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Antioxidant Vitamins and the Prevention of Coronary Heart Disease

A patient information handout on antioxidant vitamin supplements, written by the authors of this article, is provided on page 903.

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Clinical use of antioxidant vitamin supplementation may help to prevent coronary heart disease (CHD). Epidemiologic studies find lower CHD morbidity and mortality in persons who consume larger quantities of antioxidants in foods or supplements. Clinical trials indicate that supplementation with certain nutrients is beneficial in reducing the incidence of CHD events. Recent studies show that supplementation with antioxidant vitamins E and C have benefits in CHD prevention; however, supplementation with ß-carotene may have deleterious effects and is not recommended. Current evidence suggests that patients with CHD would probably benefit from taking vitamin E in a dosage of 400 IU per day and vitamin C in a dosage of 500 to 1,000 mg per day. Clinicians may also want to consider vitamin supplementation for CHD prevention in high-risk patients. Folate lowers elevated homocysteine levels, but evidence for routine supplemental use does not yet exist. Other nutritional supplements are currently under investigation. (Am Fam Physician 1999;60:895-904.)

See editorial on page 742.

Recent experimental and epidemiologic evidence suggests that some antioxidant vitamins appear to be important in reducing the risk of coronary heart disease (CHD). These antioxidants include ascorbic acid (vitamin C), a-tocopherol (vitamin E), folate, ß-carotene, ubiquinone (coenzyme Q_{10}), bioflavonoids and selenium. This article reviews evidence linking the intake of nutritional supplements with the prevention of CHD and also provides clinical recommendations.

Pathophysiology of Oxidation and Effects of Antioxidants

Low-density lipoprotein (LDL) cholesterol is the primary lipoprotein found in atherosclerotic plaque. LDL oxidation is a key factor in the development of atherosclerosis.[1-3] Excess free radicals in plasma and the arterial intima increase LDL oxidation.[1] Oxidized LDL is cytotoxic and is taken up by arterial macrophages, which is a primary factor in plaque formation and progression.

Experimental evidence suggests that antioxidant vitamins are important in reducing coronary heart disease.

Antioxidants in plasma, the LDL particle and the cell wall reduce LDL oxidation.[1] The major fat-soluble antioxidants are vitamin E and ß-carotene (a vitamin A precursor). The major water-soluble antioxidant is vitamin C. These vitamins reduce LDL oxidation and preserve vasoreactivity by increasing endothelial nitric oxide release and reducing thrombogenicity.[4,5] Antioxidant vitamins may also reduce the risk of plaque progression and rupture.[1,4,5]

Vitamin E

Vitamin E prevents the perioxidation of polyunsaturated fatty acid in membranes. The most active and available form of vitamin E is a-tocopherol. Vitamin E is incorporated into lipoproteins and cell membranes, limiting LDL oxidation. Vitamin E is the predominant antioxidant in LDL.[6,7] This vitamin also inhibits platelet activation and monocyte adhesion.[1]

Vitamin E is found in vegetable and seed oils, in wheat germ and, in smaller quantities, in meats, fish, fruits and vegetables. The recommended dietary allowance (RDA) of vitamin E is 30 IU per day (equivalent to 30 mg per day). It is difficult to obtain high doses of vitamin E in the average diet. Multivitamins usually contain 30 to 50 IU of vitamin E.

TABLE 1
Observational Studies on the Relationship Between Antioxidant Vitamins and Coronary Heart Disease (CHD)

Study	Population	Observations
WHO/MONICA[13]	16 European regions	Inverse association between plasma vitamin E level and CHD mortality; inverse association between plasma vitamin C and CHD mortality in a subset of 12 normocholesterolemic populations
Verlangieri, et al.[14]	United States	Inverse association between fruit and vegetable consumption and CHD mortality

Riemersma, et al.[15]	110 angina patients and 394 control subjects	Lower plasma vitamin E levels in angina patients than in control subjects
Luoma, et al.[16]	Northern Finland	Inverse association of plasma vitamin E level and CHD mortality

WHO = World Health Organization; MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Disease.

Information from references 13 through 16.

Vitamin C

Vitamin C is the predominant plasma antioxidant. This water-soluble vitamin scavenges plasma free radicals and prevents their entry into LDL particles.[7] Vitamin C regenerates active vitamin E and increases cholesterol excretion.

