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MANAGEMENT OF HYPERLIPIDEMIA

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DESCRIPTION

Coronary heart disease (CHD) is the one of the most prevalent diseases in the US. It is also one of the most preventable. This lesson explores the treatment of CHD through changes in lifestyle, dietary modifications, and the use of botanicals and dietary supplements.

OBJECTIVES

Upon completion of this article, participants will be able to do the following:

1. Discuss the role of lipoproteins, triglycerides, and homocysteines in CHD.
2. Examine the effect of lifestyle and diet on cholesterol levels.
3. Identify dietary supplements and botanicals that have shown efficacy in reducing risk-factors for CHD, and explain their mechanism of action, benefits, and side-effects.

Atherosclerosis is the major cause of coronary heart disease and one of the leading causes of death in the United States. While genetic variables contribute to the development of the disease in some individuals, the real tragedy is the fact that many deaths could be prevented by eating a low fat diet, exercising regularly, not smoking and maintaining a healthy body weight. New medical research is evaluating the interplay between plaque formation in atherosclerosis and inflammation with new evidence suggesting that C-reactive protein—a marker for inflammation—may be of primary importance in evaluating risks in heart disease. This section will focus primarily on the use of therapeutic lifestyle changes and the current state of evidence for diet, botanicals, and nutritional supplements that are commonly used for the prevention and treatment of coronary heart disease (CHD).

LIPIDS

Cholesterol and triglycerides comprise the major plasma lipids found in the body and are essential for human health. Cholesterol can be synthesized by the liver or absorbed through the intestine from dietary sources. It is an important component of cell membranes and serves as a precursor to bile acids and steroid hormones. Since lipids are not water-soluble, they must be transported in the blood in specialized complexes, called lipoproteins, which contain both lipid and specialized proteins (apolipoproteins). There are 3 major classes of lipoproteins: low density lipoproteins (LDL), high-density lipoproteins (HDL), and very low-density lipoproteins (VLDL). Another lipoprotein class, intermediate density lipoprotein (IDL), falls somewhere between VLDL and LDL and is included in the LDL measurement.

Triglycerides are the most prevalent form of fat in the human diet. Triglycerides are esters consisting of a glycerol molecule coupled to 3 fatty acid residues of varying carbon chain lengths and degrees of saturation. Triglycerides of plant origin (most, not all) are liquid at room temperature and are termed “polyunsaturates.” Animal triglycerides are generally solid at room temperature and are termed “saturated.”

During digestion, triglycerides are hydrolyzed to form monoglycerides and fatty acids that are subsequently absorbed into the intestinal epithelium and then re-synthesized into triglycerides. Triglycerides are found in all plasma lipoproteins but are the major

lipid component of those lipoproteins with a density less than 1.019 kg/L. These include chylomicrons, chylomicron remnants, VLDL and IDL.

The Role of Low Density Lipoproteins in CHD

Accumulating evidence over the past forty years has linked elevated total cholesterol and LDL cholesterol (LDL-C), and low HDL cholesterol (HDL-C) with the development of CHD. LDL-C is the major contributor to total cholesterol concentration in humans, accounting for one-half to two-thirds of plasma cholesterol. It contains a single apolipoprotein, apo B-100 (apo B). LDL-C is thought to be the major atherogenic lipoprotein and is the primary target of cholesterol lowering drug therapy.

New guidelines have been issued for what are considered "optimal" levels of LDL-C. These recommendations can be found in the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) that was issued through the National Institutes of Health National Heart, Lung and Blood Institute in 2001.[1] Researchers have found that any LDL-C level above 100 mg/dL appears to be atherogenic. Based upon this finding, the following targets have been recommended. Values should be based upon a lipid profile drawn after a 9-12 hour fast.

ATP III Classification of LDL-C, Total and HDL–C (mg/dL)

LDL-C	
< 100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥ 190	Very high
Total Cholesterol	
< 200	Desirable
200-239	Borderline high
≥ 240	High
HDL Cholesterol	
< 40	Low
≥ 60	High

What does this all mean? The new recommendations are to be used as "guidelines." It is important to treat each individual according to his or her own personal risk. The major risk factors that should be considered, include:

- Cigarette smoking
- Low HDL cholesterol (less than 40 mg/dL)
- Age (men ≥ 45 years; women ≥ 55 years)
- Hypertension (BP ≥ 140/90, or taking antihypertensive medication)
- Family history of a male first degree relative with CHD before age 55 or a female first degree relative with CHD before age 65.

The Framingham Point Scores for Men and Women are important tools for predicting the 10-year risk of CHD for both men and women.[2] Points are given for various risk factors with the total number providing a 10-year risk for developing CHD. Determining the 10-year risk allows practitioners to determine what target should be set for each individual.

Anyone who already has existing peripheral artery disease, clinical CHD or symptomatic carotid artery disease should have a target goal of < 100 mg/dL of LDL-C. However, if one has 0-1 risk factors, than the LDL-C goal remains at <160 mg/dL, while those with 2 or more risk factors should have a target LDL-C of < 130 mg/dL.

The Role of Serum Triglycerides in CHD

Elevated triglyceride concentrations in the fasting state are of clinical importance in a number of conditions. It is well known that severely elevated triglyceride levels (>1,000 mg/dL) pose a significant risk for developing of abdominal pain and pancreatitis. However, the relationship between elevated serum triglycerides and CHD has been debated for many years. Because elevation of triglycerides often occurs in association with obesity, cigarette smoking, hypertension, and diabetes—it has been difficult to determine if it is the "triglyceride" part of this complex equation that puts individuals at increased risk of CHD. The evidence now seems clear that elevated triglycerides increase one's risk for developing CHD. Recent meta-analyses have shown that elevated trigylcerides are an independent risk factor for heart disease.[3,4] It appears that the triglyceride-rich lipoproteins associated with atherosclerosis are the remnant lipoproteins, which include VLDL and IDL.[5]

Elevation of triglycerides and low levels of HDL-C are extremely common in patients with obesity, insulin resistance and type II diabetes. The elevation of triglycerides in individuals with insulin resistance is primarily due to an overproduction, and clearance in some instances, of VLDL.[6] Moderate exercise improves insulin sensitivity and reduces triglyceride concentrations, making it an important part of the overall treatment

plan.[7] Diet, weight loss and omega-3 fatty acids should also be considered as part of a therapeutic lifestyle approach to elevated triglycerides.

