

Therapeutic Uses of Vitamin E in Prevention of Atherosclerosis

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Abstract

Objective: The purpose of this review is to present the evidence-based pharmacotherapeutic properties of vitamin E and provide clinical recommendations for use in the arena of atherosclerosis. **Methods:** A literature search was conducted from 1966 through March 1999. All usable papers were retrieved, with large, randomized, double-blinded, clinical trials and epidemiological trials receiving emphasis. **Results:** Vitamin E, a lipid soluble vitamin, is a potent antioxidant. Several epidemiological studies have demonstrated positive relationships between vitamin E intake and the prevention of atherosclerotic heart disease; however, only one, large randomized clinical trial (The CHAOS Trial) has been conducted using more than 400 IU per day of vitamin E. Positive outcomes included a 77-percent reduction in nonfatal myocardial infarction (MI), but no corresponding reduction in mortality. Several large clinical trials are ongoing, investigating vitamin E for the prevention of atherosclerosis. Much less work has been undertaken studying vitamin E for prevention of cerebro- and peripheral vascular disease, but there appears to be promise in these areas as well. **Conclusions:** On the basis of the literature search, the authors recommend 400 IU or more per day of vitamin E to patients at high risk or already diagnosed with coronary artery disease. Vitamin E supplementation may also be beneficial in the prevention of cerebro- and peripheral vascular diseases.

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Introduction

Coronary artery disease is the number one cause of death in the United States and other industrialized countries. Hence, correspondingly greater attention is being focused on prevention of this chronic degenerative disease. In this arena, antioxidants such as vitamin E may serve an important role. Vitamin E acts as an antioxidant by donating an electron to neutralize reactive oxygen species and prevent oxidative damage thought to be responsible for atherosclerosis, oncogenesis, various neurologic problems and ophthalmic disorders. As a result, vitamin E is being investigated as a potential preventive nutrient for these common clinical disorders. Vitamin E has a favorable side effect profile and relatively low cost, making it an ideal part of a disease prevention program, provided it is indeed efficacious. This review examines the available scientific evidence for vitamin E administration in the prevention of coronary artery, and cerebro- and peripheral vascular disease.

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Vitamin E Metabolism and Deficiency States

Vitamin E is a lipid soluble micronutrient containing eight active, naturally occurring plant constituents — tocopherols and tocotrienols. Vitamin E is an essential element of human nutrition and exerts its effects in the body via a number of different mechanisms. The most abundant and active isomer is d-alpha-tocopherol, which is used to calculate the vitamin E content of food; other tocopherols include the beta, gamma, and delta isomers. Vitamin E functions primarily as an antioxidant, protecting cellular membranes from oxidative damage or destruction, and red blood cells from hemolysis. Vitamin E is also thought to enhance vitamin A utilization and, at high doses, may be involved in the inhibition of platelet aggregation. Foods rich in vitamin E include vegetable oils, green vegetables, nuts, wheat germ, and whole grains. Vitamin E distributes to all body tissues, especially adipose tissue where it is stored. Tocopherols are metabolized by the liver to glucuronides and eliminated in feces and bile.

Vitamin E deficiency in the United States is rare. Murphy et al reported that 96 percent of men and 88 percent of women achieved the RDA through diet alone in their population-based report.¹ Dietary manipulations are largely unsuccessful in increasing serum vitamin E levels significantly.² However, absorption may be as low as 10 percent, even when doses of 200 mg are administered (1 mg=1.5 IU).³ In general, vitamin E absorption (unless taken as a water-miscible supplement) is dependent on pancreatic enzymes and bile salts which enhance absorption of fats in the small intestine. Two general patient populations are at risk for vitamin E deficiency: premature, very low birth-weight infants, and patients with fat malabsorption syndromes (e.g., pancreatic insufficiency, cystic fibrosis,

betalipoproteinemia, or small intestinal resection). Premature neonates are at risk due to low fat stores, low transmission of fat across the placenta, and initial problems with intestinal absorption. Infants may develop hemolytic anemia or retrolental fibroplasia, a severe retinal disease thought to originate from oxygen therapy, in the absence of sufficient internal antioxidants.