Vitamin C improves endothelium-dependent vasodilation and reduces monocyte adhesion.[8-10] Supplementation with vitamin C (1,000 mg) and vitamin E (800 IU) before the ingestion of a high-fat meal has been found to reverse endothelial dysfunction and vasoconstriction following the meal.[11]

Dietary sources of vitamin C include citrus fruits, strawberries, cantaloupe, tomatoes, cabbage and leafy green vegetables. Cooking can destroy vitamin C; therefore, the vitamin is best obtained in raw foods or supplements. The RDA for vitamin C is 60 mg, but increased amounts are recommended for smokers, patients with healing wounds and pregnant or lactating patients.

ß-carotene

Many carotenoids are known, but their functions are not yet understood. ß-carotene is a vitamin A precursor carried in plasma and LDL.[3] It reduces oxidized LDL uptake but does not prevent LDL oxidation.[12] Sources of dietary carotenoids include fruits, yellow-orange vegetables (e.g., carrots, squash and sweet potatoes) and deep-green vegetables (e.g., spinach and broccoli). No RDA has been established for carotenoids.

Experimental Evidence

Many epidemiologic studies have linked diets high in antioxidants with reduced CHD risk *(Tables 1[13-16] and 2[17-21])*. Epidemiologic studies cannot prove causality for various reasons, such as selection bias. Thus, randomized, controlled trials are essential to assess treatment benefits.

Plasma levels of vitamins E and C, ß-carotene and selenium have been inversely correlated with cross-cultural CHD mortality *(Table 1)*.[13-16] A strong inverse correlation was found between plasma vitamin E and CHD mortality in 16 European populations.[13] A U.S. study found an inverse correlation of CHD with fruit and vegetable

consumption.[14]

Prospective cohort studies are summarized in *Table 2*.[17-21] CHD relative risk reductions of 31 to 65 percent were found with vitamin E supplementation.[5] Vitamin C studies suggested relative risk reductions of 25 to 51 percent but did not control for vitamin E intake.[5,18] In the Scottish Heart Health Study,[17] higher levels of ß-carotene intake were associated with a decreased risk of CHD.

TABLE 2
Prospective Cohort Studies on the Relationship Between Antioxidant Vitamins and Coronary Heart Disease

Study	Vitamin E	Vitamin C	ß-carotene
Scottish Heart Health Study[17]			
Men	+	+	+
Women	0	0	0
NHANES[18]	X	+	X
Nurses Health Study (females)[19]	+	0	0
Health Professionals Study (males)[20]	+	0	+(smokers only)
EPESE[21]	+	+	X

NHANES = National Health and Nutrition Examination Survey I; EPESE = Established Populations for Epidemiologic Studies of the Elderly; + = Significant inverse relationship benefit observed between vitamin and coronary heart disease; 0 = no significant relationship observed; X = vitamin not studied.

Information from references 17 through 21.

In a study of more than 121,000 female nurses between the ages of 30 and 55 years, food frequency questionnaires assessed daily intake of dietary and supplemental vitamins E, C and ß-carotene.[19] Women in the highest quintile of vitamin E intake (about 200 IU per day) had a 34 percent lower CHD risk than women in the lowest quintile (less than 3 IU per day). Risk reduction was noted with a daily intake of greater than 100 IU of vitamin E but not with daily use of multivitamins, vitamin C supplements or ß-carotene supplements.

The Health Professionals Study,[20] which included 39,910 male health care professionals, noted a 40 percent risk reduction for men in the upper quintile of vitamin E intake (about 400 IU per day) compared with men in the lowest quintile (6 IU per day). In this study, no benefits were found for vitamin C supplementation. After adjustment for risk factors and vitamin C intake, men in the highest quintile of ß-carotene intake (19,034 IU per day) demonstrated a 29 percent CHD risk reduction compared with those in the lowest quintile (3,969 IU per day); however, this benefit occurred only in smokers.

Both studies of health care professionals found that vitamin benefits occurred only after one to two years of supplementation.[19,20]

Supplement use was also examined in a study of 11,178 elderly persons.[21] In this study, vitamin E reduced the relative risk of all-cause mortality by 34 percent and the relative risk of CHD mortality by 47 percent. Combined vitamin E and C supplementation reduced total mortality by 42 percent and CHD mortality by 53 percent. The average dosage of vitamin E was greater than 100 IU per day.