Classifications of Serum Triglycerides[1]

< 150 mg/dL	Normal triglycerides
150—199 mg/dL	Borderline-high triglycerides
200—499 mg/dL	High triglycerides
≥ 500 mg/dL	Very high triglycerides

The Role of High-Density Lipoproteins in CHD

HDL-C normally makes up 20–30% of the total serum cholesterol and is often referred to as the "good" cholesterol, as high levels have been shown to be a strong, independent inverse predictor of CHD risk. As total cholesterol levels increase and HDL-C levels decrease, the incidence of myocardial infarction rises (Wilson, 1990). The good news is that for every 1% increase in HDL-C, there is a 2–3 % decrease in CHD risk .[8]

There are numerous medications that can raise HDL-C, including niacin and the fibrates. While estrogen replacement therapy increases HDL-C in postmenopausal women, this effect is modified by some progestin therapies.[9] Synthetic progestins have been shown to reverse or eliminate the beneficial effects of estrogen on lipid profiles. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, HDL-C levels were significantly higher in the conjugated equine estrogen (CEE) + micronized progesterone (MP) group compared to the CEE + medroxyprogesterone acetate (MPA) group.[10] A 1985 Swedish study included 58 postmenopausal women who received 2 mg oral estradiol daily for 3 months followed by an additional 3 month course of 2 mg estradiol daily + 10 mg MPA, 200 mg MP, or 20 mg levonorgestrel given for 20 days of each menstrual cycle. There was a significant decrease in HDL-C in the groups receiving estradiol plus MPA or levonorgestrel. No change in HDL was noted in the group receiving estradiol with MP.[11] Two other trials have shown similar results.[12,13]

The Role of Homocysteine

Homocysteine, an intermediate amino acid formed during the metabolism of methionine, has been shown to be an independent, modifiable risk factor for cardiovascular disease.[14] Plasma homocysteine is normally ≤12 µmol/L. When elevated, homocysteine can play a role in the development of cardiovascular disease. It should be duly noted that a number of patients with established coronary artery disease have relatively normal lipid values and hyperhomocystinemia (levels ≤15 mcmol/L). Researchers have noted that reductions in homocysteine levels that occurred after cardiac rehabilitation and exercise training were shown to lead to a 20% to 30% reduction in overall coronary artery disease risk.[15] Furthermore, abnormal homocysteine concentrations are prevalent in patients with diabetes[16] and obesity,[17] although its relationship with excess cardiovascular morbidity is not yet clear.

The three vitamins necessary to metabolize homocysteine are folic acid and vitamins B_6 and B_{12}. When homocysteine levels are elevated it may be due to a deficiency of folic acid, vitamin B_{12}, and to a lesser extent, vitamin B_6.[18] Vitamin B_6 is found in meat, poultry, fish, legumes, peanuts, walnuts, oats, brown rice, and whole wheat. Vitamin B_{12} is found only in animal products and supplements. Folic acid can be found in citrus fruits, tomatoes, green leafy vegetables, asparagus, broccoli, yeast, lentils, beans, eggs, beef, organ meats, whole grains, and enriched cereals.[18] The diet should provide an adequate intake of these nutrients, or if lacking, a supplement should be administered.

At this time it seems prudent to lower elevated homocysteine levels as a secondary preventative measure in patients with coronary artery disease. To measure homocysteine, total fasting plasma homocysteine levels are recommended. Levels of serum folic acid, vitamins B_6 and B_{12} and creatinine should be measured at the same time as homocysteine.

Treatment Strategies

This section will not address the use of pharmaceutical/prescription drug therapies for the treatment of hyperlipidemia. However, it is essential to recognize the important contribution the newer cholesterol-lowering medications have made in the treatment of CHD. In 1980, resins and niacin were the most commonly used lipid-lowering medications. By 1985, fibrates had caused a decline in the use of niacin and resins and by 1989; 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (HMG-CoA) statin drugs had replaced fibrates as the most heavily used lipid-lowering medications.[19] By the mid-to-latter 1990s, several landmark trials provided clear evidence that lipid-lowering therapy decreases cardiovascular events, including mortality. These studies included the Scandinavian Simvastatin Survival Study [4S], the West of Scotland Coronary Prevention Study (WOSCOPS), and the Air Force/Texas Coronary Atherosclerosis Prevention Study.

Dietary Intervention

Heart healthy diets should be considered one of the primary therapeutic lifestyle interventions for patients with any level of risk for CHD. Prevention always trumps treatment. The diet should emphasize fruits and vegetables; fat-free and low-fat dairy products; cereal and grain products; legumes and nuts; and fish, poultry, and lean meats. Eating five to seven servings of fresh fruits and vegetables can be hard for many people to obtain in this fast-food culture; however, these foods provide fiber and essential nutrients with low calories. Researchers have demonstrated that diets high in fruit and vegetable intake reduce the risk for developing heart disease, stroke, and hypertension.[20,21]

Whole grain products provide the body with complex carbohydrates, fiber and other essential nutrients. Populations that consume a diet high in grain and fiber have been shown to decrease risk of cardiovascular disease. Complex carbohydrates (bread, cereal, pasta) should be chosen over simple carbohydrates. Soluble fibers, such as pectin, oat, and psyllium, have been shown to reduce LDL-C and total cholesterol levels.

Saturated Fat and Trans-Fatty Acids

Individuals with moderate to high risk of CHD should limit their cholesterol intake to less than 200 mg/d and saturated fat should not make up more than 7% of the total daily calories. Individuals with low risk of CHD should limit their cholesterol intake to 300 mg/d and saturated fat should be limited to 10% of the total daily calories. Saturated fat is the predominant fat found in animal products (i.e., beef, pork, egg yolks, dairy products, poultry) and in coconut and palm oil. Although shellfish and eggs are high in cholesterol, they are low in saturated fat. Contrary to popular belief, studies have shown that eating shellfish and eggs does not significantly affect LDL-C levels.[22,23]

In addition to saturated fat, individuals should reduce their consumption of trans-fatty acids. Vegetable oils contain one or more double bonds between carbon atoms. When hydrogen is added to vegetable oils so that the fat becomes solid at room temperature (margarine), the hydrogens are added on in the "trans" position, or on the opposite sides of the longitudinal axis of the double bond trans-fatty acids increase LDL-C and triglycerides in the diet.[24]

Trans-fatty acids are found in baked goods, fried foods, fast foods, restaurant fare, margarine, and other products made with hydrogenated fat. In general, both saturated fat and trans-fatty acid intake should be limited to less than 10% of the total daily calories. It is essential that individuals do not substitute high-sugar, nutrient-poor, calorie-dense foods when attempting to lose weight or reduce fat in the diet.

