al, 1988). Dosing of 5 milligrams (mg) glipizide with 850 mg magnesium hydroxide led to more rapid absorption of glipizide (AUC in first half hour increased 180% and within first hour by 69%) (Kivisto & Neuvonen, 1991). Concomitant administration of oral magnesium hydroxide 85 to 1700 milligrams (mg) (Milk of Magnesia(R)) with oral mefenamic acid 500 mg resulted in an increased rate of absorption for mefenamic acid in healthy volunteers (Neuvonen & Kivisto, 1988). The absorption of tolfenamic acid was also accelerated when given with Milk of Magnesia(R) in a dose-related fashion. Norfloxacin bioavailability (as measured by 24-hour urinary excretion) was reduced between 50% to 90% by coadministration with iron, zinc, aluminum, or magnesium-containing over-the-counter medications (Campbell et al, 1992). Concomitant intravenous therapy with magnesium sulfate and ritodrine was associated with significantly greater cardiovascular toxicity than ritodrine alone in a study that

used the drugs for tocolysis during preterm labor (Prod Info Yutopar(R), 1996; Ferguson et al, 1984). Coadministration of high-dose magnesium and rocuronium has been reported to result in prolongation of neuromuscular blockade in single case report (Gaiser & Seem, 1996). Concomitant magnesium sulfate and succinylcholine therapy has been reported to result in excessive neuromuscular blockade (Aldrete et al, 1970; Ghoneim & Long, 1970; Morris & Giesecke, 1968). The combination of magnesium sulfate and succinylcholine should be used cautiously (Hansten & Horn, 1990). Magnesium sulfate prolonged the neuromuscular blockade induced by vecuronium in a 40-year-old female undergoing a cesarean section (Sinatra et al, 1985).

- REGULATORY/SAFETY INFORMATION: FDA Category A (Prod Info Magnesium Sulfate, 1995) and Category B (Briggs et al, 1998). Magnesium is available as both a drug and dietary supplement in the United States under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- COMPARATIVE EFFICACY: Magnesium infusions were compared to verapamil infusions in a randomized trial of patients with supraventricular arrhythmias (atrial fibrillation, atrial flutter or paroxysmal supraventricular tachycardias) (Gullestad, 1993). Magnesium was significantly better in converting patients to sinus rhythm at 4 hours, but the two treatments were equal in efficacy at 24 hours. No major adverse effects were observed in the magnesium group while six patients were withdrawn from verapamil due to worsened heart failure or hypotension (Gullestad, 1993). In a prospective, randomized study involving 42 patients with atrial tachyarrhythmias, intravenous magnesium sulfate (37 milligrams/kilogram (mg/kg) bolus followed by 25 mg/kg/hour (hr) infusion) was more effective than intravenous amiodarone (5 mg/kg bolus followed by 10 mg/kg/24 hr infusion) in the conversion of acute atrial tachyarrhythmias to sinus rhythm (Moran et al, 1995).
- LITERATURE REPORTS: Variant angina is associated with magnesium deficiency (Satake et al, 1996). Magnesium supplementation suppresses exercise-induced angina but not stable angina (Kugiyama et al, 1988).

Intravenous injection of magnesium has been found to be effective in the treatment of many types of cardiac arrhythmias, including multifocal atrial tachycardia, ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia. These were due to the presence of a reentrant circuit located in the atrioventricular node (Iseri, 1990; Wesley et al, 1989; Iseri et al, 1985) or chronic cardiac ischemia (Perticone et al, 1990).

In 665 men, those subsequently experiencing a cardiovascular event had daily magnesium intakes at baseline, based on 7-day weighed duplicate diet records, which were 12 percent below (36 milligrams less) those not having an event (95%

CI 2.0-69.1) (Elwood et al, 1992). One double-blind study found that those assigned to take 365 mg of magnesium daily after myocardial infarction had a 55 percent higher occurrence of another myocardial event within a year compared to those on a placebo (p=0.02) (Galloe et al, 1993).