Vitamin Supplement Studies

Randomized, controlled trials of antioxidant vitamin supplementation are summarized in *Table 3*.[22-28] The Cholesterol Lowering Atherosclerosis Study[22] evaluated the effect of reported anti-oxidant intake (non-randomized) and a cholesterol-lowering diet with either colestipol-niacin therapy or placebo (ramdomized) on the progression of CHD as evaluated by angiography. Supplementary vitamin E in a dosage of greater than 100 IU per day was associated with reduced lesion progression. Vitamin C supplementation was not associated with this benefit.

TABLE 3
Randomized Controlled Trials on the Relationship Between Antioxidants and Coronary Heart Disease (CHD)

Vitamin	Study	Dosage	Outcome
Vitamin E			
Primary prevention	ATBC[24]	50 mg per day	-
Secondary prevention	ATBC subset[25]	50 mg per day	+ (alone) - (with ß-carotene)
	CHAOS[26]	400 or 800 IU per day	+
	CLAS[22]*	>100 IU per day	+ (dose dependent)

Vitamin C			
Primary prevention	Chinese Cancer Prevention Trial[23]	125 mg per day	0
Secondary prevention	CLAS[22]		0
ß-carotene			
Primary prevention	ATBC[24]	20 mg per day	-
	Chinese Cancer Prevention Trial[23]	15 mg per day	+ (combined with vitamin E Prevention Trial[23] and selenium)
	CARET[27]		-
	Physicians' Health Study[28]		0
Secondary prevention	ATBC subset[25]	20 mg per day	- (alone and combined with vitamin E)

ATBC = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; CHAOS = Cambridge Heart Antioxidant Study; CLAS = Cholesterol Lowering Atherosclerosis Study; CARET = Beta-Carotene and Retinol Efficacy Trial; + = significant positive effect of vitamin supplementation on CHD; - = significant negative effect of vitamin supplementation on CHD; 0 = no effect of vitamin supplementation on CHD.

*--A portion of this study (on intake of vitamins C and E) was not randomized.

Information from references 22 through 28.

In another study, a single high-fat meal (i.e., 50 g of fat) reduced brachial artery vasoactivity for six hours in 20 healthy, normocholesterolemic persons.[11] Treatment with orally administered vitamin C (1,000 mg) and vitamin E (800 IU) before the meal blocked the vasoconstriction.

The Chinese Cancer Prevention Trial[23] randomized patients to receive either ß-carotene (15 mg per day), vitamin E (30 mg per day) and selenium (15 µg per day), or placebo. This study found that supplementation resulted in a 9 percent reduction in total mortality and a 21 percent decrease in deaths from gastric cancer.

The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study[24] measured the effects of vitamin E (50 IU per day) and ß-carotene (20 mg per day) supplementation on lung cancer and CHD. In this study, male Finnish smokers (n = 29,133) took supplements for six years. The incidence of nonfatal myocardial infarction was lower in all groups receiving supplementation and was significantly lower (32 percent) in the group that received vitamin E. Supplementation with vitamin E was associated with a

nonsignificant increase in cerebral hemorrhage. Supplementation with ß-carotene was associated with increased mortality rates for CHD (11 percent) and lung cancer (18 percent), as well as an increase in overall mortality (8 percent). The incidence of fatal CHD was significantly higher in the group that received ß-carotene alone (75 percent) and in the group receiving both vitamins (58 percent).[24] Male smokers with previous CHD (n = 1,862) had no difference in total mortality but demonstrated increased CHD mortality when they were given vitamin E and ß-carotene.[24,25]

Vitamin E

Vitamin E supplementation is supported by several studies *(Tables 2[17-21] and 3[22-28]).* The Scottish Heart Health Study[17] (n = 10,349) found a lower risk of undiagnosed CHD in subjects in the highest quintile of dietary vitamin E intake, but the reduction was not significant in those with known CHD or in women. Increased vitamin E levels are associated with decreased CHD mortality and inversely correlated with risk of angina.[15,16]

The Cambridge Heart Antioxidant Study[26] was a double-blind, placebo-controlled trial (n = 2,002) designed to test whether supplementation with high-dose vitamin E (400 or 800 IU per day) would reduce the risk of overall mortality in patients with CHD. Vitamin E significantly reduced the incidence of overall fatal and nonfatal CHD events by 47 percent and the incidence of nonfatal myocardial infarction by 77 percent; however, supplementation did not have a significant effect on overall mortality (relative risk: 1.18). Event reduction was better with supplementation at 400 IU per day, but the study was not powered to assess dose-response significance. This clinical trial strongly supports evidence that vitamin E in dosages greater than 100 IU per day reduces CHD events.