In summary, saturated fatty acids, trans-unsaturated fatty acids are the primary food components that raise LDL-C and should be reduced in the diet, and substituted with polyunsaturated and monounsaturated fatty acids.

Monounsaturated Fats

It is well-known that in areas of the world where olive oil is used as the primary cooking oil there is less coronary heart disease. Commonly referred to as the Mediterranean diet, studies have shown that diets low in saturated fat and rich in monounsaturated fats have a beneficial effect upon endothelial function and lipid status.[25] The Mediterranean diet can be described as the dietary pattern found in the olive growing areas of the Mediterranean region, at least up until the 1960s. Generally speaking, these diets consisted not only of generous amounts of olive oil but were also rich in fruits, vegetables, complex carbohydrates, fish and moderate amounts of wine.

Monounsaturated fatty acids have been shown to reduce LDL-C, but not HDL-C, when they are substituted for saturated fat in the diet. High intakes of polyunsaturated fatty acids found in other vegetable oils have been shown to reduce HDL-C levels, about a 1% reduction for every 2% of total calories in which polyunsaturated fatty acids replace saturated or monounsaturated fatty acids.[26] When the diet is changed to provide 10% saturated, 18% monounsaturated, and 10 percent polyunsaturated fat with a total of 250 mg/d of cholesterol, HDL-C levels were not reduced.[27] Interesingly, strict vegetarians typically have been shown to have 12% lower HDL-C levels than control nonvegetarians and 7% lower values than lactovegetarians.

Soy Protein and Isoflavones

Soy is rich in isoflavones, provides a beneficial source of fiber and is naturally low in saturated fat and cholesterol. A 1995 a meta-analysis of 38 clinical trials involving soy concluded that consumption of soy protein, in place of animal protein, significantly lowers total cholesterol, LDL-C and triglycerides. No change in HDL-C was noted.[28] Recent studies have shown that 20-50 g/d of soy protein reduces LDL-C in patients with mild elevations of cholesterol who are following a low saturated fat diet.[29,30]

In October 1999, the FDA formally approved a health claim that allows foods containing 6.25 g of

soy protein per serving (assuming 4 servings, or 25 g/d soy protein) to make the claim that the food reduces the risk of heart disease on their label. (Available at: http://circ.ahajournals.org/math/ge.gif.) A more recent review concluded that soy isoflavones had no little cholesterol lowering effect and that a better understanding of the pharmacokinetics and bioavailability of individual isoflavones was needed.[32]

Fish and the Omega-3 Fatty Acids

A growing body of evidence derived from epidemiological studies and clinical trials has consistently demonstrated that fish oil has a beneficial effect upon triglycerides and reduces the risk for a variety of cardiovascular events. Clinical trials such as the Diet and Reinfarction Trial and the Indian Experiment of Infarct Survival, have demonstrated a reduction in cardiac death rates and in the incidence of cardiac symptoms in patients receiving fish oil.[33] A recent meta-analysis of 11 trials (15,806 patients) published between 1966 and 1999 concluded that omega-3 fatty acid-enriched diets reduced the risk of nonfatal myocardial infarction, fatal myocardial infarction, and sudden death in patients with coronary heart disease.[34] The American Heart Association now recommends eating at least two servings of fish per week, especially salmon.

The beneficial fatty acids found in fish oil are eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. These fatty acids exert multiple actions that have a positive affect on vascular function. These include improved endothelial function through stimulation of nitric oxide, changes in vascular tone via actions on selective ion channels, and maintenance of vascular integrity.[35] EPA has several anti-thrombotic actions, including the inhibition of platelet activating factor,[36] prostaglandin I2 and thromboxane A2, prostaglandins involved in platelet aggregation and vasoconstriction.[37] And finally, studies have shown that omega-3 fatty acids prevent neointima formation by making smooth muscle cells less responsive to TXA2 induced proliferation of smooth muscle cells.[38] All in all, adding coldwater fish to the diet seems like a wise idea for most folks. For those who don't care for the taste of fish, fish oil supplements are available on the market.

The amount of omega-3 fatty acids needed to lower serum triglycerides is approximately 1 g/d, which can easily be provided by adding fish to the diet. Administering as little as 0.21 g EPA and 0.12 g DHA per day of omega 3 fatty acids in fish oil supplements, has been shown to significantly lower serum triglycerides in hyperlipidemics.[39] A recent Cochrane systematic review that found that fish oil supplementation reduced triglycerides in patients with type-2 diabetes but also raised LDL-C, especially those on high doses of fish oil. No beneficial or adverse effects on glycemic control were noted.[40] Patients with primarily elevation of triglycerides would seem to benefit from the addition of fish oil supplementation, however, those with elevation of LDL-C and triglycerides may be better off with combination therapy. The use of dietary interventions with lipid-lowering medications may offer a superior treatment, than either treatment alone, in patients with mixed forms of hyperlipidemia.

A randomized, controlled crossover trial was conducted over a 10 month period in 120 previously untreated hypercholesterolemic men aged 35–64 years living in Finland.[41] After a 4- 6-week placebo run-in period, participants were randomly assigned to a habitual diet (n = 60) or dietary treatment group (n = 60), and each of these groups was further randomized in a double-blind crossover fashion to receive simvastatin (20 mg/d) or placebo, each for 12 weeks (n = 30 in each group). The main goals of the dietary treatment were to reduce intake of saturated and trans-fats to no more than 10% of total calories by replacing them partly with monounsaturated and polyunsaturated fats rich in omega-3 fatty acids. Dietary treatment decreased levels of total cholesterol by 7.6% (P<.001), LDL cholesterol by 10.8% (P<.001), HDL cholesterol by 4.9% (P =.01), apolipoprotein B by 5.7% (P =.003), serum insulin by 14.0% (P =.02), and alpha-tocopherol by 3.5% (P =.04). Simvastatin decreased levels of total cholesterol by 20.8%, LDL cholesterol by 29.7%, triglycerides by 13.6%, apolipoprotein B by 22.4%, alpha-tocopherol by 16.2%, beta-carotene by 19.5%, and ubiquinol-10 by 22.0% (P<.001 for all) and increased levels of HDL cholesterol by 7.0% (P<.001) and serum insulin by 13.2% (P =.005). There were no changes in glucose levels in any group. The authors concluded, "A modified Mediterranean-type diet rich in omega-3 fatty acids efficiently potentiated the cholesterol-lowering effect of simvastatin, counteracted the fasting insulin-elevating effect of simvastatin, and, unlike simvastatin, did not decrease serum levels of beta-carotene and ubiquinol-10."