- **NIACIN**

- **EFFICACY:** Adult, effective
- **DOCUMENTATION:** Adult, excellent
- **DOSE:**
 - Hyperlipoproteinemia including hypercholesterolemia: Begin with an oral dose of 100 milligrams given three times daily which is gradually increased to an average dose of 1 gram three times daily with a maximum dose of 6 grams (Prod info Nicolar(R), 1996; Cohen & Morgan, 1988; Hoeg et al, 1986; Schaefer & Levy, 1985).
 - Hyperlipidemias, extended release tablets: Dosing begins with one 375-milligram tablet at bedtime and is increased no more than 500 milligrams per 4-week period, to a maximum of 2000 milligrams, given as 2 1000-milligram tablets at bedtime (Prod Info Niaspan(R), 1997).
- **PRECAUTIONS:** Hypersensitivity to niacin or any component Active liver disease (Britton et al, 1997; Patterson et al, 1983) Taking niacin with meals has been suggested to alleviate gastrointestinal side effects (Figge et al, 1988; Anon, 1985). Inositol hexaniacinate yields slightly better results than standard niacin and it is believed to be safer and much better tolerated, with a negligible incidence of bothersome skin flushes which occur about 30 minutes after ingestion of plain niacin (Sunderland et al, 1988; El-Enein et al, 1983; Welsh & Ede, 1961).
- **ADVERSE EFFECTS:** Glucose tolerance in diabetic patients may be worsened by niacin therapy (Crouse, 1996). Increases in aspartate aminotransferase and alkaline phosphatase which are dose related may occur; however, severe hepatotoxicity is rare (Prod Info Niaspan(R), 1997; Figge et al, 1988). 2. Sustained-release niacin has been associated with a greater degree of hepatotoxicity than has immediate-release niacin (Crouse, 1996).
- **INTERACTIONS:** The risk of myopathy is increased when lipid-lowering doses of niacin (greater than 1 gram daily) are administered concurrently with HMG-CoA reductase inhibitors such as cerivastatin. Caution is warranted if concurrent administration is deemed necessary (Prod Info Baycol(TM), 1997). The concurrent use of lovastatin and niacin in lipid- lowering doses (greater than 1 gram daily) has resulted in reversible myopathy and rhabdomyolysis (Prod Info

Mevacor(R), 1996; Cooke, 1994; Reaven & Witztum, 1988; Norman et al, 1988; Malloy et al, 1987). The incidence of myopathy which occurred during coadministration of lovastatin and niacin was 2% in early clinical studies (Prod Info Mevacor(R), 1996). However, two short-term studies have found that the combination of low-dose lovastatin plus niacin resulted in no reports of myopathy or rhabdomyolysis (Gardner et al, 1996; Vacek et al, 1995).

- **REGULATORY/SAFETY INFORMATION:** Niacin is available in the United States as a dietary supplement under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Acipimox is as effective as niacin in the treatment of hyperlipoproteinemia. Tornvall & Walldius, 1991). Clofibrate was equally effective in the treatment of type III hyperlipoproteinemia (Hoogwerf et al, 1984).
- **LITERATURE REPORTS:** The combination of pravastatin and nicotinic acid produced the greatest reduction in total cholesterol (T-C) and low-density-lipoprotein cholesterol (LDL-C) and the greatest increase in high density lipoprotein cholesterol (HDL-C) in patients with coronary heart disease (Pasternak et al, 1996; Guyton, 1998; Cashin-Hemphill et al, 1990). Niacin has proven effective, both alone and in combination with other pharmacologic agents, in reducing very low-density and low-density lipoprotein levels, while concurrently increasing high-density lipoprotein levels (Grundy, 1990a; Figge et al, 1988; Stamler, 1983).
- **FISH OILS (EICOSAPENTAENOIC ACID [EPA] and DOCOSAHEXAENOIC ACID [DHA])**
 - **EFFICACY:** Adult, possibly effective
 - **DOCUMENTATION:** Adult, good
 - **DOSE:**
 - Hyperlipidemia, oil: 6 grams daily, 1.8 to 18 grams/day of EPA alone or combined with up to 2.2 grams/day of DHA (Bonaa et al, 1992; Sanders et al, 1981a).
 - Platelet aggregation inhibition: EPA plus DHA: 2790 milligrams (mg) and 1698 mg, respectively (Tremoli et al, 1990). 2 to 11 grams daily (Li & Steiner, 1991; Thorngren & Gustafson, 1981; Siess et al, 1980).
 - Several studies have used 6 to 18 grams of MaxEPA(R) (a combined fish oil product) daily (Donadio, 1991).
 - Two servings of cold water fish per week should be considered as an