Characteristics of vitamin E deficiency include a variety of symptoms such as areflexia, psychological syndromes, cognitive dysfunction, nystagmus, ataxia, muscle weakness, and sensory loss in the arms or legs.⁴ Manifestations of vitamin E deficiency may not be completely reversible. Diagnosis is often made using serum vitamin E levels obtained as a result of clinical suspicion in high-risk individuals.

Vitamin E is well tolerated in large oral doses; up to 3200 IU per day have been administered to humans without adverse effects.⁵ Historically, experts thought vitamin E would increase the effects of warfarin by causing vitamin K deficiency. In a recent study of patients on chronic warfarin treatment, no significant effect on prothrombin times was observed when 800-1200 mg of vitamin E per day was administered.⁶ Conversely, if tissues are already vitamin K deficient, some experts suggest alpha-tocopherol may increase bleeding tendency through its mild effect on platelet aggregation at larger dosages (> 800 IU/day).⁷ Even though vitamin E is relatively non-toxic, the potential risks of long-term, megadose therapy (> 1000 IU/day) are unknown.

Natural source vitamin E (d-alpha-tocopherol) differs from synthetic vitamin E (dl-alpha-tocopherol) in its stereoisomer formation. Synthetic vitamin E is a mixture of isomers. It is thought that the bioavailability of synthetic vitamin E is essentially one-half that of natural vitamin E.⁸

Methods

A MEDLINE search using the MESH headings “vitamin E,” “heart disease,” “cerebrovascular disease,” “peripheral vascular disease,” and “therapeutic use” was conducted from 1966 through March 1999 using the PubMed search engine. Large, randomized, double-blinded, clinical trials (although few) and large epidemiological studies were emphasized in this report. Smaller and less recent studies are noted in the tables but not emphasized in the text of the article

Prevention of Coronary Artery Disease

Coronary artery disease (CAD) is the number one cause of mortality in the United States, causing over 500,000 fatalities and more than 1.25 million heart attacks per year. CAD also results in a loss of 21 billion work-days and \$40 billion annually.⁹ One theory is the major pathologic mechanism for heart disease results from oxidation of low density lipoprotein (LDL) cholesterol prior to damaging the vascular wall.¹⁰ Jialal et al examined, in a double-blind, placebo control study, two groups of 12 males, the groups receiving 800 IU/day vitamin E, 1 g/day ascorbate, and 30 mg/day beta carotene or placebo. At three months, the combined antioxidant group experienced a 40-percent decrease in oxidation rate, when compared to placebo. The combined antioxidant group was also compared with a group given 800 IU vitamin E only. There were no significant differences between the two groups with respect to LDL oxidation.¹¹ Other researchers have found at least 400 IU/day vitamin E is required for LDL to be resistant to oxidation *in vitro*.¹² While Jialal and his associates found no improvement in LDL with the addition of vitamin C and beta carotene, these same researchers have also found vitamin C and beta carotene do prevent LDL oxidation.^{13,14}

Epidemiologic Trials

Epidemiological data comprise the bulk of information about vitamin E and heart disease. These data suggest vitamin E may reduce the incidence of atherosclerosis. The first of two large prospective cohort observational studies, the Nurses Health Study, consisted of 87,000 female nurses followed for eight years. A protective effect of vitamin E was observed for women ingesting the highest dietary amount of vitamin E (17 IU/day), relative risk 0.66 (95% CI, 0.5-0.87), and in women taking vitamin E supplements, relative risk 0.59 (95% CI, 0.38-0.91).¹⁵ Another study of 39,000 male health care professionals found that men consuming 60 IU/day dietary vitamin E had a relative risk of 0.64 (95% CI, 0.47-0.84) for heart disease over a four-year period. In men taking at least 100 IU/day of supplemental vitamin E for at least two years, the relative risk of heart disease was 0.63 (95% CI, 0.47-0.84).¹⁶ A prospective study of over 2,000 Finnish men and women who were followed for 14 years showed a significant decrease in heart disease for women consuming the highest amounts of vitamin E, but these results were not reproducible in men; however, only three percent of subjects took vitamin E supplements.¹⁷