Patients who have undergone organ transplant surgery often develop dyslipidemia due to the chronic administration of corticosteroids and cyclosporine medications. Dietary interventions should be recommended and supported. However, if diet is not suffi-

cient for corrected the dyslipidemia, combined treatment with low-dose pravastatin and fish oil has been shown to be more effective than pravastatin treatment alone for improving the lipid profiles after renal transplantation.[42]

A note of caution: mercury levels in fish can range from 10-1,000 parts per billion. Mercury finds its way into rivers, lakes, and oceans from coal-burning power plants and other industrial sources and is known to cause learning disabilities and developmental delays. Eat fish high in omega-3 fatty acids that are least likely to contain mercury, such as tuna and salmon. One 3-ounce serving of salmon contains approximately 1.2–1.5 grams of omega-3 fatty acids. High-mercury content fish such as king mackerel and shark should be avoided, especially by pregnant women and children.

The Role of Plant Sterols in Controlling Cholesterol

While cholesterol is the sterol of mammalian cells, phytosterols are the sterols produced by plants. While plant sterols are similar to the structure of cholesterol, they differ by possessing a methyl or ethyl group in their side chains, making them poorly absorbed. Plant derived sterols have been shown to decrease total cholesterol levels for more than 50 years. While their success as pharmaceutical agents were never fully realized due to the introduction of more powerful drugs, plant sterols have now become part of a public health strategy for maintaining healthy lipid levels by adding them to foods, such as margarine and salad dressing.

Due to their structural similarity with cholesterol, phytosterols impair intestinal absorption of cholesterol, resulting in a 10-15% reduction in LDL-C with daily intakes of 2-3 grams.[43] The ability of plant sterols to displace cholesterol from micelles in the small intestine is part of the mechanism that inhibits cholesterol absorption.[44] It appears that esterification of these sterols increases their solubility in fat and their efficacy in lowering LDL-C[45] and most products on the market today are esterified to unsaturated fatty acids (sterol esters) or saturated fat (stanol esters). Studies have shown that both products work equally well in reducing LDL-C,[46] but neither offer any reduction in triglycerides or increase in HDL-C.

Patients taking cholesterol-lowering medications may experience additional benefit when consuming phytosterol rich margarines or spreads. A recent study of 167 patients stable on statin medications for at least 3 months found a further reduction of total cholesterol by 12% at 8 weeks, compared with a reduction in the placebo group of 5% ($P < 0.0001$) and a reduction of LDL-C of 17% compared with a 7% reduction in the placebo group ($P<0.0001$).[47]

The use of phytosterol rich margarines and spreads do not seem to adversely affect the taste of food and extensive toxicological studies have failed to reveal any significant harmful side effects with the use of these "functional" foods.[43] It should be noted, however, that there are reports of decreased serum levels of b-carotene, a-tocopherol, and/or lycopene as a result of eating foods that contain stanol and sterol esters. Additional supplementation of these nutrients may be necessary. Plant sterols are recommended by both the American Heart Association and the National Cholesterol Education Program Expert Panel as adjunct therapy for the reduction of low-density lipoprotein.

Alcohol

The evidence is convincing that the moderate consumption of alcohol (one to two drinks per day) reduces insulin resistance, lowers blood pressure and increases HDL-C.[48] A recent meta-analysis found strong and consistent evidence linking moderate alcohol intake with increased HDL-C and apolipoprotein AI levels, as well as lower concentrations of fibrinogen. The authors calculated an overall predicted 24.7% reduction in risk of coronary heart disease associated with an intake of 30 g of alcohol a day owing to changes in these markers."[49]

Exactly what type of alcohol offers the best protection against cardiovascular disease is still being debated. Some researchers believe that it is the ethanol itself that is beneficial,[50] while others contend that red wine that offers the most benefit.[51] While the verdict is still not in, a recent review of the clinical and experimental evidence suggests that red wine may offer greater cardiovascular protection than other types of alcoholic beverages.[52] This protection is believed to be due to the antioxidant, vasorelaxant and antithrombotic properties of the polyphenolic compounds present in wine.[53] These polyphenolic compounds, such as resveratrol, have been shown to prevent lipoprotein oxidation in vitro,[54] however, animal studies of the effects of resveratrol on atherosclerosis are conflicting.

What are the down sides to alcohol consumption? In addition to those that are well known, such as fetal alcohol syndrome, alcoholism and hypertension, it should be noted that even moderate amounts of alcohol can increase triglyceride levels. Research has also shown that those who consume more than three drinks per day are more likely to experience

harm than benefit.[55] There is an increased risk of breast cancer in women who consume 2 or more servings of alcohol per day, making a number of specialists opt to recommend limiting women to 1 serving of alcohol per day.[56] In summary, those who enjoy a glass of wine with dinner should be encouraged to consider it a part of a healthy lifestyle, while those who abstain from alcohol for personal reasons should not be encouraged to start drinking. And remember, the antioxidant compounds found in wine can also be found in grape juice.[57]

Weight Loss

Obesity is often associated with elevated triglycerides and low levels of HDL-C.[26] It is currently postulated that elevation of triglycerides leads to increased catabolism of triglyceride rich HDL-C, resulting in lower levels of HDL-C.[6] Weight loss in most obese individuals tends to increase plasma HDL-C levels, as well as decreasing triglyceride levels.[58] However, it is important to note that low fat diets often reduce, or fail to increase, HDL-C levels. One should replace saturated fat with monounsaturated fats in any weight loss program designed to increase HDL-C.[59]

The Framingham Study demonstrated that HDL-C in tobacco smokers averaged 13 percent less than that of nonsmokers.[60] The physiologic effects of smoking tobacco include endothelial injury, lower HDL-C, impaired exercise performance, and altered oxygen delivery.[61] Discontinuation of cigarette smoking has been shown to result in a 3- to 4-mg/dL increase in HDL-C.[48]