alternative to supplementation. Still, this may not be enough EPA to attain clinical results. A fish oil supplement that contains 350 to 700 milligrams of EPA is recommended for therapeutic purposes.

- **PRECAUTIONS:** Patients with bleeding disorders should be monitored (Goodnight, 1989). Use with caution in diabetes (Horrobin, 1991; Glauber et al, 1988). Commercial fish oil preparations are now available but these products may be potentially hazardous to consumers. Since these products are extracted from the liver and fatty tissues of fish which are possibly contaminated with pesticides and other dangerous substances (Anon, 1986).
- **ADVERSE EFFECTS:** Ingestion of large amounts of fish oils over a prolonged period of time may increase risk of mild bleeding resulting in nosebleeds and bruising. Platelet count may also decrease (Goodnight, 1989; Anon, 1987). Thrombocytopenia has been reported in some cases with increased doses of fish oils (Owens & Cave, 1990). Significant increases in packed cell volume, erythrocytes, hemoglobin, as well as increases in leukocytes and monocytes were found during treatment with fish oil (Sanders & Hinds, 1992). Studies in young infants suggest that excess doses of polyunsaturated fatty acids may, unless there is tocopherol supplementation, increase erythrocyte hemolysis (Takahata et al, 1998). While most patient's triglycerides and cholesterol levels are lowered while maintaining high density lipoprotein cholesterol (HDL), in some patients HDL is lowered and low density lipoprotein cholesterol is not, resulting in an increased LDL/HDL ratio and a potential cardiac risk (Phillipson et al, 1985; Yetiv, 1988). Some hyperlipidemic patients may actually have blood cholesterol levels increased (Horrobin, 1991). Two patients reported fatigue and somnolence during the first week of study on fish oil treatment of multiple sclerosis (Cendrowski, 1986). Severe drowsiness and an inability to arise in the morning occurred in 2 of 100 patients taking 780 milligrams/day (mg/day) of eicosapentaenoic acid and 480 mg/day of docosahexaenoic acid. The symptom was reproducible (Mehta, 1992). Some type II diabetic patients using fish oil had increased blood glucose, decreased plasma insulin, (Glauber et al, 1988; Kasim et al, 1988) and lowered glucose tolerance (Horrobin, 1991). Large doses of some fish oils, for example cod liver oil, may produce vitamin A and D toxicity (Baird & Hough, 1987). Decreased levels of vitamin E have been reported with large doses (Ruiter et al, 1978; Gudbjarnason & Hallgrimsson, 1976). Plasma tocopherol levels fell following treatment with fish oil, and rose again after the treatment was terminated (Sanders & Hinds, 1992). Animal studies suggest that large doses of fish oils may increase oxidative tissue damage, especially in the elderly (Takahata et al, 1998). Patients with x-linked retinitis (n=46) did not show a reduction in biological antioxidant activity following administration of 400 milligrams/day of DHA compared to a corn/soy oil placebo (Hoffman et al, 1999). Investigations evaluating the effects of fish oil on lipids and coronary heart disease have revealed side effects including diarrhea (in patients taking 4 to 6 capsules per day)