The Iowa Women's Health Study examined more than 34,000 postmenopausal females over a seven-year period.¹⁸ The adjusted risk of mortality from coronary disease was more reduced in the group consuming the highest amounts of dietary vitamin E (relative risk of 0.38 in the highest consumption groups of 7-10 IU/day vitamin E, (p=0.004)). Supplements did not seem to confer additional benefits, although few in this population consumed over 400 IU/day, the dosage seemingly necessary to inhibit LDL oxidation. Losonczy et al surveyed more than 11,000 elderly U.S. citizens over a six-year period. They concluded the use of vitamin E supplements (dosage unknown) reduced the risk of CAD mortality by 47 percent (RR= 0.53,95% CI, 0.532, 0.84).¹⁹

Some of the studies cited above, particularly the Nurses Health Study and the Iowa Women's Health Study, found protection with extremely low dietary intakes of vitamin E (17 IU/day and 7-10 IU/day, respectively). Because of the low levels of reported vitamin E intake, it seems likely other factors were involved.

Randomized, Controlled Trials

Only a few randomized, controlled clinical trials have been conducted examining the use of supplemental vitamin E for primary prevention of cardiovascular disease. Data from two prospective trials designed for assessment of vitamin E's effects on a different endpoint, i.e., cancer prevention (the ATBC trial and the Linxian Chinese Trial), were also analyzed for cardiovascular endpoints, but showed only an insignificant (9%) trend in reduction in incidence of MI in the supplemented group.²⁰⁻²¹ The insignificant results may have been because neither study administered large doses of vitamin E (30-50 IU/day). The ATBC trial also examined previous MI patients to see if subsequent MI rates could be reduced with administration of 50 IU/day vitamin E. No decreases in cardiac events were observed, although it should be noted the dosage was quite small.²²

A few clinical trials of vitamin E use for patients with established coronary artery disease have been conducted. A subgroup of the Cholesterol Lowering Atherosclerosis Study (CLAS) showed that doses over 100 IU/day of vitamin E slowed progression of coronary disease, demonstrated by quantitative angiography, as compared to controls after two years of supplementation.²³ A study of 115 randomized subjects who had undergone successful percutaneous transluminal coronary angioplasty (PTCA) showed 1200 mg vitamin E/day reduced the chance of restenosis, with a 35-percent incidence of restenosis in the vitamin E group versus 50-percent incidence in the control group.²⁴

Tardif et al²⁵ randomized 317 patients to probucol (an antioxidant, lipid-lowering agent) 500 mg/day, an antioxidant mixture (30,000 IU beta carotene, 500 mg vitamin C, and 700 IU vitamin E), both, or placebo twice daily for one month prior to angioplasty and six months after angioplasty. Baseline and post-treatment angiograms were compared. No apparent effect on restenosis rates was observed with the vitamin combinations; although probucol seemed to reduce restenosis rates. Probucol's mechanism of action as a lipid lowering agent is unknown, but the drug has antioxidant properties. The investigators concluded probucol's effect on restenosis rates was independent of its antioxidant properties. It may be that early restenosis after PTCA has more to do with intimal wall damage caused by physical effects of the angioplasty than plaque accumulation.

In the recent CHAOS study,²⁶ more than 2,000 patients with angiographic evidence of coronary disease were randomized to receive 800 IU/day alpha-tocopherol (first 546 patients), 400 IU/day (the remaining 1506 patients), and compared to placebo for one year. A combination of both treatment groups' relative risk of cardiovascular mortality and non-fatal MI compared to placebo was 0.53 (95% CI, 0.34-0.83). This observation was due primarily to a reduction in the risk of non-fatal MI to 0.23 (95% CI, 0.11-0.47, $p=0.005$). The different dosages were not analyzed independently.