Dietary Supplements

Niacin

Niacin, nicotinic acid, may be used to reduce serum cholesterol and triglycerides. It is currently the most effective drug available for raising HDL-C[62] and has been shown to reduce coronary death and nonfatal myocardial infarction.[63]

Three grams per day of immediate-release niacin reduces LDL-C levels by an average of 20% to 25%, while doses of 1 g/d have been shown to raise HDL-C levels by 15-20%. An extended release prescription product is available, Niaspan (KOS), which has been shown to lower LDL-C by 15% to 20% at its maximum dose of 2 g/d. Both the extended release and the immediate release niacin products taken at doses as low as 1 g/d reduce triglyceride concentrations by 20% to 35%.[1] The major limitation to the use of niacin as a lipid-lowering agent is its side effect profile, which includes flushing with both immediate- and extended-release products. Taking a baby aspirin 30 minutes before taking niacin can minimize this effect. Alcohol and hot liquids tend to intensify the flushing, so avoiding these substances when taking the daily dose of niacin is advisable.

Niacin is sometimes combined with statin medication in patients with low HDL. A 3 year double-blind, placebo controlled study of 160 adults with atherosclerosis and low HDL-C found that a combination of simvastatin and niacin improved HDL-C levels, caused artery blockages to recede and significantly lowered heart complications compared to placebo.[64] In the study, patients received either a combination of simvastatin and niacin alone, antioxidants alone (vitamins E, C, beta-carotene and selenium), simvastatin-niacin plus antioxidants, or placebo. Over 3 years, those taking the simvastatin-niacin were 60% to 90% less likely than placebo patients to have a heart attack or stroke, require angioplasty or to die from causes related to heart disease. This study found that the group receiving the combination plus antioxidants had less of an increase in their HDL-C, leading researchers to question the wisdom of combining antioxidants with statin therapy. At the time, the most that can be said from this arm of the study, is that this particular combination of antioxidants appeared to blunt some of the benefit of the simvastatin-niacin therapy. It should not be extrapolated to all patient populations and other statin treatments at this time.

As liver function tests may transiently rise, niacin should not be taken by anyone with acute liver disease. Sustained-release niacin has also been associated with severe liver toxicity when given in doses above 2 grams daily. Niacin can worsen glycemic control in patients with diabetes and aggravate gouty arthritis.

Policosanols

Policsanols are a mixture of alcohols usually extracted from sugar can wax or beeswax and composed primarily of octacosanol. They have demonstrated effectiveness in the treatment of Type II hypercholesterolemia and have been shown to be safe in studies that have run for more than three years. At doses of up to 20 mg per day policosanols have lowered total cholesterol and low-density lipoprotein (LDL) cholesterol by more than 20% and raised high-density lipoprotein cholesterol (HDL) by up to 15%. This is roughly equivalent to the effects noted in clinical trials involving patients treated with simvastatin or pravastatin. Triglyceride levels have not been shown to be influenced by treatment with policosanols. In vitro

studies suggest that policosanols may inhibit hepatic cholesterol synthesis and animal studies support the theory that LDL breakdown may be increased.[65]

Botanical therapies used for Hyperlipidemia

Red Yeast Rice (*Monascus purpureus*)

The product sold as red yeast rice is prepared from cooked, non-glutinous white rice fermented by the yeast *Monascus purpureus*, which is then sterilized, dried, ground and encapsulated. Red yeast rice is a dietary staple in many Asian countries, with typical dietary consumption ranging from 14 to 55 g/d.[66] In addition to its medicinal properities, red yeast rice has been used to make rice wine and as a food preservative for maintaining the color and taste of fish and meat.[67]

The primary active ingredient in red yeast rice is thought to be monacolin K (also known as mevinolin and lovastatin). Monacolin K inhibits the enzyme that initiates cholesterol biosynthesis, HMG-CoA reductase. It is highly unlikely that the small amount of monacolin K present in red yeast rice fully accounts for the beneficial effects on lipids seen in clinical trials, as it is present at only 0.2%. Red yeast rice also contains other potential lipid-lowering agents, such as ten other monacolin analogs, omega-3 fatty acids, isoflavones, and plant sterols (ß-sitosterol, campesterol, stigmasterol, and sapogenin).[68]

A randomized double-blind, placebo-controlled study of 83 men and women found that those taking 2.4 g/d red yeast rice significantly lowered their cholesterol from 250 mg/dL to 208 mg/dL (17%) after eight weeks compared to controls.[66] LDL-C levels dropped from 173 to 134 (22%), triglycerides dropped from 133 to 118 (12%), while HDL-C remained the same. Dietary intake was monitored, and there were no significant differences between the two groups in total calories, total fat, saturated fat, monounsaturated fat, polyunsaturated fat or fiber. No changes in liver function tests or other serious adverse events were reported.

A pilot trial of red yeast rice was conducted with 14 individuals with dyslipidemia related to human immunodeficiency virus (HIV). Patients were randomly assigned to receive either 1,200 mg/d of red yeast rice or placebo for 8 weeks in a double-blind fashion. At the conclusion of the trial there was a statistically significant reduction in total cholesterol (P=0.01) and LDL-CC (P=0.01) in the group receiving red yeast rice compared to placebo. No changes were noted in HDL-C or triglycerides and no adverse effects were reported.[69]

A recent study of commercial red yeast rice products found that there is tremendous variation in quality between products. Findings from clinical trials demonstrating significant and clinically relevant cholesterol reduction using a defined Chinese red yeast rice preparation (Cholestin) cannot be generalized to other commercially available preparations that do not contain the same levels and profile of monacolins. Citrinin, a toxic fermentation by-product, was found at measurable concentrations in 7 of the 9 preparations.[70]

It should be noted that the proprietary red yeast rice product used in the clinical trials, Cholestin, is no longer available as a dietary supplement in the US. The FDA claimed that the manufacturer was selling "lovastatin," a patented lipid-lowering drug sold by Merck. After several years of battling it out in court, Pharmanex lost the fight and Cholestin was removed from sale, though, other red yeast rice products (of questionable quality) can still be found on the shelves of health food stores. From a cost perspective, the consumer definitely got the raw end of the deal on this one. The current cost for cholesterol-lowering drugs is roughly $120–300 per month, with an average cost of $187 per month.[71] The red yeast rice product used in the clinical trials costs roughly $25-35 per month.