(Anon, 1987). Side effects in one small study of ten patients included nausea, increased belching, fishy aftertaste in one patient, and abdominal bloating in another (Salomon et al, 1990). Abdominal pain symptoms that mimicked symptoms of peptic ulcer occurred in 1 of 100 patients taking 780 milligrams of eicosapentaenoic acid and 480 mg docosahexaenoic acid daily. The symptom was reproducible (Mehta, 1992). Severe abdominal distention occurred in 1 of 100 patients taking 780 milligrams daily of eicosapentaenoic acid and 480 mg of docosahexaenoic acid. The symptom was reproducible (Mehta, 1992). A significant increase in renal clearance and an associated decrease in renal vascular resistance were noted in 10 healthy adults who were given 3.6 grams/day of eicosapentaenoic acid and 2.4 grams/day of DHA for 6 weeks (Dusing et al, 1990). Some initial irritation and a burning sensation were observed in patients using fish oils topically for the treatment of psoriasis. The topically administered oils had an unpleasant smell (Escobar et al, 1992). An urticarial rash occurred in 1 of 100 patients taking 780 milligrams/day (mg/day) of eicosapentaenoic acid and 480 mg/day of docosahexaenoic acid. The symptom was reproducible (Mehta, 1992). Three case reports of patients with familial adenomatous polyposis and multiple colorectal polyps developed cancerous lesions during a long-term trial of DHA up to 2.2 grams daily and eicosapentaenoic acid up to 0.6 gram daily (Akedo et al, 1998).

- **INTERACTIONS:** No additional hemorrhagic effect was noted when fish oil and aspirin were combined (Dehmer et al, 1988; Van den Berg et al, 1987). DHA administered with olive oil resulted in decreased anti-inflammatory activity (James et al, 1991; Cleland et al, 1990; Garg et al, 1988).
- **REGULATORY/SAFETY INFORMATION:** Fish oils and essential fatty acids are available in the United States as dietary supplements under the Dietary Supplements Health and Education Act of 1994 (DSHEA).
- **COMPARATIVE EFFICACY:** Although they have similar effects, eicosapentaenoic acid (EPA) appears to be more potent and its mechanism of action is different than docosahexaenoic acid (DHA) (Hirai et al, 1987). A combination therapy with EPA and ticlopidine was most effective in preventing platelet aggregation. A group of 10 patients with stable angina (no aspirin or cyclooxygenase inhibitors in the past 10 days) were randomized to receive either 1.8 grams EPA or 500 milligrams of ticlopidine daily for 4 weeks. After a 10-day wash-out period, all patients were given therapy with both drugs simultaneously. Ticlopidine significantly reduced platelet aggregation induced by collagen or ADP and had no effect on arachidonate metabolism. EPA altered thromboxane A₂ formation (but did not inhibit it totally) and did not alter platelet aggregation responses to ADP and collagen (Davi et al, 1990).
- **LITERATURE REPORTS:** Fish oils may exert a positive effect in preventing

coronary disease through their lipid lowering and antithrombotic activities (Schneider & Wehmeier, 1988; Skuladottir et al, 1990). Fish oils are effective in reducing triglycerides and decreasing the cholesterol/HDL cholesterol ratio (Carroll, 1986).

The effects of fish oils on total and low density lipoprotein cholesterol have been variable. Patients with serum triglycerides greater than 5.64 millimoles/liter (mmol/L) and cholesterol levels greater than 7.75 mmol/L who are refractory to dietary treatment, may benefit from medically supervised fish oil treatment (Yetiv, 1988).

EPA appears to be significantly more potent in reducing triglycerides than DHA (Rambjor et al, 1996; Conquer & Holub, 1996; Hawthorne et al, 1989). Serum concentrations of triglycerides, apolipoprotein B, apolipoprotein AI, and lipoprotein(a) did not change in a randomized, double-blind, placebo-controlled cross-over study of 14 patients with familial hypertension receiving 5.1 grams of the ethyl esters of EPA and DHA daily (Balestrieri et al, 1996) .