Vitamin C

Vitamin C significantly improves arterial vasoreactivity and vitamin E regeneration. The National Health and Nutrition Examination Survey-I cohort study[29] found an inverse relationship between the highest vitamin C intake (diet and supplements) and CHD risk over 10 years in 11,349 U.S. men and women 25 to 74 years of age.

The only large primary prevention trial has been a study of 29,584 poorly nourished residents of Linixian, China.[23] Patients were randomized to receive different combinations of 10 nutritional supplements for five years. The patients who received vitamin C in a dosage of 125 mg per day and molybdenum in a dosage of 30 µg per day demonstrated no significant reduction in total or cerebrovascular mortality.

Many studies have demonstrated the ability of vitamin C to improve arterial vasoreactivity. A single dose (2 g) of vitamin C has been found to improve vasoreactivity in chronic smokers,[8] patients with hypercholesterolemia[10] and patients with CHD.[30] These findings support the antioxidant and endothelial effects of vitamin C.

ß-carotene

Research supports the benefit of a

carotenoid-rich diet, but not ß-carotene supplementation. The Beta-Carotene and Retinol Efficacy Trial[27] combined ß-carotene and retinol supplementation in 18,314 smokers and patients with asbestos exposure. However, the study was terminated prematurely because of a significant increase in lung cancer mortality and a nonsignificant increase in CHD mortality.

> Supplementation of ß-carotene is not recommended because possible harm has been demonstrated in several studies.

In 12 years of ß-carotene supplementation in 22,071 male physicians, no significant beneficial effects on CHD mortality, nonfatal MI or stroke were found.[28] In addition, no interactive effect with cigarette smoking (i.e., no harm or benefit) was demonstrated. A nonsignificant 20 to 30 percent reduction in CHD events occurred in the physicians who had clinical evidence of atherosclerosis.

Safety of Antioxidant Vitamins

Vitamins C, E and ß-carotene have few side effects. No significant toxicity has been noted for vitamin E in dosages of 800 to 3,200 IU per day.[31] Vitamin E has been found to prolong thrombin time in some animals, and it may increase vitamin K requirements. Therefore, caution is recommended when vitamin E supplementation is used in patients receiving anticoagulant therapy. In vitamin E clinical trials, no significant differences in bleeding rates were noted in supplemented and unsupplemented subjects.[32]

> Based on current evidence, patients with coronary heart disease should probably take 400 IU per day of vitamin E and 500 to 1,000 mg per day of vitamin C.

Vitamin C supplementation is usually nontoxic, although diarrhea, bloating and false-negative occult blood tests can occur at dosages greater than 2 g per day. The intestinal absorptive capacity for vitamin C is approximately 3 g per day.[32] Excess vitamin C is excreted in the urine but does not increase urinary oxalic acid. However, confusion arises about excess vitamin C intake causing increased oxalic acid excretion (and, thus, a possibly increased risk of oxalate kidney stones) as urinary vitamin C is converted to oxalate with air exposure.[32]

Given in dosages of 30 to 180 mg per day, ß-carotene has minimal side effects.[31] This carotenoid is not teratogenic, although trials in smoking patients suggest an increased cancer risk.[27] Carotenoid consumption of more than 30 mg per day eventually causes high serum carotene levels and skin yellowing.[32] Because of inefficient intestinal absorption and a slow rate of conversion into vitamin A, carotenoids do not produce hypervitaminosis A.[32] However, vitamin A is toxic in large doses.

Other Antioxidants

Other antioxidants that may provide protection against CHD include selenium,

bioflavonoids and ubiquinone. One study[33] found that selenium levels are inversely associated with CHD mortality. One review[7] noted that conflicting results were reported in other studies.