Garlic (*Allium sativum*)

Garlic is perhaps the best known of the lipid-lowering herbs amongst the lay public. The lipid lowering effects of garlic have been demonstrated in both animal studies and human clinical trials. A number of meta-analyses have been performed over the years, demonstrating a reduction in total cholesterol of 5-12%.[72-75] While the evidence does support a small but statistically significant decrease in lipid levels at 3 months follow-up, pooled analyses of placebo-controlled trials failed to demonstrate significant reductions of total cholesterol at six months. The recent report by the Agency for Healthcare Research and Quality (AHRQ) concluded "it is not clear if statistically significant positive short-term effects—but negative longer term effects—are due to: systematic differences in studies that have longer or shorter follow-up durations; fewer longer term studies; or time-dependent effects of garlic."[76]

Most studies suggest a possible short-term benefit of garlic on lipid levels, insignificant effects on blood pressure, and no effect on glucose levels. The trials are difficult to assess, as a whole, given their

short duration and the unpredictable release and inadequate definition of active constituents in the garlic preparations used in the studies. Most garlic supplements are standardized on allicin potential and are enteric-coated to prevent gastric acid inactivation of the allicin-producing enzyme, alliinase. A recent evaluation of garlic powder tablets used in clinical trials (1989-1997) found that the there was great variation in the amount of allicin released when subject to the United States Pharmacopoeia (USP) acid disintegration test (724A). Older batches were found to be more resistant to acid-disintegration and released three times more allicin (44% vs 15% of their potential, $P<0.001$) than newer lots. Conflicting trial results may be the result of lower amounts of bioavailable allicin in some products.[77] Another study found that 23 out of 24 brands tested released only 15% of their allicin potential when subjected to the USP testing method. To assure greater bioavailability, garlic powder supplements should no longer be standardized to allicin potential, but on dissolution allicin release.[78] Until test products can be assured of containing and making bioavailable the key active constituents in garlic–conducting and evaluating clinical trials will be extremely difficult to do.

The benefits of long-term garlic consumption may have more to do with cardiovascular benefits other than simply lowering lipids. Garlic has been shown to have mild anti-hypertensive,[79] antiarrhythmic,[80,81] antithrombotic and antiatherogenic activity. The latter properties are due to inhibition of platelet aggregation, inhibition of cholesterol biosynthesis and enhancing fibrinolysis.[80,81] The lipid lowering effects of garlic are though to be due to inhibition of HMG-CoA reductase[84] and increased catabolism of fatty acid containing lipids, especially triglycerides.[85] Garlic oil, aged garlic, fresh garlic, and garlic powder have been shown to inhibit platelet aggregation via interference with the cyclooxygenase mediated thromboxane synthesis pathway.[86] Raw garlic inhibited cyclooxygenase activity non-competitively and irreversibly.[87] After 26 weeks of garlic consumption, there was roughly an 80% reduction in serum thromboxane in healthy male volunteers eating 3 grams fresh garlic daily.[87] Cooked garlic has a lower inhibitory effect upon platelet aggregation than raw garlic.[88]

The antiatherogenic activity of garlic has been demonstrated in a clinical study conducted in Europe. A four-year study was conducted with 152 men and women diagnosed with advanced plaque accumulation and one other cardiac risk factor (high cholesterol, hypertension). Patients were randomized to take 900 mg garlic (Kwai) or placebo for 48 months. Ultrasound was used to measure plaque in carotid and femoral arteries at 0, 16, 36, and 48 months. At 48 months: a 2.6% reduction in plaque volume was noted in the garlic group, compared to a 15.6% increase in the placebo group.[89] While encouraging, methodological limitations prevent any concrete conclusions.

Potential adverse effects of garlic that should be noted by health care practitioners include cases of postoperative bleeding during augmentation mammaplasty[90] and transurethral resection of the prostate[91] in patients taking garlic prior to surgery. There is also a report of spontaneous spinal epidural hematoma.[92] Evidence is lacking for a direct interaction of warfarin with garlic. Three cases of hemorrhage with garlic have been reported but none of the patients were taking warfarin.[93] It is well known, however, that anti-platelet agents can increase the risk of major bleeding when combined with warfarin. Practitioners should be watchful of patients on warfarin who consume generous amounts of garlic.

Fresh garlic and dried garlic powder are probably the best preparations for patient use, as commercial garlic powder tablets can provide differing clinical results. In conclusion, garlic appears to have a mild, yet beneficial, effect upon the cardiovascular system and should be considered part of a heart healthy diet when making therapeutic lifestyle changes. The lipid-lowering effects are mild and may not be sustained, thus garlic should be not be considered a primary therapy for patients with moderate to severe forms of dyslipidemia.

Guggul (*Commiphora mukul*)

The guggul tree grows in dry areas of India, Pakistan and Afghanistan. For thousands of years, healers have tapped the trees to make medicines used to control weight and to treat other ailments. Since the 1960s, research has focused upon its lipid-lowering activity and today it is an approved lipid-lowering agent in India. While it is known that guggul appears to prevent oxidation of LDL,[94] more recent research seems to indicate that the guggulsterones (4,17(20)-pregnadiene-3, 16-dione) found in guggul are highly efficacious antagonists of the farnesoid X receptor (FXR), a nuclear hormone receptor that is activated by bile acids. The FXR receptor controls cholesterol by regulating the level of bile acids in the body. Blocking the action of FXR helps the body rid itself of more cholesterol. Guggulsterone treatment decreased hepatic cholesterol in mice fed a high cholesterol diet, but was not effective in mice without the FXR receptor.[95]

Older studies have demonstrated a reduction in total serum cholesterol, LDL-C, VLDL and triglycerides, with an increase in HDL-C.[96-97] One trial found guggul to be as effective as clofibrate in reducing cholesterol levels,[98] while another study of 61 patients with hypercholesterolemia found 50 mg guggulsterones twice daily to be superior to placebo in reducing lipids over a 24-week period. Guggul decreased total cholesterol levels by 11.7%, LDL-C by 12.5%, triglycerides by 12.0%, with no change noted in HDL-C.[99]

While intriguing, these studies suffer from methodological flaws that make any definitive conclusion about lipid-lowering effects premature. However, given the in vitro, animal and human data, this herb warrants further study as it may prove to be a beneficial, well-tolerated and cost-effective treatment for dysplipidemia.