A study from India examined 63 inpatients with a diagnosis of acute myocardial infarction.²⁵ Subjects were randomized to an antioxidant mixture containing vitamin A (50,000 IU), vitamin C (1 g), beta carotene (25 mg) and vitamin E (400 IU), administered IV daily for the first three days after hospital admission. Compared to controls, the treatment group showed significantly lower peaks in CPK-MB (a measure of extent of heart muscle damage) levels (92.4 +/- 25 vs. 110.4 +/- 28, $p < 0.05$), lower incidence of angina

Table 1: Studies on Vitamin E and Atherosclerosis

Study	Study Population	Dosage	Study Length	Findings
Gey, Puska (35) Case-control study	16 European study populations	N/A	N/A	Inverse association between serum alpha-tocopherol and CV mortality
Kushi et al (18) Cohort study	34,486 post-menopausal females	N/A	7 years	Adjusted risk of mortality from CAD reduced proportionally in higher quintiles of vitamin E intake (RR=0.38 in highest, p = 0.004)
Street et al (36) Case-control study	123 cases w/MI	N/A	N/A	Higher serum vitamin E levels associated with protective effect only in those with elevated cholesterol levels
Riemersma et al (37) Case-control study	110 patients w/angina, 394 controls	N/A	N/A	Lower serum alpha-tocopherol levels in patients with angina than in controls
Nurses Health Study (15) Health Professional Prospective cohort study	87,245 U.S. female nurses	Various dietary intakes of vitamin E and 13% using supplements	8 years	Supplements of over 100 IU/day for greater than 2 years was associated with reduced risk (RR=0.31, 95% CI, 0.03-0.51)
Follow-up Study (16) Prospective Cohort study	39,910 U.S. male health professionals	Various vitamin E dietary intakes and 17% taking supplements	4 years	Men with intakes in highest quintile of vitamin E (410 IU/day) had RR of 0.41 (95% CI, 0.19-0.56)
Losonczy et al (19) Prospective Cohort study prospective	11,178 elderly U.S. citizens	Yes/no to use of vitamin E supplements at two 3-yr intervals	6 years	Use of any supplemental vitamin E reduced risk of death by CAD by 53% (95% CI, 0.53-0.84)
Knekt et al (17) Prospective Cohort study	2748 Finnish men	Various vitamin E intakes but only 3% took supplements	14 years	Men had risk reduction of 34% which was not statistically significant
Knekt et al (17) Prospective Cohort study	2385 Finnish women	Various vitamin E intakes but only 3% took supplements	14 years	Women had a risk reduction of 65% (95% CI, 12% to 86%)
Gillilan et al (38) RCT	52 patients w/stable angina	1600 IU/d	6 monthss	No effects on exercise time, angina patterns or LV function
Anderson et al (5) RCT	50 patients w/angina	3200 IU/d	9 weeks	No change in anginal patterns
ATBC Trial (20) RCT	29,133 Finnish male smokers	50 mg (75 IU/day)	6 years	No effect on CV mortality but mild reduction (9%) in incidence of angina (RR-0.91; 95% CI 0.85-0.91)
CHAOS (26) RCT	2002 British men & women with CAD on angiography	800 IU/day	Median follow-up of 510 days	77% reduction in nonfatal MI but no change in mortality rates
Linxian study (21) RCT	29,584 adults in China	30 mg/day (45 IU/day)	5 years	An insignificant trend in reduction of CV mortality (9%, CI from 8% to 24%)
CLAS (23) RCT	156 patients w/previous CABG	100 IU/d	2 years	Less progression of coronary lesions per quantitative cath
DeMaio et al (24)	100 patients with CAD on angiography	1200 IU/day	4 months	Reduction in restenosis rate from 50% to 35%
Tardif et al (25) RCT	317 patients w/CAD on angiography	700 IU/day	6 months	No effect on restenosis rates
ATBC subgroup (22) RCT	1862 men with MI	50 mg/d (75 IU)	5 years	No effects on major CV endpoints (i.e., MI, death)
Singh et al (27) RCT	63 patients with acute MI	400 IU/day	3 days	Reduced levels of CPK-MB, angina pectoris, L.V. dysfunction, PVCs