Complementary Therapies

Acupuncture has been shown to help relax the myocardium and improve circulation (Cau et al, 1990; Chau et al, 1999).

Chelation therapy using intravenous EDTA has been used for many years to treat CAD. Despite many claims of benefit, adequate research that convincingly documents efficacy is lacking (Elihu et al, 1998; Grier & Meyers, 1993).

Relaxation techniques, yoga, and stress management techniques are indispensable for patients with CAD (Blanchard & Miller, 1977) and for reducing the risk of recurrent cardiac complications (Blumenthal et al, 1997). An attitude of hostility has been strongly associated with a higher incidence of cardiac events (Mendes de Leon et al, 1991) and cynical distrust with accelerated progression of carotid atherosclerosis (Matthews et al, 1998).

Meditation improves exercise tolerance and decreases electrical changes associated with poor circulation to the heart (Zamarra et al, 1996). Meditation has also been shown to lower cholesterol (Cooper & Aygen, 1978) and reverse carotid artery atherosclerotic intima-medial thickening (Castillo-Richmond et al, 2000). Poorly controlled stress may have an adverse effect on blood lipids (Stoney et al, 1999; Agarwal et al, 1997).

Wellness Recommendations

Several other factors may be helpful in an integrative approach to CAD prevention and treatment. A vegetarian diet reduces the risk of CAD (Appleby et al, 1999) and may even reverse existing CAD when combined with other lifestyle changes (Ornish et al, 1998). A Mediterranean diet that uses olive oil can reduce the risk of CAD (Massaro et al, 1999; Visioli et al, 1998).

There are other herbs that may be useful for patients with CAD. They are included here in addition to or rather than above due to limited research available. Bilberry has antioxidant properties that reduce oxidation of LDL cholesterol (Laplaud et al, 1997). Curcumin has antioxidant properties (Quiles et al, 1998) and decreases the proliferation of smooth muscle factors in blood vessels (Chen & Huang, 1998) that can lead to atherosclerosis formation. Fenugreek lowers cholesterol levels (Bordia et al, 1997; Stark & Madar, 1993; Sharma et al, 1990), especially in conjunction with diabetes. Ginger can reduce cholesterol levels (Bhandari et al, 1998) and also has anti-coagulant properties at a dose of 10 grams per day (Bordia et al, 1997)

Ginkgo biloba has antioxidant properties (Clostre, 1999), can reduce anxiety (Hasenohrl et al, 1996; Satyan et al, 1998), improve symptoms of angina (Chen et al, 1996) and decrease coagulation at a dose of 240 milligrams per day (Witte et al, 1992). Grape juice may also help decrease coagulation (Osman et al, 1998). Chondroitin sulfate may have a role in preventing atheromatous plaque formation (Kruse et al, 1996; Laurora et al, 1993). Flavonoids, which are present in many yellow/orange fruits and vegetables, appear to reduce the risk of developing CAD (Hertog et al, 1993; Hertog et al, 1995; Knekt et al, 1996). Pantethine, the stable form of pantothenic acid (vitamin B5) has been shown to have significant lipid-lowering activity (Donati et al, 1989; Hiramatsu et al, 1981). Doses of pantethine typically range from 500 to 1,000 milligrams daily. Resveratrol, which is found concentrated in grape skins, decreases smooth muscle proliferation and contraction in blood vessels (Chen & Pace-Asciak, 1996; El-Mowafy & White, 1999; Jager et al, 1999). Resveratrol also seems to reduce damage associated with impaired circulation (Das et al, 1999). In addition to the use of garlic preparations, garlic consumption as a food should be encouraged (despite its odor) in patients with high cholesterol levels and high blood pressure.

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