The purified, standardized extract of the plant is much better tolerated than the raw herb, which was reported to cause numerous side effects including abdominal pain, diarrhea and skin rash. Most extracts are standardized to 5% guggulsterone content and the therapeutic dose is 500 mg. taken three times per day, so as to provide 25 mg guggulsterone three times daily.

Side effects reported in clinical trials were minor and included diarrhea, mild nausea, headache, and restlessness.[99] Guggul is contraindicated during pregnancy due to purported uterine stimulating properties.[100] Guggul has been reported to reduce the effectiveness of propranolol and diltiazem.[101]

Globe Artichoke (*Cynara scolymus*)

Artichoke leaf has been used as a treatment for dyspepsia since ancient times. More recently, researchers have found that the leaf extract has lipid-lowering activity. In vitro research seems to indicate that the mechanism of action appears to be an indirect inhibition of HMG-CoA reductase.[84] While there are likely multiple active constituents, luteolin exerted the highest inhibitory potency and effectively blocked the stimulation of cholesterol biosynthesis by insulin. Artichoke extracts also enhance biliary cholesterol excretion,[102] which may also contribute to its lipid lowering effects.

An older study of seventeen outpatients with familial Type IIa or Type IIb hyperlipoproteinemia was undertaken to determine the efficacy of cynarin for lowering lipids in this population. The patients were treated with either 250 mg or 750 mg of cynarin for three months. There were no significant changes noted in serum cholesterol and triglyceride levels.[103] Of course, this study used an isolated constituent from artichoke, which, at least according to recent in vitro data, is not the main lipid-lowering agent.

A recent randomized, placebo controlled multicenter trial examined the efficacy and tolerability of 450 mg per tablet artichoke dry extract (drug/extract ratio 25-35:1, aqueous extract, CY450) versus placebo for the treatment of hyperlipidemia. The study enrolled 143 adult patients with initial total cholesterol of greater than 280 mg/dl and randomized them to receive either 1,800 mg artichoke dry extract per day or placebo for 6 weeks. Changes of total cholesterol and LDL-cholesterol from baseline to the end of treatment showed a statistically significant superiority (P = 0.0001) of artichoke dry extract over placebo. The decrease of total cholesterol in the CY450 group was 18.5% compared to 8.6% in the placebo group. LDL-cholesterol decrease in the CY450 group was 22.9% and 6.3% for placebo. LDL/HDL ratio showed a decrease of 20.2% in the CY450 group and 7.2% in the placebo group. No adverse events were noted in the study.[104]

The adverse effect profile for artichoke in the literature is very good. The only contraindication at this time is for use in those with bile duct obstruction. This is due to the choleretic activity of the extract.

Flavonoid Rich Herbs

Flavonoids are responsible for the colors of flowers, fruit, and sometimes leaves and a wide variety of flavonoid classes may be found amongst fruits, vegetables and beverages, such as tea and wine. Flavonoids have biological properties that have been shown to promote health and help reduce the risk of disease. Flavonoids possess anti-oxidant, anti-neoplastic and anti-inflammatory activity; extend the activity of vitamin C, and exert positive effects upon the cardiovascular system.[105,106] Polyphenolic flavonoids are thought to reduce the risk of coronary artery disease through the inhibition of platelet aggregation, reducing injury from ischemia and reperfusion, reducing plasma cholesterol levels and/or through the inhibition of LDL oxidation.[107,108] For instance, licorice extract (free of glycyrrhizinic acid, the component associated with water retention and hypertension) and the isoflavane glabridin, a major polyphenolic compound found in licorice, were both shown to markedly inhibit LDL oxidation in 10 normolipidemic individuals during one study.[109]

Diets that are rich in plant polyphenols, such as red wine or tea, are thought to offer a beneficial effect upon the cardiovascular system. The following herbs are rich in flavonoids that, when regularly consumed

in the diet, may offer some cardiovascular protection. More rigorous research is required before any formal recommendations can be made regarding treatment, however, enough preliminary data exists to suggest that these spices should be considered part of a healthy heart diet.

Tea (*Camellia sinensis*)

Tea is second only to water as the most common drink in the world. Green tea from *Camellia sinensis* has been shown to lower plasma cholesterol in animal models of hypercholesterolemia.[110] Prospective studies have suggested that the polyphenolic flavonoids in tea may exert a protective effect against cardiovascular disease. A potential mechanism put forth for such an effect has been inhibition of lipid peroxidation by polyphenolic antioxidants. However, a recent study challenges this hypothesis as the polyphenolic compounds from tea failed to inhibit in vivo lipid peroxidation.[111] Other researchers have suggested that tea increases the expression of the hepatic LDL-C receptor, a cell surface protein involved in the control of plasma cholesterol,[112] and increases the fecal excretion of bile acids and cholesterol.[113] The purported beneficial effects might also be explained by the ability of green tea catechins and gallate esters to reduce intestinal cholesterol absorption and inhibit platelet aggregation.

A meta-analysis of tea consumption in relation to stroke, myocardial infarction, and all coronary heart disease was conducted based on 10 cohort studies and seven case-control studies.[114] The authors concluded that, "The incidence rate of myocardial infarction is estimated to decrease by 11% with an increase in tea consumption of 3 cups per day (fixed-effects relative risk estimate = 0.89, 95% confidence interval: 0.79, 1.01) (1 cup = 237 ml). However, evidence of bias toward preferential publication of smaller studies that suggest protective effects urges caution in interpreting this result." The study-specific effect estimates for stroke and coronary heart disease were found to be too heterogeneous to allow for summarization.

The authors clearly point out the limitations of their findings. When evaluating studies, they found that many failed to precisely identify the type of tea being used or consumed—studies referring to the test item simply as "tea." This represents a significant problem with evaluating the evidence as "tea" actually represents a very heterogeneous group of beverages, which can include fermented black tea, half fermented oolongs, unfermented green tea, and sweetened or unsweetened ice tea, and other very distinct herbal teas.