Abbreviations: ATBC=Alpha-tocopherol, beta carotene trial; CAD=coronary artery disease; CHAOS=Cambridge Heart Antioxidant Study; CPK-mb=myocardial band; CV=cardiovascular; PVC=premature ventricular contraction; RCT=randomized, controlled trial; RR=relative risk; LV=left ventricular.

pectoris (10 supplemented patients versus 17 control patients, $p < 0.05$), lower incidence of left ventricular dysfunction (10 supplemented patients versus 16 control patients, $p < 0.05$), and lower number of total ectopic beats (7 supplemented versus 13 control patients, $p < 0.05$). The investigators concluded the antioxidants, including vitamin E, may play a role in the management of acute MI by limiting damage to the myocardium.

Economists estimate a savings of \$5-6 billion annually could be achieved if all adults over age 50 years took at least 100 IU vitamin E daily.²⁸ Since vitamin E was shown to be efficacious for reducing coronary disease in the large randomized clinical trial (CHAOS), has shown promise in large epidemiological trials, and is essentially nontoxic, supplementation with doses of 400 IU vitamin E to persons over the age of 50 with cardiovascular

risk factors or with cardiac disease may be prudent. See Table 1 for a summary of studies on vitamin E and atherosclerosis.

Vitamin E for Prevention of Cerebrovascular Disease

The use of vitamin E in the prevention and treatment of cerebrovascular disease has been examined in preliminary studies (Table 2). The Chinese Linxian study of 29,000 subjects examined the secondary endpoints of cerebral vascular events.¹⁹ There was a small reduction in the incidence of stroke in the vitamin E group ($rr=0.91$; 91% CI, 0.762 to 1.07); however, the dosage of 50 IU/day was low.

All other trials involving vitamin E and cerebrovascular disease have used carotid wall thickness or carotid lesions on ultrasound as endpoints. In a study by Kritchevsky et al, 6,318 females and 4,989 males were

Table 2: Studies on Vitamin E and Cerebrovascular Disease

Study	Study Population	Dose	Study Length	Findings
Kritchevsky et al (29) Cohort Data	6318 females, 4989 males	Mean intakes in highest quartile = 49 mg/d	N/A	Those women age 55-64 w/ highest intakes of vitamin E had thinnest carotid wall; older men had insignificant trend only
Steiner et al (32) RCT	100 patients w/ TIAs or other minor CVA-like events	400 IU/d plus 325 mg ASA compared w/ ASA alone	2 years	3/52 CVAs in vitamin E group vs. 6/48 in control
Tomeo et al (31) RCT	50 patients w/ cerebrovascular disease	Mix of 240 mg of vitamin E isomers	18 months	6/25 regression of carotid lesions in vitamin E group vs. 0/25 regression in controls
Linxian study (21) RCT	29,584 Chinese	Vitamin E & beta-carotene	5 years	Small reduction in CVA incidence in vitamin E group (RR=0.91;95% CI, 0.76-1.07)

CVA = Cerebrovascular accident
TIA = Transient ischemic attack
RCT = Randomized, controlled trial