Flavonoids are antioxidants found in tea, wine, fruits and vegetables. These antioxidants reduce platelet activation, but studies do not yet support an associated reduction in CHD.[34,35] One epidemiologic study[35] found an inverse correlation between dietary flavonoid intake and CHD.

Ubiquinone, a reduced form of coenzyme Q_{10}, decreases LDL oxidation, but no event reduction data are available.[36] Ubiquinone may reduce symptoms and improve ejection fractions in patients with heart failure.[36-38]

The results of studies of garlic supplements have been conflicting regarding lipoprotein and platelet effects.[39] At best, garlic minimally reduces cholesterol levels.[40,41] No clinical event data on garlic are available.

The B-complex vitamins, especially folate, pyridoxine (vitamin B_6) and cyanocobalamin (vitamin B_{12}), may reduce CHD risk through a lowering of homocysteine levels.[42-44] Homocysteine is an amino acid that promotes LDL oxidation and is toxic to arterial endothelium. Folic acid supplementation in a dosage greater than 200 µg per day reduces the plasma homocysteine level.[45] The recent fortification of flour with folate will increase dietary folate levels by about 100 µg per day. Use of a daily multivitamin supplement containing folate (400 µg) would reduce plasma homocysteine levels in most persons.[46] Folate therapy may be beneficial in patients with elevated homocysteine levels, but clinical trials are just under way.

Conclusions and Recommendations

Oxidized LDL is atherogenic, and specific antioxidants can inhibit LDL oxidation. Epidemiologic studies report inverse relationships between

TABLE 4
Recommendations for Patient Care

Patients should consume a varied diet that contains five to seven servings of fruits and vegetables each day.
Patients should receive lifestyle counseling and continue cholesterol treatment when indicated.
Patients with known CHD should probably take vitamin E in a dosage of 400 IU per day and vitamin C in a dosage of 500 to 1,000 mg per day.
Supplementation of ß-carotene for CHD prevention is not routinely recommended.
Obtaining homocysteine levels should be considered in all high-risk patients (i.e., known CHD, family history of premature CHD or multiple risk factors), and treatment should be considered if the plasma homocysteine level is greater than 11 mg per dL.
Patients at high risk for CHD and low-density lipoprotein cholesterol oxidation (i.e., those with diabetes or hypertension, and those who smoke) may benefit from supplementation of vitamin E in a dosage of 400 IU per day and vitamin C in a dosage of 500 to 1,000 mg per day.

CHD and supplementation with vitamins E, C and ß-carotene. Clinical trials to reduce CHD events currently support vitamin E supplementation in dosages greater than 100 IU per day. Vitamin C promotes vitamin E regeneration and significantly improves vasoreactivity, but clinical event reduction has not been established. The results of ß-carotene studies have generally been unfavorable, primarily for smokers. Folate reduces serum homocysteine levels, but trials focusing on CHD events have not been completed. Ubiquinone, flavonoids, garlic and other supplements have not been adequately tested for CHD event reduction, appropriate dosing, reliability or long-term safety.

Supplements of other antioxidant nutrients are not recommended at this time.

Physicians should watch for results of upcoming clinical trials on vitamin supplements.

CHD = coronary heart disease.

Because of the benefits from dietary antioxidants and other micronutrients, physicians should recommend consumption of a diet containing five to seven servings of fruits and vegetables per day *(Table 4).*

Based on current evidence, patients with CHD should probably take vitamin E in a dosage of 400 IU per day; vitamin C supplementation in a dosage of 500 to 1,000 mg per day should also be considered in these patients. Patients receiving warfarin (Coumadin) therapy should limit vitamin E intake to 200 IU per day and should avoid vitamin E if they are at high risk for bleeding. Cohort studies suggest that patients with conditions in which LDL oxidation is common (i.e., diabetes, smoking, hypertension) may benefit from vitamin E supplementation in a dosage of 200 to 400 IU per day.

Supplementation of ß-carotene is not recommended for CHD prevention because of the possible harm demonstrated in several studies. A high-quality diet or a daily multivitamin may be a useful way to obtain important B vitamins, especially folate (400 µg per day), which lowers homocysteine levels.[42,45] Clinical trials are necessary to determine the potential benefits and optimal dosing of other supplements.

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