Also lacking in most studies was how the tea was prepared. How long was the herb steeped and was milk added to the beverage? These are important questions that must be adequately addressed as these variables can affect the content of the tea.[114]

Turmeric (*Curcuma longa*)

Turmeric is a member of the ginger family and has been used as a spice for millennia. The rhizome contains 0.3-5.4% curcumin, the substance that gives turmeric its lovely orange-yellow color. Curcumin has been shown to possess anti-inflammatory, anti-oxidant and lipid-lowering effects. Animal studies have shown that rats fed 0.2 g curcuminoids per 100 g diet experience a reduction in total cholesterol and triglycerides when compared to control animals.[115] Other studies have confirmed the lipid-lowering effects of curcumin in animals.[116,117] The lipid-lowering effects are thought to be due to alterations in fatty acid metabolism, or through enhancing the conversion of cholesterol to bile acids. It is important to note that no human clinical trials could be found to confirm the lipid lowering effects of curcumin, or turmeric, and what dose would be necessary for efficacy.

Curcumin inhibits platelet aggregation mediated by the platelet agonists: epinephrine, ADP, platelet-activating factor, collagen, and arachidonic acid.[118] Adverse effects are minor but can include gastrointestinal disturbances and contact dermatitis. Patients with gallstones or bile duct obstruction should avoid this herb, as curcumin has been shown, by ultrasound examination, to induce contraction of the gallbladder in humans.[119]

While turmeric is commonly used as a spice, most research has been conducted on the isolated curcuminoids. The dose generally recommended is 400-600 mg three times daily. At this time, the addition of turmeric to the diet may be considered part of a heart healthy diet for those who enjoy the flavor of this spice, however, it is premature to recommend curcumin as a primary treatment for hyperlipidemia.

Ginger (*Zingiber officinale*)

Ginger is a commonly used culinary herb. It has been used for thousands of years in China and India for medicinal purposes. In vitro research has shown that constituents within ginger have an inhibitory effect upon cholesterol biosynthesis.[120] Animal studies have also demonstrated lipid-lowering activity with ginger via enhancing the activity of hepatic cholesterol-7-hydroxylase, the rate-limiting enzyme in bile

acids biosynthesis, thereby stimulating cholesterol conversion to bile acids, an important mechanism for eliminating cholesterol from the body.[121] A study in rabbits found that an orally administered ethanolic extract of ginger (200 mg/kg) reduced lipids after 10 weeks of being fed a cholesterol rich diet. The authors found, at this dose, ginger produced similar results as gemfrimbrozil.[122]

In contrast to the in vitro and animal data, a clinical trial involving patients with coronary artery disease, 4 grams per day dried ginger powder for 3 months failed to inhibit ADP- and epinephrine-induced platelet aggregation, alter fibrinolytic activity, or effect blood lipids or blood sugar.[123] It should be noted, however, that a single dose of 10 g powdered ginger administered to these patients produced a significant reduction in platelet aggregation.

Standardized ginger extract had no significant effects on coagulation parameters or on warfarin-induced changes in blood coagulation in rats.[124] Evidence is lacking for a direct interaction between warfarin and ginger.[93] When ginger is used as a spice or at doses of 3 grams per day or less, there should be little concern for interaction with this category of medication.

Administration of 6 g dried ginger powder increased exfoliation of gastric surface epithelial cells in human test subjects. This dose may cause gastric irritation and is potentially ulcerogenic. It is recommended that consumption be less than 6 g/d dried ginger. Patients treated with ginger have reported flatulence and heartburn but the rhizome should be considered quite safe when used as a spice in food.

Hawthorn (*Crataegus laevigata*)

Hawthorn is a fruit-bearing shrub that has a long and distinguished history as a medicinal agent. It has been used primarily to treat digestive and cardiovascular disorders. Most contemporary research of hawthorn has focused on its use in treating a variety of cardiovascular conditions. The cardiovascular effects are believed to be the result of positive inotropic activity, ability to increase the integrity of the blood vessel wall and improve coronary blood flow, and positive effects on oxygen utilization. Flavonoids are postulated to account for the majority of these effects.

Hawthorn has been shown to reduce cholesterol in rabbits fed a high cholesterol diet.[125-126] This study found that supplementation of hawthorn fruit did not affect the activities of HMG-CoA reductase or cholesterol 7alpha-hydroxylase (CH) but it did suppress the activity of intestinal acyl CoA:cholesterol acyltransferase (ACAT) ($p < 0.05$). The authors conclude that the lipid lowering effects of hawthorn may be due, at least in part, to the inhibition of cholesterol absorption mediated by down-regulation of intestinal ACAT activity.

Though hawthorn is often found in dietary supplements designed to reduce cholesterol, there are no human clinical trials to review to determine if the fruit, leaves or flowers lower lipids humans, and if they do—to what extent and at what dose. Hawthorn appears to have a low level of toxicity, however, practitioners should be aware of potential interaction with certain medications. Hawthorn preparations may potentiate the activity of cardiac glycoside medications such as digitalis.[100] Hawthorn exerts a positive inotropic effect that is not caused by phosphodiesterase inhibition or a beta-sympathomimetic effect, as the L-type calcium current is not affected.[127] The positive inotropic action of hawthorn appears to be cAMP-independent, similar to cardiac glycosides,[128] which may explain an additive effect when the herb is taken with digitalis. Crataegus extract blocks repolarizing potassium currents in ventricular myocytes, similar to the action of class III antiarrhythmic drugs and might be the basis of the antiarrhythmic effects described for hawthorn.[127]

Other Botanicals

Bishop's Weed (*Ammi visnaga*)

The fruit of this plant have been used since ancient times for its medicinal effects. Papyrus writings from Egypt describe the use of Ammi visnaga for the treatment of asthma, painful kidney stones and angina. Khellin has been shown to exert lipid-lowering effects in animal studies.[128] A study of khellin in 20 non-obese men with normal lipid levels found a significant increase in HDL-cholesterol levels, although, total cholesterol and triglyceride concentrations remained unchanged. Unfortunately, nausea and vomiting were responsible for the withdrawal of four volunteers, and elevation of liver enzymes caused the withdrawal of an additional two participants.[129] These side effects are not generally noted with standardized preparations of the whole fruit.

Visnadin dilates the coronary vessels and brings about an increase in coronary circulation.[130] The German Commission E approved the use of Ammi visnaga for the treatment of mild anginal symptoms. Standardized preparations of this herb may be useful for mid angina, especially in those patients who do not tolerate nitroglycerin. Generally, standardized extracts are recommended that provide an equivalent of 20 mg khellin per day.

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