Table 3: Vitamin E and Peripheral Vascular Disease

Study	Study Population	Study Length	Dose	Findings
Boyd et al (39) Clinical trial	81 patients w/ claudication	At least 3 months	200 mg/d (300 IU)	Good improvement in 32, some improvement in another 32
Ratcliffe (40) Controlled trial	41 patients w/ PVD, 25 controls	3 months	400 mg/d (600 IU/d)	34/41 improved in vitamin E group, 5/20 improved in control group
Livingstone (44) Controlled trial	20 patients w/ PVD	40 weeks	600 mg/d (900 IU/d)	13/17 patients on vitamin E improved walking, 2/17 in placebo improved
Williams HTG (42) Controlled trial	45 patients w/ PVD	3-83 months	1600 mg/d (2400 IU/d)	Increase in walking distances in those with distal disease and trend for patients on vitamin E longer
Haeger (43) Controlled trial	47 male patients w/ PVD	2-5 years	300 mg/d (450 IU/d)	Increase in walking distances after 4-6 mos. Increased blood flows after 20-25 mos. per noninvasive testing
Hamilton (44) RCT	41 patients w/ PVD	3 months	400 IU/day	no significant change in treatment groups symptoms
Birkenstock (45) RCT	390 patients w/ PVD	4-72 months	200 mg/d (300 IU/d)	72% noted symptom improvement
Donnan et al (33) Cross-sectional	1592 men and women	N/A	N/A	Increased ankle brachial pressure index (ABPI) w/higher vitamin E intakes (median 12 IU/day)
ATBC Trial (20) RCT	26,289 men w/o symptoms of claudication	4 years	50 mg (75 IU) of vitamin E with or without beta- carotene	No protective effect of either vitamin for PVD
Haeger (46) Clinical trial	158 patients w/ claudication	1-16 years	300 mg/d (450 IU/d)	62% of treated patients were \geq 30% improved clinically compared to small control group and 73% had improved blood flow per angiographic results ($< 0 .01$)

RCT = Randomized, controlled test
PVD = Peripheral vascular disease

questioned regarding dietary vitamin E intake.²⁹ The women, age 55-64, with the highest intakes of vitamin E, had small decreases in carotid wall thickness. Older men had a trend, though nonsignificant, towards decreased carotid wall thickness. However, as in many trials, the highest vitamin E dose was 49 mg per day (about 75 IU/day).

Two other small, randomized controlled trials have shown vitamin E supplements (of at least 100 IU/day) either reduced progression of carotid lesions²⁸ or caused regression.³¹ One small, randomized trial compared 400 IU per day vitamin E to aspirin. Incidence of CVA was lower in the vitamin E group than the aspirin group (3/52 in vitamin E group versus 6/48 in the aspirin group).³⁰

Vitamin E and the Prevention of Peripheral Vascular Disease (PVD)

The clinical trials assessing vitamin E in the treatment of peripheral vascular disease were flawed overall, as they had insufficient sample sizes or poor design (Table 3). A recent cross sectional survey by Donnon et al was conducted on approximately 1,500 men and women in Britain.³³ The investigators used a dietary survey and measured ankle and arm blood pressures. Subjects with the highest vitamin E intakes had the best peripheral arterial flow as indicated by ankle brachial pressure indexes. Peripheral artery disease was examined in the ATBC trial of 26,000 men without symptoms of claudication. No preventive effect was observed from the ingestion of 50 mg (75 IU) vitamin E per day.³⁴ More studies need to be conducted on vitamin E for its

effect in the prevention of peripheral and cerebrovascular disease.

Conclusions

It is the opinion of the authors that current scientific evidence is adequate to recommend 400 IU vitamin E per day for those at high risk for coronary artery disease or those with already established CAD. Although data from large-scale trials is limited, vitamin E may be warranted for patients with cerebro- and peripheral vascular disease. Because the potential benefits far outweigh the risks, it seems reasonable to recommend vitamin E as part of a therapeutic regimen for these conditions. Large clinical trials are needed to further elucidate specific indications, doses, and other unanswered questions. See Table 4 for ongoing trials.

Table 4: Ongoing Trials of Vitamin E in Cardiovascular Disease

Trial	Study Population	Dose	End-points
WHS	40,000 postmenopausal nurses	600 IU/d	MI, CVA, Death from CVD
HPS	20,000 patients w/angina CVA, PVD or DM	600 IU/d w/beta-carotene and vit C	Total mortality
HOPE	9541 patients w/CAD, CVA, PVD and DM	400 IU/d	MI, CVA, death from CVD
WACDT	8000 female nurses w/ previous CVD	400 IU/d compared to vitamin C and beta-carotene	MI, CVA, coronary revascularization, death from CVD
GISSI	12,000 patients w/ recent MI	300 mg/d	Total mortality
SECURE	732 patients w/CAD, PVD, CVA	400 IU/d	Progression of atherosclerosis on carotid ultrasound
SMARTFED	154 patients w/DM and Hyperlipidemia	400 IU/d	Progression of CAD on cath

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